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# Original Article

# Factors Associated with Weight Loss in a National Longitudinal Study among Community-Dwelling Individuals 45 Years and Older in Thailand in 2015-2022

Supa Pengpid <sup>1,2,3</sup>, Karl Peltzer <sup>1,4,5\*</sup>, André Hajek <sup>6</sup>, Razak M. Gyasi <sup>7,8</sup>

- <sup>1.</sup> Department of Health Education and Behavioral Sciences, Faculty of Public Health, Mahidol University, Bangkok, Thailand
- Department of Public Health, Sefako Makgatho Health Sciences University, Pretoria, South Africa
- 3. Department of Healthcare Administration, College of Medical and Health Science, Asia University, Taichung, Taiwan, China
- <sup>4.</sup> Department of Psychology, University of the Free State, Bloemfontein, South Africa
- 5. Department of Psychology, College of Medical and Health Science, Asia University, Taichung, Taiwan, China
- <sup>6.</sup> Department of Health Economics and Health Services Research, University Medical Center Hamburg-Eppendorf, Hamburg Center for Health Economics, Hamburg, Germany
- 7. African Population and Health Research Center, Nairobi, Kenya
- 8. National Centre for Naturopathic Medicine, Faculty of Health, Southern Cross University, Lismore, NSW, Australia

# ABSTRACT

# Article history

Received 5 Mar 2025 Accepted 21 Jun 2025 **Introduction: :** Only a small number of research has evaluated the determinants of weight loss among ageing adults in poorly resourced countries. Thus, using longitudinal and nationally representative community-dwelling data from 2015 to 2022 in Thailand, also stratified by sex, this study sought to examine the factors associated with weight loss among those 45 and older.

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**Methods:** Four waves of Health, Ageing, and Retirement in Thailand (HART) investigations were analyzed in 2015, 2017, 2020, and 2022 (analytical baseline sample N=2775). Weight loss (>5kg in the past 12 months) was assessed by self-report. The time-variant factors and outcomes were evaluated using conditional fixed-effects logistic regression.

**Results:** Regressions found that increasing age (AOR = 1.07, 95% CI: 1.03-1.07, p < 0.001), transitioning to not working (AOR = 1.47, 95% CI: 1.10-1.96, p = 0.009), decreasing economic status (AOR = 0.94, 95% CI: 0.89-0.99, p = 0.035), an increase in hospitalisation (AOR = 1.58, 95% CI: 1.22-2.04, p < 0.001), an increase in multimorbidity (AOR = 1.42, 95% CI: 1.01-2.00, p = 0.043), an increase in functional disability (AOR = 1.52, 95% CI: 1.28-1.81, p < 0.001), an increase in wearing dentures (AOR = 1.66, 95% CI: 1.07-2.58, p = 0.025), increasing depressive symptoms (AOR = 1.06, 95% CI: 1.02-1.10, p < 0.001), and increasing social participation (AOR = 1.32, 95% CI: 1.01-1.71, p = 0.041) were significantly associated with weight loss. In addition, among men, transitioning to living alone (AOR = 2.12, 95% CI: 1.23-3.66, p = 0.009) was associated with increased weight loss.

**Conclusion**: This long-term study improves our knowledge of the factors that contribute to weight loss in people 45 years of age and older. We found that health and psychosocial factors were associated with weight loss. The early detection and management of these identified associated factors may be important for preventing weight loss, especially among underweight older adults in Thailand.

