Lifestyle changes and outcomes of elderly people with mild cognitive impairment: a 4-year longitudinal study

CURRENT STATUS: POSTED

Osamu Katayama
Department of Preventive Gerontology, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology
katayama.o@ncgg.go.jp Corresponding Author
ORCiD: https://orcid.org/0000-0003-1885-527X

Sangyoon Lee
Department of Preventive Gerontology, Center for Gerontology and Science, National Center for Geriatrics and Gerontology

Seongryu Bae
National Center for Geriatrics and Gerontology

Keitaro Makino
National Center for Geriatrics and Gerontology

Yohei Shinkai
National Center for Geriatrics and Gerontology

Ippei Chiba
National Center for Geriatrics and Gerontology

Kenji Harada
National Center for Geriatrics and Gerontology

Hiroyuki Shimada
National Center for Geriatrics and Gerontology

DOI: 10.21203/rs.3.rs-15861/v1

SUBJECT AREAS
Geriatrics & Gerontology Neurology

KEYWORDS
Mild cognitive impairment, Multidomain, Lifestyle activities, Instrumental activities of
daily living, Cognitive activity, Social activity, Productive activity, Latent class analysis
Abstract
Background Longitudinal studies have shown that mild cognitive impairment (MCI; a precursor of dementia) reverts to normal cognition (NC). However, we couldn’t find any reports that have examined the lifestyle activity change patterns of elderly people diagnosed as having MCI and their outcomes in a longitudinal study. We determined the lifestyle activity change patterns among elderly people with MCI.

Methods The participants in this study were 769 community-dwelling elders who were ≥65 years old with MCI at baseline. Four years later, participants were classified into reverters who recovered from MCI to NC, maintainers who maintained MCI, and converters who had global cognitive impairment (GCI) or Alzheimer disease (AD). We used latent class analysis (LCA) to classify changes in instrumental activities of daily living (IADL), and cognitive, social, and productive activities of the participants. Subsequently, we performed a multinomial logistic regression analysis with reversion status as dependent variable (the most typical, converters as reference group) and cluster membership as independent variables.

Results The reversion rate of 769 participants was 33.3%. The reverters were maintaining multidomain lifestyle activities, converters had discontinued multidomain lifestyle activity or were inactive, and maintainers were maintaining productive activities. According to logistic regression analysis, the activity pattern of continuing to engage in multidomain lifestyle activities and start activity were more likely to recover from MCI to NC (P < .05).

Conclusions Elderly participants with MCI who continued their multidomain lifestyle activities were more likely to recover to NC. Even if it does not lead to NC, continuing productive activities is important to maintaining MCI without converting.

Background
The number of people with dementia is expected to reach about 47 million people worldwide in 2015 and will almost triple to 131 million by 2050 [1], which will make it the largest global health and social care issue in the 21st century [2]. About 35% of dementia is reportedly caused by a combination of nine factors: less education, hearing loss, hypertension, obesity, smoking, depression, physical
inactivity, social isolation, and diabetes, which are modifiable risk factors [2]. Longitudinal studies have shown that mild cognitive impairment (MCI), which has clinical significance as a precursor of dementia, reverts to normal cognition (NC) function [3, 4]. In previous studies investigating factors related to reversion from MCI to NC function, modifiable factors, such as memory, visual spatial cognitive function, neuropsychological function, personality, and lifestyle, have been reported [5-7]. A randomized controlled trial (RCT) has shown that simultaneous intervention against these modifiable risk factors may prevent dementia [8, 9]. Our previous studies revealed that lifestyle activities, such as instrumental activities of daily living (IADL), cognitive activities, social activities, and productive activities, were reversible predictors of MCI reversion to NC [7].

A recent study in individuals with MCI characterized eight subgroups by IADL, neuropsychiatric, and cognitive functions by using latent class analysis (LCA) [10]. This result suggested that there are various lifestyle activity patterns in elderly people with MCI. However, we couldn't find any reports that have examined the lifestyle activity change patterns of elderly people diagnosed as having MCI and their outcomes in a longitudinal study.

We hypothesized that there are multiple lifestyle activity change patterns in elderly people with MCI that are associated with outcomes. The aim of this study was to determine the lifestyle activity change patterns among community-dwelling elderly people with MCI after 4 years by using the National Center for Geriatrics and Gerontology-Study of Geriatric Syndromes (NCGG-SGS) database [11].

