



Original Article

Tailoring multidomain intervention programs to reduce cognitive and physical decline in older adults: Examining rural-urban differences in a nationwide cluster-randomized controlled trial



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ABSTRACT

Background: Frailty and cognitive impairment are major challenges in aging populations. Multidomain interventions targeting physical, cognitive, and nutritional health show promise; however, evidence on rural-urban differences in efficacy remains limited.

Objectives: To evaluate the impact of rural-urban disparities on the clinical efficacy of a 12-month multidomain intervention for cognitive and physical outcomes in older adults.

Design: Cluster-randomized controlled trial.

Setting: Community clusters in five cities/counties across Taiwan.

Participants: A total of 1082 adults aged ≥ 65 years from 40 community clusters were randomized to intervention or control groups.

Intervention: The intervention group received a 12-month program including physical exercise (45 min/session), cognitive training (1 hour/session), and nutritional guidance (15 min/session). The control group received telephone-based health education. This trial was registered at ClinicalTrials.gov (NCT03056768)

Measurements: Outcomes included walking speed, grip strength, physical activity (METs), frailty (CHS score), and cognitive function (MoCA), assessed at baseline, 6, and 12 months.

Results: Urban participants showed significantly greater gains in visuospatial/executive function at the 12 month (rural-urban difference 0.63, 95 % CI: 0.26 -1.03), and walking speed at the 12 month (rural-urban difference 0.12 m/s, 95 % CI: 0.05 - 0.19). Rural participants demonstrated better improvements in grip strength at the 12 month (rural-urban difference -2.59 kg, 95 % CI: -3.91 - -1.27) and language function (rural-urban difference -0.38, 95 % CI: -0.68 - -0.09). Frailty reduction was more pronounced in urban areas at the 12 month (-0.21 , 95 % CI: -0.38 - -0.03 , $p = 0.025$), but showed minimal change in the rural participants.

Conclusion: Rural-urban disparities influence the effectiveness of multidomain interventions. Tailored strategies are needed to optimize health outcomes across diverse settings.

1. Introduction

Healthy aging, defined as maintaining functional ability and well-being in older age, has become a global priority in the context of rapidly

aging populations [1,2]. The challenges of aging, including increasing rates of cognitive decline and physical frailty, pose significant burdens on individuals, families, and healthcare systems. Multidomain interventions, which integrate physical activity, cognitive training, and nutri-

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tional guidance, have emerged as promising strategies to address these challenges, promoting healthy aging and enhancing quality of life by targeting multiple domains of health simultaneously [3–5].

While multidomain interventions have shown efficacy in improving health outcomes, evidence regarding their effectiveness across populations with different socioeconomic status remains limited. Rural populations, in particular, often experience pronounced disparities in health-care access, education, and socioeconomic resources, which may influence the outcomes of multidomain interventions [6]. Previous studies have highlighted contrasting health patterns in urban and rural settings, with urban populations demonstrating higher rates of frailty, [7] while mild cognitive impairment is more prevalent in rural populations, as shown in studies conducted in Taiwan and US [8,9]. Similar rural-urban disparities were also identified in a recent systematic review on sarcopenia [10]. These findings underscore the complex interplay between geographic location, socioeconomic status, baseline health characteristics, and intervention efficacy. Rural populations are disproportionately affected by health inequities, including higher rates of frailty, lower cognitive performance, and limited access to preventive healthcare. These disparities present unique challenges to implementing and scaling effective multidomain interventions in underserved areas. Understanding these differences is critical for developing effective health interventions tailored to the needs of both rural and urban populations, ultimately contributing to ensure intervention effects and supporting healthy aging across diverse settings.

In clinical trials, participants were selected using identical inclusion and exclusion criteria and underwent standardized intervention protocols; however, intervention efficacy often varies among individuals. This heterogeneity in response may be attributable to socioeconomic factors or rural-urban disparities. Therefore, this study sought to investigate the influence of rural-urban disparities on the clinical efficacy of multidomain interventions targeting frailty and cognitive decline, utilizing data from a nationwide cluster-randomized controlled trial.

2. Materials and methods

2.1. Participants and study design

This was an exploratory analysis focusing on rural-urban differences in the clinical efficacy of a 12-month community-group multidomain intervention. The analysis utilized data from the Taiwan Health Promotion Intervention Study for Community Elders (THISCE), a clustered randomized controlled trial aimed at mitigating physical and cognitive decline in community-dwelling older adults with impaired instrumental activities of daily living, slow gait speed or subjective memory declines. Details of the original study protocol and design have been described previously [11].

Between February 12, 2014, and May 5, 2016, THISCE recruited participants aged 65 years and older from 40 community-center/neighborhood clusters across five cities/counties in Taiwan, encompassing both urban and rural regions. Participants were eligible for inclusion if they were aged ≥ 65 years, enrolled in Taiwan's National Health Insurance program, and exhibited subjective memory impairment, a loss of ≥ 1 instrumental activity of daily living (IADL), or a timed 6-meter walk speed ≤ 1 m/s. Exclusion criteria included a diagnosis of dementia; severe hearing or visual impairments; documented depression or anxiety; any serious illness with a life expectancy of less than 6 months; significant illness that could compromise compliance; total or partial dependence in activities of daily living (ADL); institutionalization; or participation in other clinical studies or research. Community-based group intervention trials often face challenges such as contamination between groups and difficulties in maintaining participant blinding. To address these issues, a clustered randomized design was utilized, which minimizes contamination between groups and improves the evaluation of implementation effectiveness. Independent researchers, who were not involved in outcome assessments, used a random number se-

quence generated by Excel (Excel 2013) for a 1:1 allocation of participants to either the intervention or control groups within the clusters. To ensure blinding, interventions were assigned using sealed envelopes for both participants and assessors. This subgroup analysis was based on data from the original THISCE study and focused on participants residing in either rural or urban areas. (Fig. 1)