Keywords: Weight loss, Correlates, Longitudinal study, Thailand

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<sup>\*</sup> Corresponding Author: Department of Health Education and Behavioral Sciences, Faculty of Public Health, Mahidol University, Bangkok, Thailand. Tel: + 66852471427, Email address: kfpeltzer@gmail.com

#### Introduction

Weight loss is one of the most prevalent ageingrelated deficits. Indeed, weight loss is a sign of catabolism and macronutrient deficiencies (1). As defined globally in studies as a reduction of 5 kg or more or 5% of normal body weight during 5-10 years, weight loss occurs in 15%-20% of cases (2). For example, among middle-aged and older adults in Germany, the prevalence of unintentional weight loss of more than 5kg in weight in the past 12 months was 6.9% (3). Weight loss can lead to a catabolic cascade of unfavorable events that increase morbidity and death (1, 4, 5). In addition to disease processes like catabolic events, disease or age-related anorexia (also known as "anorexia of aging"), and consequently inadequate dietary intake, the causes of weight loss in later life are complex and include depressive or cognitive disorders, increased inflammatory status (6), and a decline in socioeconomic status (7). However, ageing processes and age-related changes can affect physiology and metabolism, gradually deteriorating older persons' nutritional status even when disease or apparent abnormalities are absent (1, 8).

Several studies investigated health and psychosocial factors associated with weight loss. For example, health factors associated with weight loss include hospitalisation (9), functional impairment (9, 10), multimorbidity (11), current smoking status (4), having less than one meal a day (9) and oral problems with chewing or swallowing food (9, 12). Psychosocial factors associated with weight loss include depressive symptoms (3, 13, 14), positive affect, lack of selfesteem (3), feeling lonely (3, 13), social isolation (3), reduced social activity (9), and bereavement (15). In South Korea, significant weight reduction was associated with older men moving to live alone without changing their marital status. The risk factor for older women was moving out on their own independently after divorce or widowhood (16). Living alone was linked to 5 kg or more of weight loss and fewer meals for older women (13). However, most of these studies have been conducted in high-income countries and did not include longitudinal national data on weight loss, which led to this study.

Given the dearth of information on this topic, especially in relation to longitudinal studies in lower-income countries, our study sought to investigate the relationships between health and psychosocial factors and weight loss (> 5 kg in the past 12 months) among persons 45 years and older. It was based on national, longitudinal community-dwelling data in Thailand from 2015 to 2022. Developing strategies to help older adults requires understanding the factors that contribute to weight loss.

#### Methods

Sample and protocols

Four waves of Health, Ageing, and Retirement in Thailand (HART) investigations conducted in Thailand in 2015, 2017, 2020, and 2022 were analyzed using an

analytical baseline sample of N=2775. Using a multistage national sample approach, one adult (over 45) was chosen at random from each household (as the inclusion criterion) and interviewed in the home; additional information is provided elsewhere (17). Participants provided signed informed permission, and the study's protocol was approved by the National Institute for Development Administration's Human Research Ethics Committee (ECNIDA 2020/00012). Every procedure followed the Declaration of Helsinki and complied with all applicable rules and regulations.

Measures

Outcome variable

Weight loss was assessed with the question, "Have you lost more than 5 kilograms in the last year?" (Yes/No), as in previous studies (5, 13, 16).

Independent variables

Sociodemographic factors

Time-varying sociodemographic factors included selfreported marital age, (single/divorced/separated/married and widowed), living situation (living alone and living with others), work status (working and not working), and subjective economic standing. "How satisfied are you with your economic situation?" was the question used to assess the latter. Higher economic status is indicated by higher scores ranging from 0 to 10. "Are you currently working?" was one of the inquiries used to gauge work status (Yes/No). Individuals who reported having just one household member as opposed to one or more others were considered to be living alone. Sex was utilized in a gender-stratified model, and time-constant factors such as educational attainment, urban/rural residency, and sex were employed to describe the sample.

Health factors

Hospitalisation was assessed by the number of hospital inpatient stays in the past 12 months (1 = any and 0 = none).

Diabetes, hypertension, bone diseases, cardiovascular disease, psychiatric/emotional disorders, brain illness/dementia, liver/gastrointestinal disease, renal disease, lung disease, and cancer were among the chronic conditions (0–10) evaluated by medical professionals. Multimorbidity was defined as having two or more chronic conditions.