Methods
Study participants, design, and setting
Participants were selected from adults enrolled in a population-based cohort study titled “The Obu Study of Health Promotion for the Elderly (OSHPE)” [12], which is part of the NCGG-SGS [11]. In the present study, we analyzed longitudinal data from 444 community-dwelling adults aged ≥ 65 years (mean age, 70.9 ± 4.5 years; men, 211; and women, 233), who had participated in both the first and second waves of the OSHPE and had MCI at the time of the first-wave assessment. The first wave of the OSHPE was held between August 2011 and February 2012. During this wave, 5104 community-
dwelling elderly people participated in a baseline OSHPE assessment. Of these, 3095 (60.6%) took part in a second-wave cognitive examination between August 2015 and August 2016. The inclusion criteria were residence in Obu-city and age ≥ 65 years at the time of the first examination (August 2011 to March 2013). The baseline exclusion criteria were health problems, such as Alzheimer disease (AD), Parkinson disease, or stroke (n = 312) and symptoms of depression (n = 200); inability to perform basic tasks of daily living, such as eating, grooming, bathing, and climbing up and down stairs (n = 24); need for support or care as certified by the Japanese public long-term care insurance system because of disability (n = 86); missing data regarding the exclusion criteria (n = 2); inability to complete cognitive tests at the baseline assessment (n = 142); relocation (n = 29) or death (n = 51) during the follow-up period; NC (n = 2935); and global cognitive decline at the baseline assessment (n = 554). Of the 769 potential participants, 325 did not receive the second-wave cognitive examination (Fig. 1). Finally, we analyzed data from 444 participants.

Multivariate normal imputation was used to adjust for selection bias and loss of information because we identified potential bias in baseline data of the sample for those who remained versus those who were lost to follow-up (Supplementary Table 1). The multivariate normal imputation utility imputes missing values based on the multivariate normal distribution. The algorithm uses least squares imputation. The covariance matrix was constructed using pairwise covariances. The diagonal entries (variances) were computed using all non-missing values for each variable. The off-diagonal entries for any two variables were computed using all observations that were non-missing for both variables. In cases in which the covariance matrix was singular, the algorithm used minimum norm least squares imputation based on the Moore–Penrose pseudo-inverse. Multivariate normal imputation allows the option to use a shrinkage estimator for the covariances. The use of shrinkage estimators is a method of improving the estimation of the covariance matrix [13]. We imputed reversion status, which was divided into reverters who recovered from MCI to NC, maintainers who maintained MCI, and converters who had global cognitive impairment (GCI), as indicated by a Mini Mental State Examination (MMSE) [25] score of < 24 and/or AD, for participants with missing data. All participants provided their informed consent before being included in the study. The study protocol was approved.
by an institutional review board.

Measurements of lifestyle activity
Participants completed a questionnaire comprising eight questions on IADL, cognitive activity, social activity, and productive activity as different elements of lifestyle activity. The following questions were asked: items that measured IADL were (1) “Do you go shopping for daily necessities?” and (2) “Do you use maps to go to unfamiliar places?”; items that measured cognitive activity were (3) “Do you read books or newspapers?” and (4) “Do you engage in cultural classes?”; items that measured social activity were (5) “Do you attend meetings in the community?” and (6) “Do you engage in hobbies or sports activities?”; and items that measured productive activity were (7) “Do you engage in housecleaning?” and (8) “Do you engage in fieldwork or gardening?” Answers of “yes” were determined to be positive responses. Of the participants who answered “yes” at baseline for lifestyle activities, we defined those who answered “no” in the second wave as discontinued and those who answered “yes” as active. On the contrary, of those who answered “no” at baseline for lifestyle activities, those who answered “no” in the second wave were defined as inactive and those who answered “yes” were defined as start of activities.

Measurement of cognitive functions and incident AD
We used the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT), which is an iPad application, to conduct cognitive screening [14]. The NCGG-FAT includes the following domains: (1) memory (word-list memory-I [immediate recognition] and word-list memory-II [delayed recall]), (2) attention (a tablet version of the Trail Making Test-part A; TMT-part A), (3) executive function (a tablet version of the TMT-part B), and (4) processing speed (a tablet version of the Digit Symbol Substitution Test). The NCGG-FAT has been shown to have high test–retest reliability and moderate-to-high criterion-related validity [14] and predictive validity [15] among community-dwelling older persons. Cognitive assessments were conducted by staff who received training from the authors. Potential participants with MCI were identified after reviewing available clinical, neuropsychological, and laboratory data at meetings involving study neurologists and neuropsychologists, as previously described [12]. In brief, MCI participants were independently
recruited by using the NCGG-FAT, which has two memory tasks, tests of attention and executive function, and a processing speed task. Using established criteria [16], we diagnosed MCI in individuals who exhibited cognitive impairment but were functionally independent in terms of basic daily life activities. For all cognitive tests, we used established standardized thresholds in each corresponding domain for defining impairment in population-based cohorts comprising community-dwelling older persons (scores > 1.5 standard deviations [SDs] that specified age and educational means). We used the MMSE to measure global cognitive function [17]. Specifically, we used < 24 points on the MMSE as a cutoff score for GCI, in accordance with previous findings [18]. Participants whose cognitive tests scores were > 1.5 SD units above the mean were classified as belonging to the NC group. Participants were tracked monthly for newly incident AD, as recorded by the Japanese National Health Insurance and Later-Stage Medical Care systems [19]. Participants were considered to have AD if they had been diagnosed by a physician according to the International Classification of Diseases, 10th revision. The incidence of AD was based on diagnoses by third-party physicians who were blinded to the design and participant groups of the study. Participants were allocated to the following three groups: reverters who had NC at the follow-up; maintainers who maintained MCI; and converters who had GCI and/or AD at the follow-up.