2.2. Ethical compliance and trial registration

The THISCE study complied with the ethical principles outlined in the 1964 Declaration of Helsinki and its subsequent amendments. Ethical approval was granted by the Joint Institutional Review Board of Taiwan (No: 14–001-A), and all participants provided written informed consent prior to study-related procedures. The trial was registered at ClinicalTrials.gov (NCT03056768) on February 17, 2017.

2.3. Procedures

The Taiwan Health Promotion Administration organized community health promotion activities for all participants in the THISCE study. Participants in the usual health education group (HE) received regular telephone-based health education provided by local health bureau staff, while those in the multidomain intervention group (MDI) participated in a 12-month multidomain intervention modified from the Multidomain Alzheimer Preventive Trial (MAPT) based on Taiwanese context [12]. The intervention followed a structured schedule: four sessions in the first month, two sessions in the second month, and monthly sessions for the subsequent 10 months. Details of the intervention schedule and activities have been described in prior publications.

Each intervention session included a standardized program comprising 45 min of physical fitness exercises focusing on strength, balance, and flexibility, 1 hour of cognitive training to enhance reasoning and memory, and 15 min of nutritional guidance based on the Taiwan Health Promotion Administration's dietary recommendations. Participants received periodic health education on topics such as healthy aging, dementia, osteoporosis, sarcopenia, and cardiovascular risk factors.

2.4. Assessments and outcomes

2.4.1. Demographic characteristics

Baseline demographic and health-related data included participants' age, sex, tobacco smoking and alcohol consumption habits, as well as self-reported physician-diagnosed histories of hypertension, diabetes mellitus, cardiovascular disease, and stroke. Physical, cognitive, and functional performance were assessed at baseline, 6 months, and 12 months.

2.4.2. Definition of rural and urban areas

This study evaluates urbanization by utilizing a validated urbanization index that has been previously established and widely applied in the large cohort study [7,13]. Regions with an urbanization index score of 3 or lower are classified as urban areas, while those with a score above 3 are categorized as rural areas.

2.4.3. Physical and cognitive assessments

Physical measurements included walking speed, determined by the time taken to walk 6 m at a usual pace. Handgrip strength was measured using a dynamometer (Smedley's Dynamo Meter, TTM, Tokyo, Japan), with thresholds for weakness set at less than 28.0 kg for men and less than 18.0 kg for women. Physical activity levels were expressed in metabolic equivalent of task (MET) units, [14] derived from a validated Leisure-Time Physical Activity questionnaire [15].

Frailty was classified using modified Cardiovascular Health Study (CHS) criteria, [16] which included measures of weak handgrip strength, slow walking speed (less than 1 m/s), self-reported exhaustion