The inability to dress, wash, eat, or bathe by oneself was characterized as a functional constraint (18). Higher scores (0-4) indicated more functional limitations. It has a Cronbach's  $\alpha$  of 0.95.

Substance use included current smoking (yes/no) and current alcohol use (yes/no).

Meal skipping (0-6) was assessed with the question: "How many meals have you had in the last 2 days?" "Yesterday (breakfast, lunch, dinner; yes/no) and the day before yesterday (breakfast, lunch, dinner; yes/no)." (19).



The inquiry, "How often do you exercise?" was used to gauge the frequency of physical activity or exercise. "One equals zero days, two to one day, three to four days, four to five or seven days per week." Wearing dentures was assessed with the question," Do you wear dentures?" (Yes/No)

#### Psychosocial factors

Self-rated mental health status was sourced from the item, "In general, how would you rate your mental health status?" reported on a "0 (= very poor) to 10 (= excellent) scale". Poorer self-rated mental health status was reverse scored, with higher scores indicating poorer self-rated mental health status. Single-item self-rated health measures have been found to be valid (20).

The Center for Epidemiologic Studies Depression Scale (CES-D-10) was used to measure depressed symptoms; the loneliness item was not included. The total scores ranged from 0 to 27, where higher scores indicated more depressive symptoms (21). Cronbach's alpha was 0.69. A CES-D-10 question (21) asking, "How often did you experience feeling lonely in the past week?" was used to quantify loneliness. defined as "very rarely (less than one day) or none"= 0 and "almost always (5-7 days), often (3-4 days), or sometimes (1-2 days)"= 1. Higher scores indicated greater loneliness because the items were scored in reverse.

Quality of life (QoL)/happiness was assessed with the question, "Overall, how satisfied are you with your quality of life (or how happy do you feel)?" reported on a "0 (= very poor) to 10 (= excellent) scale". Single-item QoL measures have been found to be valid (22).

Religious involvement was sourced from four items: 1) "Making merit and giving alms according to respected religious principles," 2) "Prayer in the morning/before going to bed," 3) "Performing meritmaking activities at religious places according to the religions that the interviewees respect on important religious days," and 4) "Observing important religious days that the interviewee respects." (23). The Cronbach alpha was 0.80. Responses ranged from 0 = never to 3=always, for a total range of 0-12. Higher scores indicated stronger religious commitment.

Participation in at least one of six activities religious, social, athletic, musical, artistic, cultural, volunteer, and/or political-was considered social involvement. The Cronbach's alpha was 0.68.

Furthermore, self-reported height and weight were used to calculate the body mass index (BMI).

### Data analysis

The sample was described using descriptive statistics. The longitudinal relationships between time-varying independent factors and time-varying weight loss (the likelihood of changing from a non-weight loss state to a weight loss state) were estimated using conditional fixed effects (FE) logistic regressions for the four study waves spanning 2015-2022. As a result, only those whose weight loss status changed over the observation period were added to FE models. Because these individuals only altered their weight loss status throughout the observation period, only 1876 observations were used in the FE regression analysis. The findings of the FE regressions can be understood as average treatment effects on the treated because it focuses on individuals who actually reported such changes over time (24). The conditional FE logistic regression was chosen based on the Hausman specification test between the FE model and the random-effects model [(170.07) p < 0.001]. Based on previous reviews (3, 4, 9-11, 13-15), time-varying independent variables were included. In addition, in sensitivity analysis, the main model was extended by including an interaction term consisting of residence status and weight loss (urban-rural residence x weight loss). FE regressions cannot contain sex and education as main effects since they are instances of time-invariant variables, which typically do not change over time among individuals. P < 0.05 was deemed significant, and only full instances (missing cases were < 4% in study variables) were examined. For statistical analysis, StataSE 18.0 (College Station, TX, USA) was utilized.