**Statistical analysis**
We calculated the reversion rates from MCI to NC during the follow-up assessments. The Pearson chi-squared test and one-way ANOVA used to examine differences in baseline participant characteristics and between the reverter, maintainer, and converter groups. Subsequently, we used the chi-squared test with adjusted standardized residuals to determine whether MCI status significantly affected the class extracted by LCA. Residuals followed the t distribution: t > 1.96 was accepted as indicating P < .05 and t > 2.56 as indicating P < .01.

We used LCA for the clustering of lifestyle data. JMP ver. 14.2 software (SAS Institute Inc., Cary, NC, USA) was used in which LCA fits a latent class model to categorical response variables and determines the most likely cluster or latent class for each observation. The fit statistics are the negative loglikelihood (− LogLikelihood), the Akaike Information Criterion (AIC), and Bayesian
Information Criterion (BIC) [20, 21]. Smaller values of each indicate better fit. We identified the optimal number of clusters using the AIC and BIC. Subsequently, we performed a multinomial logistic regression analysis with reversion status as dependent variable (the most typical, converters as reference group) and cluster membership as independent variables. First, we used unadjusted models. Second, for cluster membership, we adjusted for covariates age, sex and education. Data are presented as ORs with 95% CI. The significance level was set at \( P < .05 \). All analyses were performed using IBM SPSS v.25.0 (IBM Japan, Tokyo) and JMP ver. 14.2 (SAS Institute Inc.).

Results

**Baseline characteristics of the participants**

In the initial group of 444 participants, 232 (52.3%) participants reverted to NC from MCI. The reversion rate for participants for whom we imputed samples was 33.3%. Table 1 details the participant baseline characteristics for those grouped according to the change patterns from MCI in the imputed group. Age, sex, educational level, walking speed, MMSE, GDS score, MCI status, and lifestyle activities differed significantly between reverters, maintainers, and converters (Table 1).

**Latent class of lifestyle change patterns**

The fit criteria for the LCA of 769 participants are provided in Table 2. The AIC information criterion and \(-\text{LogLikelihood}\) continued to decline with the addition of further latent class, and BIC was reversed. AIC and \(-\text{LogLikelihood}\) suggested that the seven-class model can fit well. The lowest value of BIC suggested that a four-class model was preferred. The fit criteria were equivocal in highlighting the best fitting model. The seven-class model included a small number of cases, which would create cells with an insufficient number of cases in subsequent analyses. Therefore, we decided that a four-class model can fit best.

According to the prior probability shown in Fig. 2, we labeled classes as starting and maintaining lifestyle activity (Fig. 2A; \( n = 273, 35\% \)), maintaining lifestyle activity (Fig. 2B; \( n = 248, 32\% \)), maintaining productive activity (Fig. 2C; \( n = 207, 27\% \)), and discontinuing or becoming inactive regarding lifestyle activity (Fig. 2D; \( n = 41, 6\% \)). Participants assigned to the starting and maintaining
lifestyle activity class maintained their lifestyle activities, such as IADL, cognitive activities, social activities, and productive activities, moreover they were mostly inactive regarding the question of engaging in cultural classes. Although, they were more likely to start multidomain lifestyle activities. Participants in the maintaining lifestyle activities maintained almost all lifestyle activities. However, there seemed to be fewer start of lifestyle activities compared to the starting and maintaining lifestyle activity class. Participants in the maintaining productive activity class were inactive in IADL, cognitive activity, and social activity but tended to maintain productive activity. Participants in the discontinuing or inactive lifestyle activity class tended to discontinue almost all lifestyle activities or become inactive.

**Demographical and lifestyle cluster characteristics**

Table 3 shows raw baseline data of demographics, duration of education, underlying disease, walking speed, GDS and lifestyle activities characteristics by cluster. We observed group differences for sex, education, walking speed, GDS and lifestyle activities. Post hoc differences are given in table 3. The LCA class and MCI status are presented in Table 4. The reverters in starting and maintaining lifestyle activity class had more participants than those in the other classes ($P < .05$). In addition, the maintaining productive activity class had fewer reverters than those in the other classes ($P < .05$). The maintainers in the maintaining productive activity class had more participants than those in the other classes ($P < .05$). The converters in discontinuing or inactive lifestyle activity class had more participants than those in the other classes ($P < .05$).