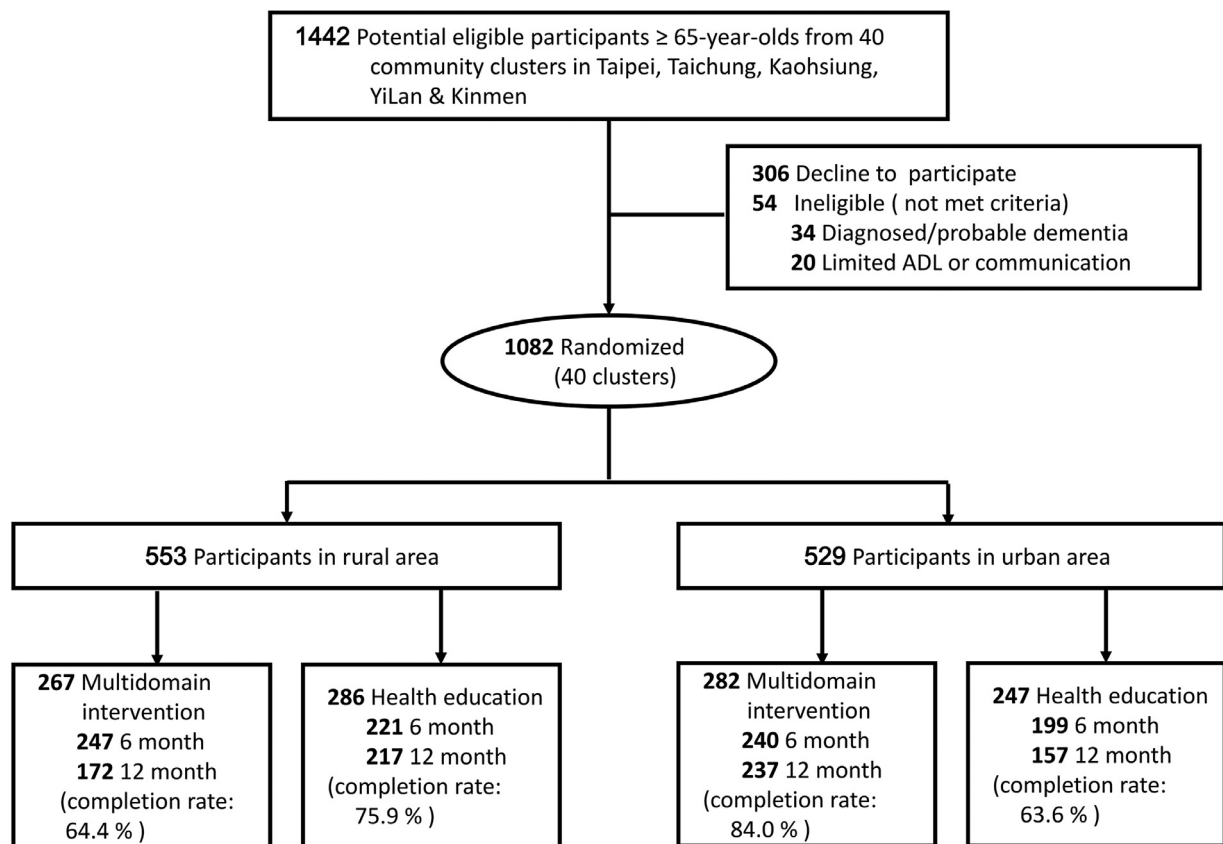


Fig. 1. Flow chart of the participant selection, randomization, intervention and follow-up.

on more than three days per week, unintentional weight loss exceeding 5.0 kg or 10 % of body weight in the past year, and low physical activity (below 3.75 MET/h for men or 2.5 MET/h for women, representing the lowest quintile of sex-specific baseline values). Participants meeting three or more of these criteria were classified as frail; those meeting one or two were classified as prefrail, and those meeting none were considered robust.

Cognitive performance was evaluated using the Montreal Cognitive Assessment (MoCA) screening tool, with adjustments for Taiwanese Chinese users, where an additional point was awarded to participants with fewer than 12 years of education [17]. The MoCA battery assessed key domains affected by mild cognitive impairment, including visuospatial and executive function, naming, attention, language, abstract reasoning, delayed recall, and orientation. This comprehensive evaluation provided detailed insights into participants' baseline physical and cognitive capacities.

2.4.4. Outcomes

The study outcomes included changes from baseline in CHS frailty score, walking speed, grip strength, and MoCA scores, adjusted for education level.

2.5. Statistical analysis

Continuous variables were summarized as mean \pm standard deviation, while categorical variables were reported as counts and percentages. The baseline characteristics and functional status were compared between the intervention and control groups using independent sample *t*-tests for continuous variables and chi-square tests for categorical variables. Changes in the MoCA and CHS frailty scores within each group over time were analyzed using paired Student's *t*-tests. Missing data was not imputed. A generalized linear mixed model (GLMM), which

assumed the data were missing at random, was employed to analyze changes in the MoCA and CHS frailty scores as functions of treatment group, time, and the Group \times Time interaction. A random effect was applied at the cluster level to account for participant clustering within each community. To investigate whether urban or rural residence influenced the effects of the multidomain intervention on changes in the MoCA and CHS frailty scores during follow-up, a three-way interaction term (Time \times Intervention \times Urbanization) was included in the GLMM. Baseline covariates that significantly differed between the intervention and control groups were adjusted for in the analysis. To assess attrition bias, we compared baseline characteristics between 12-month completers and non-completers, finding no differences in age, sex, education, or frailty, but lower baseline MoCA scores and physical activity levels among non-completers (Supplementary Table S3). To further reduce potential bias, we performed multiple imputations using chained equations with relevant baseline variables; while the findings remained largely consistent (Supplementary Figures S1–S3), caution is warranted due to potential residual bias from unmeasured factors. Given the number of cognitive and physical performance outcomes tested, we applied the Benjamini-Hochberg procedure to control the false discovery rate (FDR). Statistical significance was set at $p < 0.05$, and the analyses were conducted using SPSS software (IBM SPSS Statistics, Version 24.0).

3. Results

3.1. Demographic characteristics

The study included 1082 participants, with 553 (51.1 %) from rural and 529 (48.9 %) from urban areas. The mean age was 75.1 years, with no significant difference between groups. Rural participants had lower education levels (4.9 ± 4.0 vs. 8.4 ± 4.2 years, $p < 0.001$) and

Table 1
Baseline characteristics of the participant stratified by rural-urban group.