#### Ethical considerations

The study received ethical approval from the "Ethics Committee in Human Research, National Institute of Development Administration - ECNIDA (ECNIDA 2020/00012)", and participants provided written informed consent. Data is publicly available at Health, Aging, and Retirement in Thailand (HART): https://hart.nida.ac.th/download-center

## Results

#### **Participants**

The baseline analytical sample consisted of 2775 participants. The prevalence of weight loss across the four survey waves was 5.2%, 5.6% among women and 4.8 % among men. Among those who had weight loss, 33.7 % measured a body mass index of less than 20 kg/m<sup>2</sup>. Time-constant variables (excluded in FE regressions) indicate 56.2 % were females, 93.0 % had primary or more education, and 51.2% lived in rural areas. The mean age was 65.2 years (ranging from 45 to 106 years), 62.7% were married or cohabiting, and 51.5% were currently working. Almost one in ten (8.0 %) living alone, and 6.7 (0-10) had a subjective economic status. The prevalence of multimorbidity was 15.0 %, and 11.9 % were current smokers, 12.6% were currently drinking alcohol, and 20.1% were wearing dentures. The average poor self-rated mental health state was 2.1 (SD = 1.9), the mean of depressive symptoms was 5.7 (SD = 3.0), and the average level of QoL/happiness was 7.9 (SD = 1.5) (Table 1).

#### Determinants of weight loss

FE logistic regressions showed that increasing age (OR: 1.07, 95% CI: 1.03-1.10), transitioning to nonworking (OR: 1.47, 95% CI: 1.10-1.96), decreasing subjective economic status (OR: 0.94, 95% CI: 0.89-0.99), increases in hospitalisation (OR: 1.58, 95% CI: 1.22 to 2.04), increases in multimorbidity (OR: 1.42,



95% CI: 1.01-2.00), increases in functional disability (OR: 1.52, 95% CI: 1.28-1.81), increase in wearing dentures (OR: 1.66, 95% CI: 1.07-2.58), increases in depressive symptoms (OR: 1.06, 95% CI: 1.02-1.10) and increases in social participation (OR: 1.32, 95% CI: 1.01-1.71) increased the odds of weight loss. (Table 2)

Furthermore, the interaction term (urban-rural residence x weight loss) did not achieve statistical significance (p > 0.05).

In sex-stratified analysis, among men, transitioning to living alone (OR: 2.12, 95% CI: 1.23-3.66) increased weight loss. In addition, only among men and not women, transitioning to non-working, decreasing subjective economic status, increases in multimorbidity, and increases in social participation increased weight loss, while only among women and not men, increases in wearing dentures increased weight loss. (Table 3)

#### Discussion

This study's objective was to use national, longitudinal, community-based data from 2015 to 2022

to determine for the first time the predictors of weight loss (>5kg/past year) among Thailand's individuals 45 years and older. The prevalence of weight loss of 5.2% in this study was lower than among persons 40 years and older in Germany (6.9%) (3) and among middleaged (13.0%) and older adults (17.3%) in South Korea (5). Among those who had weight loss, 33.7% measured a body mass index of less than 20 kg/m2, indicating dangerous underweight.

The country differences (Thailand and Germany or South Korea) in the prevalence of weight loss among ageing adults are influenced by various factors, including cultural norms, dietary habits, healthcare access, and socioeconomic conditions.

FE Regressions showed that increasing age, transitioning to not working, decreasing economic status, an increase in multimorbidity, increasing functional disability, increase in wearing dentures, increasing depressive symptoms and increasing social participation were significantly associated with weight loss. In addition, among men, transitioning to living alone was associated with increased weight loss.