Table 5 shows OR’s and 95% CI’s estimated by unadjusted and adjusted multinomial logistic regression analyses with reversion status as dependent variable (with converters group as reference) and the LCA class as independent variables. After adjusting for age, sex, education history, heart disease, pulmonary disease, hypertension, diabetes mellitus, walking speed, MMSE, and GDS. Class 1 (OR: 4.20; 95% CI: 1.34–13.15) had significantly greater odds of being reverters. Additionally, the Class 1 (OR: 2.58; 95% CI: 1.04–6.43) had significantly greater odds of being maintainers.

**Discussion**
The MCI to NC reversion rate has been reported to range from 10–50%, although it varies depending on the follow-up period and MCI subtype [3, 4]. In a previous study with the study population similar to ours and follow-up, the reversion rate was 35% [22], which is similar to the rate of 33.3% in our study [22].

Age is the strongest known risk factor for dementia [23]. Our study results showed that reverters and maintainers were significantly younger at baseline than converters. Although modification of risk factors is important in dementia prevention, age is unmodifiable [2]. A strong association also has been well established between high educational attainment and reduced risk of cognitive impairment and dementia [24]. Indeed, reverters and maintainers had a significantly longer education history at baseline than did converters. Although these factors are difficult to correct, lifestyle activities, including physical activity that can be corrected, cognitive activities, social activities, and productive activities, have been shown to be associated with a decreased risk of dementia [7, 23, 25].

The 4-year change patterns of such modifiable lifestyle activities were classified into four classes by LCA in this study. In class 1 (Fig. 2A, starting and maintaining lifestyle activity), there was a certain degree of allowance for discontinuation in all lifestyle activity domains, and only the culture classes had the most inactivity. However, in other lifestyle activities, more likely to start and maintenance were the largest. Participants in class 2 (Fig. 2B, maintaining lifestyle activity) maintained activity in all lifestyle activities. In class 3 (Fig. 2C, maintaining productive activity), shopping for daily necessities, reading a book or newspaper, and productive activity were maintained, whereas other lifestyle activities were not observed. In class 4 (Fig. 2D, discontinuing or inactive lifestyle activity), there were discontinuations and inactivity in all lifestyle activities except reading of books or newspapers. From the results of the chi-squared test with adjusted residuals, there were more reverters in class 1 than in the other classes. In contrast, there were fewer reverters in class 3. There were more maintainers in class 3 than in the other classes, and the converters in class 4 than in the other classes. From the results of the adjusted multinomial logistic regression analyses, Class 1 had significantly greater odds of being reverters. On the other hand, the Class 1 had significantly greater odds of being maintainers.
Previous RCTs have shown that multidomain interventions that simultaneously intervene in these multidomain lifestyle activities may prevent cognitive decline [8, 9, 26–28]. Our results suggested that maintaining multidomain lifestyle activities of MCI persons was important for reversion from MCI to NC. There were more maintainers in class 3, which maintained productive activity, unlike in some other classes. In terms of productive activities, countrywide and population-based research has indicated that gardening may be beneficial for adult mental health, including self-rated health and psychological distress [29]. In addition, participation in productive activity has been shown to reduce the risk of cognitive decline [30]. The results of this study suggested that productive activity was related to maintaining MCI status. There were more converters in class 4 than in other classes. Physical inactivity, low frequency of social contact, and low social participation increased the risk of dementia [31, 32]. Considering that class 4 participants had suspended or become inactive in multidomain lifestyle activities, it has been suggested that maintaining multidomain lifestyle activities is important for recovery or maintenance from MCI. Finally, class 2 was the only class that maintained all activities, including engaging in cultural classes. However, class 2 was not statistically associated with recovery from MCI to NC. It was similar to Class 1 in maintaining lifestyle activities, but there seemed to be a few starts of activities. It may suggest that in order to recover from MCI to NC, it is important not only to maintain lifestyle activities but also to start.

Of the limitations of our study, the finding that the reversion rate from MCI to NC before imputed samples was 52.3% may have been affected by false positives, making it difficult to accurately determine the influence of lifestyle activities on recovery from MCI to NC. In addition, participants were not randomly recruited, and about 42% of participants were lost to follow-up. This rate may have led to underestimation of cognitive decline. Furthermore, because we did not cover all lifestyle activities, it was not possible to consider the effect of other lifestyle activities. This study had the following strengths and implications. Our findings were consistent with those of comprehensive geriatric assessments designed to collect information about lifestyle activity. In addition, to the best of our knowledge, this is the first study to categorize multidomain lifestyle activities into four change patterns and clarify the relationship with MCI status.
Conclusions
The study results indicated that among the elderly judged as having MCI, the activity pattern of continuing to engage in multidomain lifestyle activities and start activity were more likely to recover from MCI to NC. Furthermore, even if it does not lead to recovery of NC, continuation of productive activities was suggested to be important for maintaining MCI without converting. These results may provide useful information for designing interventions to prevent cognitive decline and dementia in persons with MCI.