Characteristics: data show mean \pm SD [number] or number/total (%)	Total (N = 1082)	Rural (n = 553)			Urban (n = 529)			p-value for rural-urban difference
		Rural (n = 553)	MDI (n = 267)	HE (n = 286)	Urban (n = 529)	MDI (n = 282)	HE (n = 247)	
Age (years)	75.1 \pm 6.4	75.0 \pm 6.1	75.0 \pm 6.0	75.0 \pm 6.2	75.2 \pm 6.7	75.5 \pm 6.7	74.9 \pm 6.6	0.541
Male	339 (31.3)	202 (36.5)	73 (27.3)	129 (45.1) ^a	137 (25.9)	66 (23.4)	71 (28.7)	<0.001
Education (years)	6.6 \pm 4.5	4.9 \pm 4.0	5.0 \pm 4.1	4.8 \pm 3.9	8.4 \pm 4.2	8.5 \pm 4.2	8.3 \pm 4.3	<0.001
Education (\leq 6 years)	693 (64.3)	446 (80.8)	208 (78.2)	238 (83.2)	247 (47.0)	130 (46.4)	117 (47.8)	<0.001
Current drinker	155 (14.4)	70 (12.7)	26 (9.7)	44 (15.4) ^a	85 (16.1)	46 (16.4)	39 (15.9)	0.147
Current smokers	58 (5.4)	43 (7.8)	13 (4.9)	30 (10.5) ^a	15 (2.9)	4 (1.4)	11 (4.5) ^a	<0.001
Chronic conditions								
Hypertension	556 (51.4)	294 (53.2)	140 (52.4)	154 (53.8)	262 (49.6)	150 (53.2)	112 (45.5)	0.330
Diabetes	256 (23.7)	114 (20.6)	52 (19.5)	62 (21.7)	142 (26.9)	69 (24.5)	73 (29.7)	0.048
Stroke	41 (3.8)	22 (4.0)	14 (5.2)	8 (2.8)	19 (3.6)	12 (4.3)	7 (2.8)	0.147
Heart disease	232 (21.5)	115 (20.8)	48 (18.0)	67 (23.4)	117 (22.2)	61 (21.7)	56 (22.8)	0.330
Physical performance								
Frail status								<0.001
Robust	374 (35.3)	143 (26.0)	77 (29.1)	66 (23.2)	231 (45.4)	120 (44.9)	111 (45.9)	
Prefrail	605 (57.2)	357 (65.0)	167 (63.0)	190 (66.9)	248 (48.7)	131 (49.1)	117 (48.3)	
Frail	79 (7.5)	49 (8.9)	21 (7.9)	28 (9.8)	30 (5.9)	16 (6.0)	14 (5.8)	
CHS score	1.0 \pm 1.0	1.2 \pm 0.9	1.1 \pm 0.9	1.3 \pm 0.9	0.9 \pm 1.0	0.9 \pm 1.0	0.8 \pm 0.9	<0.001
Grip strength (kg)	22.7 \pm 8.3	22.7 \pm 8.8	21.8 \pm 7.6	23.6 \pm 9.8 ^a	22.7 \pm 7.7	22.8 \pm 7.6	22.6 \pm 7.8	0.997
Walking speed (m/s)	1.0 \pm 0.3	0.8 \pm 0.3	0.9 \pm 0.3	0.8 \pm 0.3 ^a	1.1 \pm 0.3	1.1 \pm 0.3	1.1 \pm 0.3	<0.001
Physical activity(MET)	14.3 \pm 16.9	12.6 \pm 13.5	12.2 \pm 11.3	13.0 \pm 15.3	16.1 \pm 19.7	15.2 \pm 17.9	17.2 \pm 21.5	0.001
Cognitive Function								
MoCA	20.2 \pm 5.7	18.8 \pm 5.6	19.2 \pm 6.0	18.4 \pm 5.2	21.6 \pm 5.5	21.7 \pm 5.6	21.5 \pm 5.4	<0.001
Visuospatial/Executive	2.6 \pm 1.7	1.9 \pm 1.7	2.1 \pm 1.8	1.8 \pm 1.6 ^a	3.3 \pm 1.5	3.3 \pm 1.5	3.3 \pm 1.5	<0.001
Naming	2.4 \pm 0.9	2.3 \pm 1.0	2.4 \pm 0.9	2.3 \pm 1.0	2.4 \pm 0.9	2.4 \pm 0.9	2.4 \pm 0.9	0.147
Concentration	4.4 \pm 1.6	4.0 \pm 1.6	4.0 \pm 1.7	4.0 \pm 1.5	4.8 \pm 1.5	4.7 \pm 1.5	4.9 \pm 1.4	<0.001
Language	1.7 \pm 1.0	1.7 \pm 0.9	1.8 \pm 0.9	1.7 \pm 0.9	1.6 \pm 1.1	1.8 \pm 1.0	1.4 \pm 1.1 ^a	0.0131
Abstract Thinking	0.6 \pm 0.8	0.4 \pm 0.7	0.5 \pm 0.7	0.4 \pm 0.6	0.9 \pm 0.8	0.9 \pm 0.8	0.9 \pm 0.8	<0.001
Delayed Recall	2.3 \pm 1.7	2.1 \pm 1.6	2.1 \pm 1.6	2.0 \pm 1.5	2.5 \pm 1.8	2.4 \pm 1.8	2.5 \pm 1.7	<0.001
Orientation	5.3 \pm 1.1	5.3 \pm 1.1	5.2 \pm 1.2	5.3 \pm 1.0	5.4 \pm 1.1	5.5 \pm 1.0	5.3 \pm 1.2 ^a	0.147

^a Statistically significant between-group difference by Student's *t*-test.

higher rates of smoking (7.8 % vs. 2.9 %, $p < 0.001$). Urban participants also had better baseline physical and cognitive performance, including higher walking speeds (1.1 \pm 0.3 m/s vs. 0.8 \pm 0.3 m/s, $p < 0.001$) and MoCA scores (21.6 \pm 5.5 vs. 18.8 \pm 5.6, $p < 0.001$). (Table 1) These disparities highlight key differences between rural and urban populations at baseline.