Table 1. Sample characteristics at baseline (N = 2775)

Time-constant variables		N (%) M (SD)
Sex	Female	1559 (56.2)
	Male	1216 (43.8)
Education	None	195 (7.0)
	Primary	2136 (77.0)
	>Primary	442 (15.9)
Residence status	Rural	1422 (51.2)
	Urban	1353 (48.8)
Independent variables		
Age in years (45-106)		65.2 (10.9)
Marital status	Married/cohabiting	1718 (62.7)
	Widowed/single/divorced/separated	1021 (37.3)
Work status	Working	1397 (51.5)
	Not working	1314 (48.5)
Living arrangement	Living with others	2548 (92.0)
	Living alone	223 (8.0)
Subjective economic status (0-10)		6.7 (1.8)
Multimorbidity		416 (15.0)
Functional limitations (0-4)		0.05 (0.4)
Current smoking		330 (11.9)
Current alcohol use		348 (12.6)
Meal skipping (0-6)		0.1 (0.5)
Physical activity (1-5)		2.5 (1.7)
Wears dentures		557 (20.1)
Poor self-rated mental health (0-10)		2.1 (1.9)
Depressive symptoms (0-27)		5.7 (3.0)
Loneliness (1-4)		1.2 (0.5)
Quality of life/happiness (0-10)		7.9 (1.5)
Religious involvement (0-12)		6.5 (3.4)
Social participation		1046 (37.7)

Table 2. Determinants of weight loss. Results of conditional fixed effects logistic regression (waves 1, 2, 3 and wave 4), HART, 2015-2022, 45 years and older

	COR (95% CI)	р	AOR (95% CI) <sup>1</sup>	р
Sociodemographic factors				
Age	1.08 (1.05 to 1.11)	< 0.001	1.07 (1.03 to 1.10)	< 0.001
Marital status				
Married/cohabiting	(Reference)		(Reference)	
Widowed/single/divorced/separated	0.96 (0.65 to 1.42)	0.829	0.84 (0.55 to 1.28)	0.422
Work status				
Working	(Reference)		(Reference)	
Not working	1.63 (1.25 to 2.12)	< 0.001	1.47 (1.10 to 1.96)	0.009
Living arrangement				
Living with others	(Reference)		(Reference)	
Living alone	1.16 (0.86 to 1.58)	0.328	1.27 (0.91 to 1.76)	0.158
Subjective economic status	0.94 (0.88 to 0.98)	0.020	0.94 (0.89 to 0.99)	0.035
Health factors				
Hospitalisation (yes/no)	1.85 (1.45 to 2.36)	< 0.001	1.58 (1.22 to 2.04)	< 0.001
Multimorbidity (yes/no)	1.74 (1.27 to 2.40)	< 0.001	1.42 (1.01 to 2.00)	0.043
Functional disability (0-4)	1.62 (1.39 to 1.89)	< 0.001	1.52 (1.28 to 1.81)	< 0.001
Currently not smoking (yes/no)	0.84 (0.54 to 1.32)	0.445	0.65 (0.38 to 1.09)	0.100
Currently not drinking alcohol (yes/no)	1.16 (0.77 to 1.74)	0.488	1.14 (0.71 to 1.83)	0.579
Meal skipping (0-6)	1.15 (1.02 to 1.29)	0.026	1.05 (0.93 to 1.20)	0.416
Exercise frequency (1-5)	1.05 (0.98 to 1.11)	0.148	1.06 (0.99 to 1.13)	0.083
Wears dentures (yes/no)	1.70 (1.14 to 2.52)	< 0.001	1.66 (1.07 to 2.58)	0.025
Psychosocial factors				
Poorer self-rated mental health status (0-10)	0.97 (0.91 to 1.02)	0.227	0.97 (0.90 to 1.04)	0.345
Depressive symptoms (0-27)	1.05 (1.02 to 1.09)	0.002	1.06 (1.02 to 1.10)	< 0.001
Loneliness (1-4)	1.12 (0.96 to 1.31)	0.157	0.90 (0.74 to 1.09)	0.293
Quality of Life/Happiness (0-10)	0.97 (0.91 to 1.03)	0.370	1.02 (0.94 to 1.10)	0.676
Religious involvement (0-12)	1.01 (0.98 to 1.05)	0.449	0.99 (0.96 to 1.03)	0.686
Social participation (yes/no)	1.31 (1.02 to 1.68)	0.021	1.32 (1.01 to 1.71)	0.041
Observations	1876			
Individuals	559			
Pseudo R <sup>2</sup>	0.06			