Abbreviations
AD, Alzheimer disease; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; GCI, Global cognitive impairment; GDS, Geriatric Depression Scale; IADL, Instrumental activities of daily living; JST, Japan Science and Technology; LCA, Latent class analysis; MCI, Mild cognitive impairment; MMSE, Mini Mental State Examination; NC, Normal cognition; OSHPE, Obu Study of Health Promotion for the Elderly; RCT, Randomized controlled trial; SD, Standard deviations.

Declarations
Acknowledgments
We thank the healthcare staff for their assistance with the assessments.

Funding
This work was supported by a Health and Labour Sciences Research Grant (Comprehensive Research on Aging and Health) (grant number H23-tyoujyu-ippan-001), the Research Institute of Science and Technology for Society (RISTEX) from the Japan Science and Technology Agency (JST) for redesigning communities for an aged society in 2012, a Grant-in-Aid for Scientific Research (B) (grant number 23300205), JSPS KAKENHI Grant Number JP19K24188, and Research Funding for Longevity Sciences (grant number 22-16) from the National Center for Geriatrics and Gerontology, Japan. No support was received from sources associated with industry.

Availability of data and materials
The datasets used and/or analyzed during the present study are available from the corresponding
author on reasonable request.

**Authors’ contributions**

OK planned the study, wrote the first draft of the manuscript, and coordinated the review and editing process leading to the final manuscript. HS participated in the design of the study and wrote the paper. SB, KM, YS, IC, KH and SL collected the data and contributed to the editorial process and review of the manuscript. All authors carried out critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

**Competing interest**

The authors declare that they have no competing interests.

**Ethics approval and consent to participate**

All participants gave their informed consent before they were included in the study. The study protocol was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology.

**Consent for publication**

Not applicable.

**Author details**

Department of Preventive Gerontology, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, 7-430 Morioka-cho, Obu City, Aichi Prefecture 474-8511, Japan.

**References**

[1] Prince M WA, Geurchet M, Ali G, Wu Y, Prina M. . The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends. . Alzhiemer’s Disease International 2015.

[2] Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. The Lancet. 2017;390:2673-734.
[3] Shimada H, Makizako H, Doi T, Lee S, Lee S. Conversion and Reversion Rates in Japanese Older People With Mild Cognitive Impairment. J Am Med Dir Assoc. 2017;18:808 e1- e6.

[4] Ganguli M, Jia Y, Hughes TF, Snitz BE, Chang CH, Berman SB, et al. Mild Cognitive Impairment that Does Not Progress to Dementia: A Population-Based Study. J Am Geriatr Soc. 2019;67:232-8.

[5] Park MH, Han C. Is there an MCI reversion to cognitively normal? Analysis of Alzheimer's disease biomarkers profiles. International Psychogeriatrics. 2014;27:429-37.

[6] Pandya SY, Clem MA, Silva LM, Woon FL. Does mild cognitive impairment always lead to dementia? A review. J Neurol Sci. 2016;369:57-62.

[7] Shimada H, Doi T, Lee S, Makizako H. Reversible predictors of reversion from mild cognitive impairment to normal cognition: a 4-year longitudinal study. Alzheimers Res Ther. 2019;11:24.

[8] Moll van Charante EP, Richard E, Eurelings LS, van Dalen JW, Ligthart SA, van Bussel EF, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. Lancet. 2016;388:797-805.

[9] Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol. 2017;16:377-89.

[10] Hanfelt JJ, Wuu J, Sollinger AB, Greenaway MC, Lah JJ, Levey AI, et al. An exploration of subgroups of mild cognitive impairment based on cognitive, neuropsychiatric and functional features: analysis of data from the National Alzheimer's Coordinating Center. Am J Geriatr Psychiatry. 2011;19:940-50.

[11] Shimada H, Makizako H, Lee S, Doi T, Lee S, Tsutsumimoto K, et al. Impact of Cognitive Frailty on Daily Activities in Older Persons. J Nutr Health Aging. 2016;20:729-35.

[12] Shimada H, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, Anan Y, et al. Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people. J Am Med Dir Assoc. 2013;14:518-24.

[13] Schafer J, Strimmer K. A shrinkage approach to large-scale covariance matrix estimation and implications for functional genomics. Stat Appl Genet Mol Biol. 2005;4:Article32.
[14] Makizako H, Shimada H, Park H, Doi T, Yoshida D, Uemura K, et al. Evaluation of multidimensional neurocognitive function using a tablet personal computer: test-retest reliability and validity in community-dwelling older adults. Geriatr Gerontol Int. 2013;13:860-6.