3.2. Cognitive outcomes

The MDI group in urban settings showed significant improvement in MoCA scores at 12 months (mean change: +1.83, 95 % CI: 1.33 – 2.33, $p < 0.001$), compared to rural settings, which demonstrated no significant change (–0.32, 95 % CI: –0.84 – 0.20). Concentration function improved significantly in urban participants undergoing MDI (12-month change: +0.54, 95 % CI: 0.25 – 0.83, interaction $p = 0.003$), while rural participants exhibited marginal improvement in language (+0.28, 95 % CI 0.08 – 0.48, interaction $p = 0.056$) and concentration (+0.34, 95 % CI: 0.06 – 0.61, interaction $p = 0.059$). (Fig. 2 and Supplementary Table S1)

3.3. Physical outcomes

Walking speed improved more in urban MDI participants (mean change: +0.12 m/s, 95 % CI: 0.09 – 0.15 at 12 months, $p = 0.004$) than in rural participants (+0.04 m/s, 95 % CI: 0.01 – 0.08, $p = 0.036$). Physical activity levels increased in urban MDI participants at the 6 months (+5.47 MET, 95 % CI: 1.74 – 9.19, $p = 0.090$) but showed minimal change in the rural group (+0.32 MET, 95 % CI: –1.45 – 2.08). (Fig. 3 and Supplementary Table S2)

3.4. Intervention effects on frailty

Urban participants experienced larger improvement in walking speed (0.08 m/s, 95 % CI: 0.03 – 0.13, interaction $p = 0.004$), whereas

rural participants were insignificant (–0.04 m/s, 95 % CI: –0.09 – 0.01). The disparity in CHS frailty score reduction between urban (–0.21, 95 % CI: –0.38 – –0.03 $p = 0.025$) and rural participants (–0.08, 95 % CI: –0.27 – 0.11 $p = 0.424$) were significant. (Fig. 3 and Supplementary Table S2)

3.5. Disparity of rural-urban intervention effects

We summarize all intervention effects on 6-month and 12-month physical and cognitive performance stratified by rural, urban and rural-urban differences in Fig. 4. Interaction terms of urbanization \times intervention \times time were applied to assess the impact of urbanization on the clinical efficacy of MDI. Significant results were observed, with grip strength favoring rural areas at the 12 month ($p < 0.001$), walking speed favoring urban areas at the 12 month ($p = 0.002$), physical activity favoring urban areas at the six month (4.92, 95 % CI: 0.11 – 9.74, $p = 0.090$), visuospatial executive function favoring urban areas at the 12 month ($p = 0.008$), and language function favoring rural areas at the 12 month ($p = 0.048$).

4. Discussion

The present study demonstrated significant rural-urban disparities in the clinical efficacy of MDI targeting cognitive and physical outcomes after adjusting baseline characteristics with significant differences. Urban participants showed better visuospatial executive function and showed greater improvements in walking speed following MDI. In contrast, rural participants experienced more significant improvements specifically in grip strength and language functions.

Compared to urban participants, rural participants have more unfavorable health behaviors such as smoking, lower education years, poor baseline physical and cognitive performance [7,10,18]. These findings align with previous research, which indicates that urban populations generally have better baseline cognitive and physical health. This advantage is likely attributable to greater access to healthcare and edu-