COR = Crude Odds Ratio; AOR=Adjusted Odds Ratio; 95% Confidence Interval = CI; <sup>1</sup>Adjusted for all variables in the table, and study wave

Regarding health factors, consistent with some previous investigations (9-11), this study found that an increase hospitalisation, an increase in multimorbidity and functional disability increased the odds of weight loss. Weight loss may be caused by a flare-up of chronic illness and an increase in comorbidities (11). It is possible that patients with functional disability need help with eating or meal preparation, which may not always be readily available, leading to reduced food intake and weight loss (9). Furthermore, an increase in wearing dentures increased weight loss in this study. Wearing dentures may be related to oral problems with chewing or swallowing, reducing food intake and thereby leading to weight loss (9, 12). In contrast to changes in denture mastication, involuntary weight loss may result from deliberate alterations in food intake and avoidance (25). A previous study in Germany (3) showed that life satisfaction was negatively associated with weight loss, while our measure of quality of life/happiness did not show a significant association with weight loss. A possible explanation for the non-significance between quality of life/happiness and weight loss may be related to the fact that life satisfaction or quality of life was only assessed with one item rather than a scale.

In terms of psychosocial factors, consistent with previous research (3, 14, 16), this study showed a positive association between depressive symptoms and weight loss. This may be explained by depressive symptoms being often associated with

loss of appetite or low motivation to prepare food (26). It is also possible that depressive symptoms and weight loss have a bidirectional relationship. In our study, among men, transitioning to living alone was associated with an increase in weight loss, which is consistent with a study in South Korea, living alone was linked to 5 kg or more of weight loss among older men without any changes in marital status (16). Although previous research showed that bereavement was associated with weight loss (15), we did not find that transitioning to widowhood was associated with increased weight loss. It's likely that the weight loss in our study brought on by spousal loss was simply temporary and would eventually return (16). The finding that transitioning to living alone was associated with weight loss in men but not women may point to a lower social support network among men compared to women (27). Unlike some previous research (3, 13) that found an association between loneliness and weight loss, we did not find significant associations between men and women. Interestingly, however, increased social participation was associated with increased weight loss in men. In a study of recipients of home care in 11 sites in Europe, reduced social activity was associated with weight loss (9). The association between increased social participation and weight loss in men in this study may be because social participation can influence eating habits, physical activity, and overall well-being, which can contribute to weight management.



Table 3. Determinants of weight loss by sex. Results of conditional fixed effects logistic regression (waves 1, 2, 3 and wave 4), HART, 2015-2022, 45 years and older