[15] Shimada H, Makizako H, Park H, Doi T, Lee S. Validity of the National Center for Geriatrics and Gerontology-Functional Assessment Tool and Mini-Mental State Examination for detecting the incidence of dementia in older Japanese adults. Geriatr Gerontol Int. 2017;17:2383-8.

[16] Petersen R. Mild cognitive impairment as a diagnostic entity. 2004.

[17] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98.

[18] O’Bryant SE, Humphreys JD, Smith GE, Ivnik RJ, Graff-Radford NR, Petersen RC, et al. Detecting dementia with the mini-mental state examination in highly educated individuals. Arch Neurol. 2008;65:963-7.

[19] Ministry of Health Labour aWoJ. Annual Health, Labour, and Welfare Report 2011-2012. https://www.mhlw.go.jp/english/wp/wp-hw6/dl/02epdf Accessed 30 Jul 2019 2012.

[20] Akaike H. A New Look at the Statistical Model Identification. IEEE Transactions on Automatic Control. 1974;19:716-23.

[21] Schwarz G. Estimating the dimension of a model. Annals of Statistics. 1978;6:461-4.

[22] Ravaglia G, Forti P, Montesi F, Lucicesare A, Pisacane N, Rietti E, et al. Mild cognitive impairment: epidemiology and dementia risk in an elderly Italian population. J Am Geriatr Soc. 2008;56:51-8.

[23] Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol. 2018;14:653-66.

[24] Ngandu T, von Strauss E, Helkala EL, Winblad B, Nissinen A, Tuomilehto J, et al. Education and dementia: what lies behind the association? Neurology. 2007;69:1442-50.

[25] Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. BMC Public Health. 2014;14:510.

[26] Kamegaya T, Araki Y, Kigure H, Yamaguchi H. Twelve-week physical and leisure activity
programme improved cognitive function in community-dwelling elderly subjects: a randomized controlled trial. Psychogeriatrics. 2014;14:47-54.

[27] Sindi S, Ngandu T, Hovatta I, Kareholt I, Antikainen R, Hanninen T, et al. Baseline Telomere Length and Effects of a Multidomain Lifestyle Intervention on Cognition: The FINGER Randomized Controlled Trial. J Alzheimers Dis. 2017;59:1459-70.

[28] Solomon A, Turunen H, Ngandu T, Peltonen M, Levalahti E, Helisalmi S, et al. Effect of the Apolipoprotein E Genotype on Cognitive Change During a Multidomain Lifestyle Intervention: A Subgroup Analysis of a Randomized Clinical Trial. JAMA Neurol. 2018;75:462-70.

[29] Shiue I. Gardening is beneficial for adult mental health: Scottish Health Survey, 2012-2013. Scand J Occup Ther. 2016;23:320-5.

[30] Niti M, Yap KB, Kua EH, Tan CH, Ng TP. Physical, social and productive leisure activities, cognitive decline and interaction with APOE-epsilon 4 genotype in Chinese older adults. Int Psychogeriatr. 2008;20:237-51.

[31] Kuiper JS, Zuidersma M, Oude Voshaar RC, Zuidema SU, van den Heuvel ER, Stolk RP, et al. Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev. 2015;22:39-57.

[32] Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. The Lancet Neurology. 2014;13:788-94.