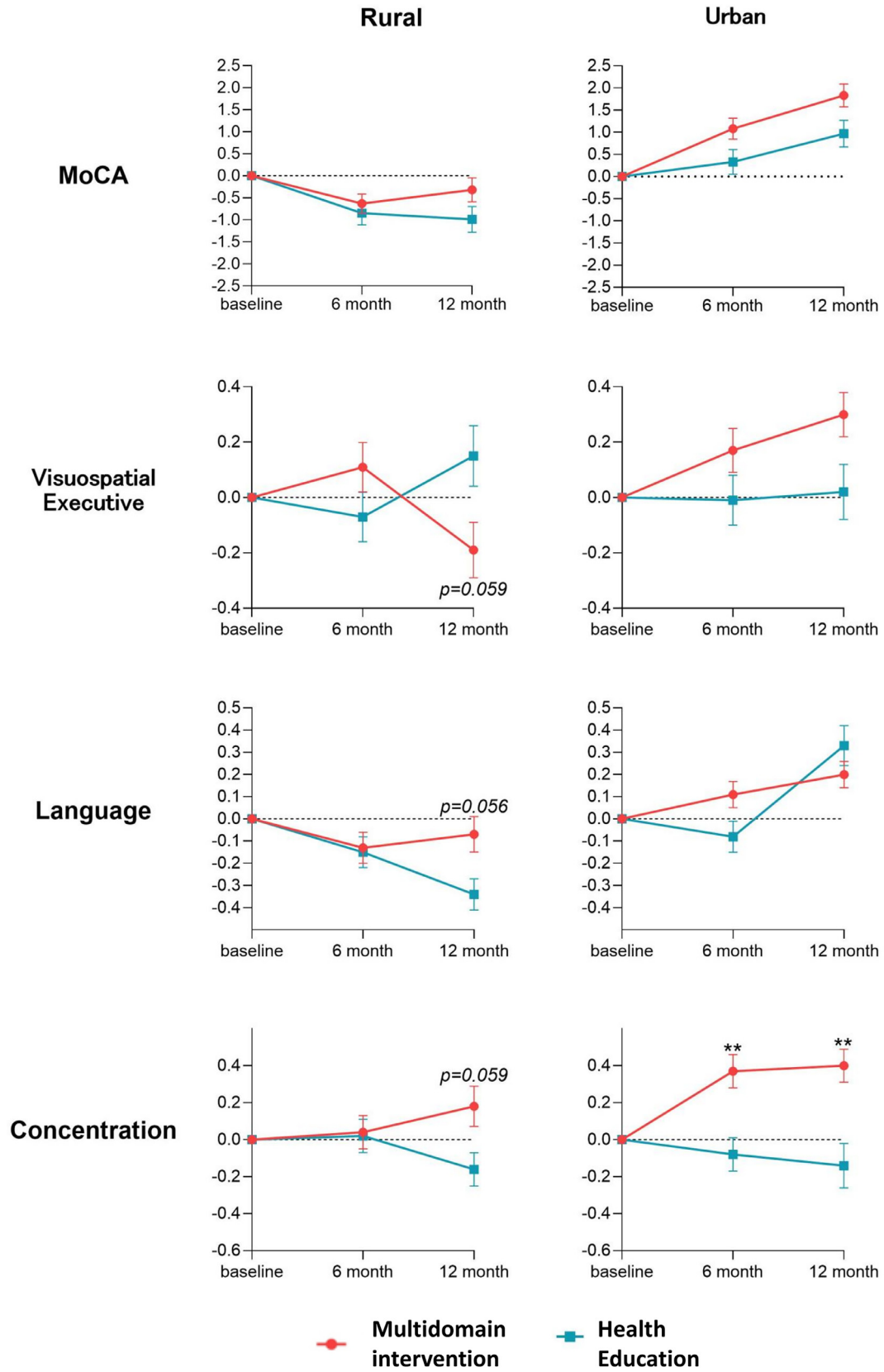


Fig. 2. Mean changes from baseline cognitive performance.

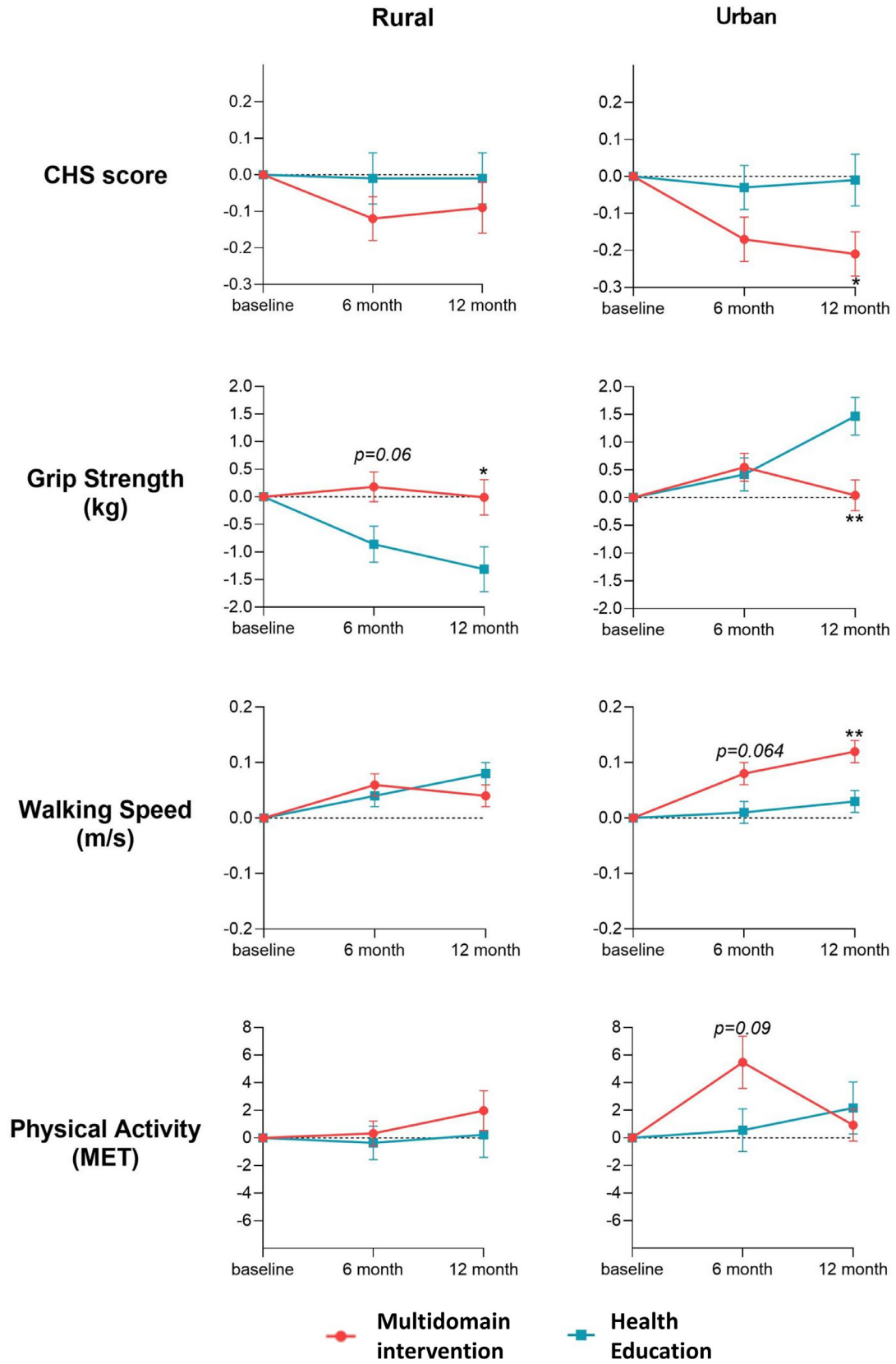


Fig. 3. Mean changes from baseline physical performance.