Independent variables	Male	Male		Female	
	<b>AOR</b> (95% CI) <sup>1</sup>	р	<b>AOR</b> (95% CI) <sup>1</sup>	р	
Sociodemographic factors					
Age	1.09 (1.02 to 1.15)	0.007	1.06 (1.02 to 1.11)	0.007	
Marital status					
Single/divorced/separated/married	(Reference)		(Reference)		
Widowed	1.48 (0.64 to 3.41)	0.354	0.84 (0.51 to 1.39)	0.494	
Work status					
Working	(Reference)		(Reference)		
Not working	1.51 (1.06 to 2.08)	0.003	1.35 (0.92 to 1.98)	0.126	
Living arrangement					
Living with others	(Reference)		(Reference)		
Living alone	2.12 (1.23 to 3.66)	0.007	0.97 (0.62 to 1.51)	0.891	
Subjective economic status	0.92 (0.86 to 0.97)	0.009	0.97 (0.91 to 1.04)	0.394	
Health factors					
Hospitalisation	1.81 (1.18 to 2.76)	0.006	1.49 (1.07 to 2.08)	0.019	
Multimorbidity	2.33 (1.24 to 4.38)	0.008	1.10 (0.72 to 1.68)	0.671	
Functional disability	1.92 (1.35 to 2.73)	< 0.001	1.54 (1.26 to 1.88)	< 0.001	
Currently not smoking	0.73 (0.41 to 1.31)	0.294	0.80 (0.20 to 3.27)	0.760	
Currently not drinking alcohol	1.12 (0.63 to 2.02)	0.697	1.26 (0.54 to 2.95)	0.588	
Meal skipping	1.15 (0.93 to 1.41)	0.200	1.05 (0.89 to 1.24)	0.570	
Exercise frequency	1.06 (0.95 to 1.18)	0.303	1.07 (0.99 to 1.17)	0.098	
Wears dentures	1.37 (0.62 to 3.04)	0.438	1.91 (1.12 to 3.25)	0.018	
Psychosocial factors					
Poorer self-rated mental health status	0.95 (0.89 to 1.08)	0.431	0.97 (0.89 to 1.05)	0.456	
Depressive symptoms	0.98 (0.92 to 1.04)	0.404	1.09 (1.04 to 1.15)	< 0.001	
Loneliness	1.01 (0.70 to 1.45)	0.947	0.87 (0.68 to 1.11)	0.253	
Quality of Life/Happiness	1.00 (0.88 to 1.14)	0.986	1.03 (0.93 to 1.14)	0.530	
Religious involvement	0.95 (0.89 to 1.00)	0.056	1.03 (0.98 to 1.07)	0.225	
Social participation	1.76 (1.11 to 2.77)	0.016	1.18 (0.84 to 1.65)	0.344	
Observations	697		1154		
Individuals	211		342		
Pseudo R <sup>2</sup>	0.05		0.07		

AOR = Adjusted Odds Ratio; 95% Confidence Interval=CI; Adjusted for all variables in the table, and study wave

#### Conclusions

We found that the prevalence of weight loss was 5.2%, and increasing age, transitioning to not working, decreasing economic status, transitioning to living alone, an increase in hospitalistion, an increase in multimorbidity, increasing functional disability, increase in wearing dentures, increasing depressive symptoms and increasing social participation was significantly associated with weight loss. The early detection and manangement of these identified associated factors (especially actionable recommendations such as routine screening for depression/denture fit) in older adults with weight loss may be important for preventing weight loss, especially among underweight older adults in Thailand.

#### **Study limitation**

A nationwide, longitudinal community-dwelling population is included in the study, and HART employed validated metrics, such as the CES-D, from the Korean Longitudinal Study of Aging (KLoSA) and the Health and Retirement Study (HRS). Using panel FE

regression models, we reduced the problem of unobserved heterogeneity. Study measures were assessed by self-report, including weight loss, which may have biased responses. Although the study adjusted for a wide range of covariates, we cannot rule out reverse causality. The statistical power for some of the sub-group analyses may be limited. Some variables, such as cognitive impairment, that might influence weight loss (28) were not assessed in this study and should be incorporated in future studies. A sample selection bias cannot be ruled out. However, the loss to the follow-up sample did not significantly differ regarding key variables, including weight loss, with the sample that stayed in the study. Further study limitations include that the intentionality of weight loss, and key nutritional variables (protein intake, caloric intake, swallowing difficulties beyond dentures), objective health markers (inflammatory markers like CRP, nutritional biomarkers like albumin) and devicemeasured physical activity were not assessed, and should be included in future studies.

#### **Conflict of interests**

The authors declare that they have no competing interests.

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#### **Authors' contributions**

All authors fulfill the criteria for authorship. SP, KP, AH, and RG conceived and designed the research, performed statistical analysis, drafted the manuscript, and made critical revisions of the manuscript for key intellectual content. All authors read and approved the final version of the manuscript and have agreed to the authorship and order of authorship for this manuscript

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