Tables

Table 1. Comparison of baseline characteristics between reverters, maintainers, and converters
| Parameter                                      | Reverters (n = 256) | Maintainers (n = 395) | Converters (n = 118) | P value |
|-----------------------------------------------|---------------------|-----------------------|----------------------|---------|
| Age (years) *                                 | 69.6 (3.5)          | 72.3 (5.2)            | 76.4 (6.5)           | <0.01^a |
| Sex (% male)                                  | 41.0^d              | 46.8                  | 55.9^c               | <0.05^b |
| Education (years) *                           | 11.9 (2.4)          | 11.1 (2.4)            | 10.6 (2.7)           | <0.01^a |
| Current smoking (% yes)                       | 10.2                | 12.2                  | 7.6                  | >0.05^b |
| Heart disease (% yes)                         | 16.4                | 16.7                  | 19.5                 | >0.05^b |
| Pulmonary disease (% yes)                     | 8.2                 | 10.4                  | 7.6                  | >0.05^b |
| Hypertension (% yes)                          | 42.6                | 49.4                  | 51.7                 | >0.05^b |
| Diabetes mellitus (% yes)                     | 12.9                | 15.2                  | 16.9                 | >0.05^b |
| Walking speed (m/s) *                         | 1.3 (0.2)           | 1.2 (0.2)             | 1.1 (0.3)            | <0.01^a |
| Mini Mental State Examination (points) *      | 26.9 (1.9)          | 26.4 (1.7)            | 26.1 (1.7)           | <0.01^a |
| Geriatric Depression Scale (points) *         | 2.6 (2.3)           | 3.0 (2.4)             | 3.3 (2.5)            | <0.05^a |
| Category of MCI                               |                     |                       |                      |         |
| Amnestic MCI single domain                    | 16.4                | 14.7                  | 5.9^d                |         |
| Non-amnestic MCI single domain                | 72.7^c              | 55.7^d                | 56.8                 |         |
| Amnestic MCI multiple domain                  | 4.7^d               | 7.1                   | 15.3^c               |         |
| Non-amnestic MCI multiple domain              | 6.3^d               | 22.5^c                | 22.0                 |         |
| Instrumental activities of daily living (% yes)|                     |                       |                      |         |
| Shopping for daily necessities                | 98.0                | 95.9                  | 93.2                 | >0.05^b |
| Using map to go unfamiliar place              | 64.8^c              | 55.9                  | 50.8                 | <0.05^b |
| Cognitive activity (% yes)                    |                     |                       |                      |         |
| Reading of a book or newspaper                | 97.7^c              | 94.9                  | 84.7^d               | <0.01^b |
| Culture lesson                                | 44.5                | 37.6                  | 37.3                 | >0.05^b |
| Social activity (% yes)                       |                     |                       |                      |         |
| Attending a meeting in the community          | 58.4^c              | 51.6                  | 43.6^d               | <0.05^b |
| Hobby or sport activity                       | 75.4                | 67.3                  | 65.8                 | >0.05^b |
| Productive activity (% yes)                   |                     |                       |                      |         |
| Housecleaning                                 | 89.1                | 89.1                  | 75.4^d               | <0.01^b |
| Field work or gardening                       | 75.3                | 71.1                  | 70.1                 | >0.05^b |

* Mean (standard deviation).

^aP values reported from one-way ANOVA.

^bP values obtained from Pearson chi square test.

^cStatistically significant association by adjusted standardized residual > 1.96 (P < 0.05).

^dStatistically significant association by adjusted standardized residual < −1.96 (P < 0.05).

R, Reverters; M, Maintainers; C, Converters.

| Classes (N) | Parameters (N) | -LogLikelihood | BIC     | AIC     |
|-------------|----------------|----------------|---------|---------|
| 4           | 99             | 4868.8         | 10395.4 | 9935.5  |
| 5           | 124            | 4827.2         | 10478.4 | 9902.4  |
| 6           | 149            | 4798.8         | 10587.7 | 9895.6  |
| 7           | 174            | 4771.2         | 10698.7 | 9890.4  |

BIC, Bayesian Information Criterion; AIC, Akaike Information Criterion.
|                                | Class 1 n=273(35%) | Class 2 n=248(32%) | Class 3 n=207(27%) | Class 4 n=41(6%) | p Value Post hoc analyses |
|--------------------------------|--------------------|--------------------|--------------------|-----------------|--------------------------|
| **Age (years)***               | 71.6±5.0           | 71.9±5.0           | 72.8±6.2           | 71.9±6.0        | >0.05                    |
| Sex (% male)                   | 178(65.2)          | 72(29.0)           | 74(35.7)           | 32(78.0)        | <0.001                   |
| Education (years)*             | 11.7±2.6           | 11.6±2.4           | 10.5±2.3           | 10.7±2.6        | <0.001 1>3, 2>3          |
| Current smoking (% yes)        | 35(12.8)           | 14(5.6)            | 19(9.2)            | 15(36.6)        | <0.001                   |
| Heart disease (% yes)          | 57(20.9)           | 39(15.7)           | 29(14.0)           | 6(14.6)         | >0.05                    |
| Pulmonary disease (% yes)      | 25(9.2)            | 20(8.1)            | 19(9.2)            | 7(17.1)         | ns                       |
| Hypertension (% yes)           | 118(43.2)          | 122(49.2)          | 104(50.2)          | 21(51.2)        | ns                       |
| Diabetes mellitus (% yes)      | 41(15.0)           | 32(12.9)           | 32(15.5)           | 8(19.5)         | ns                       |
| Walking speed (m/s)*           | 1.3±0.2            | 1.3±0.2            | 1.2±0.2            | 1.1±0.2         | <0.001 1>3, 2>3          |
| Mini-mental state examination (points)* | 26.6±1.8    | 26.5±1.9           | 26.5±1.8           | 26.4±1.7        | ns                       |
| Geriatric depression scale (points)* | 2.7±2.2  | 2.3±2.1            | 4.0±2.6            | 3.1±2.4         | <0.001 1>3, 2<3          |
| Category of MCI                |                    |                    |                    |                 |                          |
| amnestic MCI single domain     | 46(16.8)           | 27(10.9)           | 27(13.0)           | 7(17.1)         | ns                       |
| non-amnestic MCI single domain | 173(63.4)          | 165(66.5)          | 115(55.6)          | 20(48.8)        | ns                       |
| amnestic MCI multiple domain   | 18(6.6)            | 16(6.5)            | 20(9.7)            | 4(9.8)          | ns                       |
| non-amnestic MCI multiple domain | 36(13.2)          | 40(16.1)           | 45(21.7)           | 10(24.4)        | ns                       |
| Instrumental activities of daily living (% yes) |  |  |  |  | |
| Shopping for daily necessities | 268(98.5)          | 246(99.2)          | 201(97.1)          | 24(58.5)        | <0.001                   |
| Using map to go unfamiliar place | 219(80.2) | 162(65.3)          | 48(23.2)           | 18(43.9)        | <0.001                   |
| Cognitive activity (% yes)     |                    |                    |                    |                 |                          |
| Reading of book or newspaper   | 271(99.3)          | 243(98.0)          | 180(87.0)          | 31(75.6)        | <0.001                   |
| Culture classes                | 41(15.0)           | 248(100.0)         | 2(1.0)             | 15(36.6)        | b<0.001                  |
| Social activity (% yes)        |                    |                    |                    |                 |                          |
| Attending a meeting in the community | 147(53.8)  | 177(71.4)          | 65(31.6)           | 15(37.5)        | <0.001                   |
| Hobby or sports activity       | 228(83.8)          | 235(95.1)          | 45(21.7)           | 27(65.9)        | <0.001                   |
| Productive activity (% yes)    |                    |                    |                    |                 |                          |
| Housecleaning                  | 229(83.9)          | 239(96.4)          | 191(92.7)          | 9(22.0)         | <0.001                   |
| Field work or gardening        | 222(81.6)          | 184(74.8)          | 125(60.4)          | 23(56.1)        | <0.001                   |