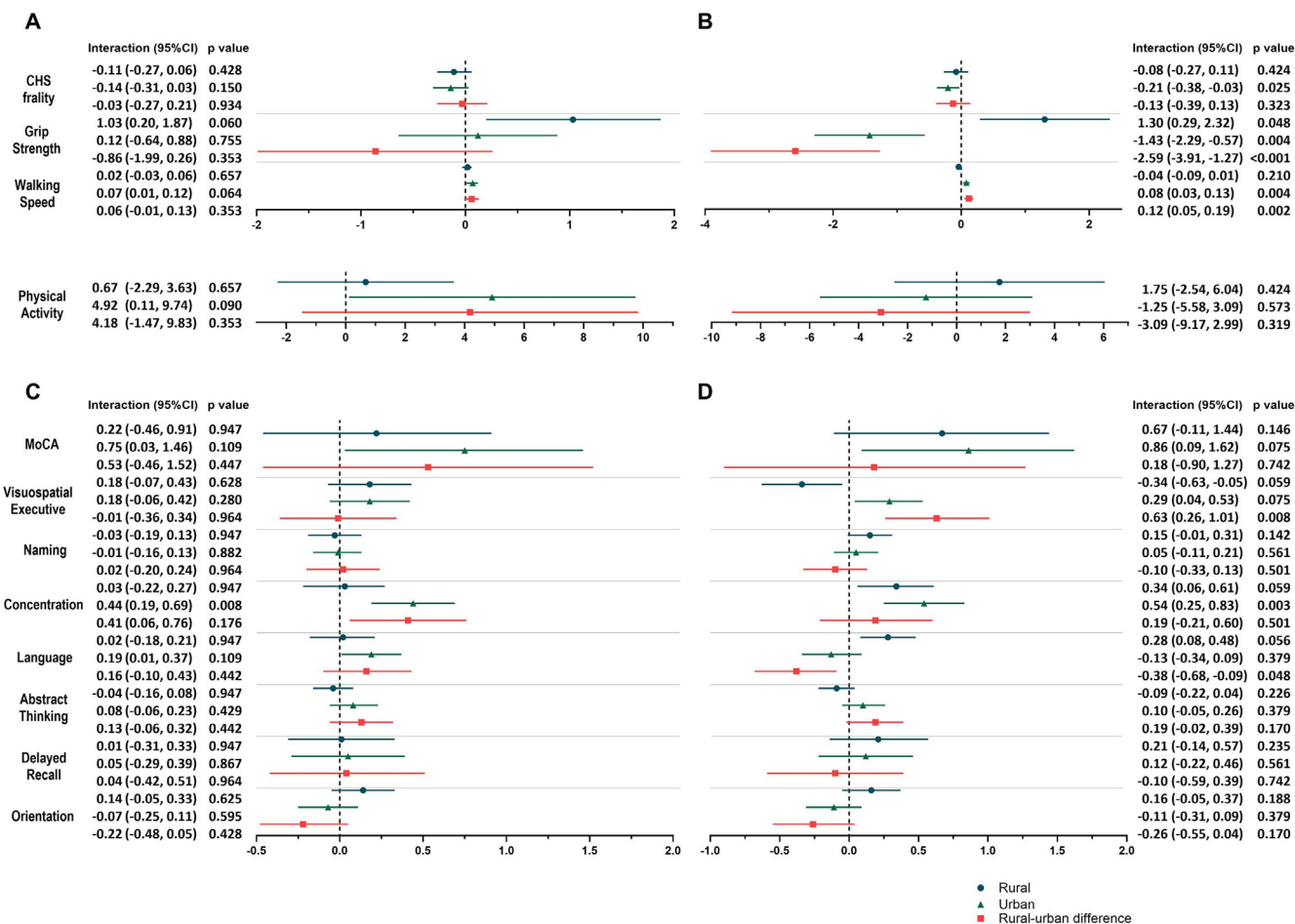


Fig. 4. Intervention effects on (A) 6-month and (B) 12-month physical, and (C) 6-month and (D) 12-month cognitive performance.

educational resources, a concept often referred to as community resilience [19]. While previous studies have highlighted rural-urban disparities in the clinical effectiveness of cancer treatments, [20] cardiovascular outcomes, [21] and vaccine immunization, [22] research on the impact of these disparities in multidomain interventions for frailty and cognitive declines remains limited. One study focused on structured pulmonary rehabilitation for COPD patients reported poorer six-minute walking performance among rural participants [23]. Our study observed a significant rural-urban gap in the benefits of interventions, particularly for walking speed. Our findings extend the current understanding from improvements in endurance among hospitalized COPD rehabilitation patients to community-dwelling older adults.