* Mean (standard deviation).

**P** values reported from one-way ANOVA. Significant difference obtained by Games-Howell post-hoc test.

b**P** values obtained from Pearson chi square test.

CStatistically significant association by adjusted standardized residual > 1.96 (**P** < 0.05).

dStatistically significant association by adjusted standardized residual < -1.96 (**P** < 0.05).

1, Class 1; 2, Class 2; 3, Class 3; 4, Class 4.
### Table 4. Comparison of classes between reverters, maintainers, and converters

| Class   | Class 1 | Class 2 | Class 3 | Class 4 |
|---------|---------|---------|---------|---------|
| Reverters | 104 (38.1)<sup>a</sup> | 91 (37.1) | 52 (25.1)<sup>b</sup> | 8 (19.5) |
| Maintainers | 135 (49.5) | 119 (48.0) | 120 (58.0)<sup>a</sup> | 21 (51.2) |
| Converters | 34 (12.5) | 37 (14.9) | 35 (16.9) | 12 (29.3)<sup>a</sup> |

Values are presented as n (%).

<sup>a</sup>Statistically significant association by adjusted standardized residual > 1.96 (P < 0.05).

<sup>b</sup>Statistically significant association by adjusted standardized residual < −1.96 (P < 0.05).

### Table 5. Multinomial logistic regression analysis with cluster membership as independent variable and maintainers and reverters as dependent variable

#### Unadjusted models

| Class | Class 4 (Discontinuing or becoming inactive regarding lifestyle activity) | Class 1 (Starting and maintaining lifestyle activity) | Class 2 (Maintaining lifestyle activity) | Class 3 (Maintaining productive activity) | Age (years) | Sex (male) | Education history (years) | Current smoking (yes) | Heart disease (yes) | Pulmonary disease (yes) | Hypertension (yes) | Diabetes mellitus (yes) | Walking speed (m/s) | MMSE (points) | GDS (points) |
|-------|----------------------------------------------------------------|--------------------------------------------------|------------------------------------------|-------------------------------------------|-------------|-----------|--------------------------|---------------------|-----------------|-------------------------|------------------|------------------------|-------------------|--------------|-------------|
|       | Reference | 2.27 (1.02–5.06) | < .05 | 1.84 (0.83–4.09) | >.05 | 1.96 (0.88–4.37) | >.05 | - | - | - | - | - | - | - | - |
|       | Reverters (N = 256) | Reference | 4.59 (1.73–12.16) | 3.73 (1.41–9.86) | 2.23 (0.83–6.01) | - | - | - | - | - | - | - | - | - |
|       | Maintainers (N = 395) | | | | | | | | | | | | | | |

### Figures
Figure 1

Flow diagram of sample selection
Figure 2

Latent class of lifestyle change patterns The 4-year change patterns of modifiable lifestyle activities were classified into four classes by latent class analysis. Bars represent the discontinued or decrease (black bar), inactive (dark gray bar), active or maintain (gray bar), and activity start or improve (white bar). A, class 1; B, class 2; C, class 3; D, class 4

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

Supplementary_Table_1.docx