One of the key findings in this study is the differing improvements in cognitive domains between rural and urban participants following multidomain interventions. Urban participants experienced greater advancements in global cognitive function, visuospatial/executive function, and concentration, while rural participants showed better progress in language function. These disparities may be partially explained by the cognitive training procedures and underlying differences in baseline characteristics. Previous research suggests that higher education enhances cognitive reserve and responsiveness to interventions in domains like visuospatial and executive function [24,25]. The FINGER trial demonstrated significant multidomain intervention efficacy regardless of baseline characteristics, with neither education nor socioeconomic status moderating primary outcomes, yet post-hoc analyses revealed differential cognitive domain responses based on educational level—lower-educated participants showing greater executive function improvements while higher-educated participants exhibited stronger memory bene-

fits—suggesting that although intervention effectiveness is universal, neuroplastic responses vary according to educational background and may benefit from personalization [26]. In the THISCE study, the implementation of commercial cognitive training products (Tangram, Sudoku, block-stacking toys) that predominantly engage visuospatial processing and executive function domains may have contributed to the observed differential cognitive outcomes between rural and urban cohorts, with urban participants exhibiting superior improvement potentially attributable to higher educational attainment and increased prior exposure to similar cognitive tasks in urban environments. On the other hand, rural participants displayed more significant improvements in language function. This suggests that although the training emphasized visuospatial problem-solving and logic, rural participants seemed to benefit more from interactive activities involving verbal communication and naming, which aligns with the language subdomains of MoCA. This finding is in line with studies indicating that linguistic tasks are influenced by cultural and environmental factors, such as the close-knit community interactions typical of rural settings [27]. The linguistic richness of these environments, often characterized by frequent verbal exchanges, may enhance language skills and support improvements in naming and fluency tasks [28].

A further explanation lies in the health literacy, which motivates the participants to change their attitude to maintain and improve their healthy behavior to gain interventions goods [18]. The better outcomes observed in urban participants may be attributed to their higher health literacy, [29] which likely enhanced their ability to engage with and benefit from the intervention. However, rural participants may have faced limitations due to relatively reduced access to healthcare ser-

vices, which could have hindered their ability to fully engage in optimal chronic condition management, particularly the cardiometabolic risk. Evidence from the U.S. Health and Retirement Study further supports our observation, showing that improved education levels lead to greater cognitive benefits for rural populations [30]. The differences in cognitive improvements highlighted in this study underscore the need for culturally sensitive and equitable cognitive training programs that incorporate familiar tasks for diverse populations. In rural areas, engaging activities like storytelling or local games can enhance effectiveness, while promoting e-health literacy and using remote tools, such as mobile apps and virtual consultations, can bridge the rural-urban gap [31]. Additionally, community-based programs incorporated with age-friendly healthcare access are crucial in addressing systemic inequities, [4] ultimately enhancing intervention efficacy and supporting healthy aging in diverse populations.

These rural-urban differences may reflect variations in baseline cognitive reserve, educational attainment, and prior familiarity with the intervention content. Urban participants may have had greater prior exposure to structured cognitive activities, enhancing their responsiveness in visuospatial and executive domains. In contrast, rural participants, who often engage in more communal verbal interaction, may have benefited more from language-focused group tasks. In terms of physical performance, the observed greater improvement in walking speed among urban participants may reflect their more sedentary lifestyle, which allowed for a larger intervention effect. By contrast, rural participants may already engage in frequent walking and daily physical tasks due to their environment and occupation, limiting the potential for further gains in walking speed despite the intervention.

Despite all efforts ran into the study, there were several limitations. First, as a secondary analysis of the original cohort, the reduced sample size may have limited the statistical power to detect subtle differences in the effectiveness of the interventions. Second, the absence of laboratory and neuroimaging data limited our ability to assess underlying biological or pathological mechanisms, such as neurodegenerative or vascular conditions, which may have influenced participants' responses to the intervention. The lack of data on health literacy and social participation constrained our ability to evaluate their moderating effects on intervention outcomes. Future cohort designs should incorporate these domains to better capture contextual factors influencing multidomain intervention efficacy. Lastly, the study employed a general multidomain intervention approach rather than domain-specific protocols tailored to individual cognitive or physical needs. While this broad approach allowed for the inclusion of multiple intervention components, it complicates the interpretation of which specific elements contributed to the observed improvements, particularly in areas such as visuospatial and language functions. Despite the aforementioned methodological constraints, this study definitively elucidated rural-urban disparities in MDI clinical efficacy. The observed global physical and cognitive improvements among study participants do not fully address the challenges inherent in community implementation protocols, thereby providing critical implications for future MDI trial design and systematic community-based implementation strategies.

5. Conclusions and implications

Our findings suggest potential rural-urban disparities in the clinical response to multidomain interventions. While the results highlight areas for tailoring interventions, they warrant confirmation in prospective trials with stratified designs and robust adjustment for contextual variables.

Declaration of competing interests

All authors declare no competing interests.

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Ethical standards

The THISCE study followed ethical principles in accordance with the 1964 Declaration of Helsinki and national regulations, obtaining approval from the Joint Institutional Review Board of Taiwan (JIRB No. 14-001-A), and was registered at ClinicalTrials.gov (NCT03056768).

Consent statement

All participants provided written informed consent.

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

AI was not used in the preparation of this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Min-Yin Ho: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Wei-Ju Lee:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Ko-Han Yen:** Writing – review & editing. **Chih-Kuang Liang:** Writing – review & editing. **Li-Ning Peng:** Writing – review & editing. **Ming-Hsien Lin:** Writing – review & editing. **Ching-Hui Loh:** Writing – review & editing. **Fei-Yuan Hsiao:** Writing – review & editing. **Liang-Kung Chen:** Writing – review & editing, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.tjpad.2025.100231](https://doi.org/10.1016/j.tjpad.2025.100231).

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