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Original Research

Unintentional weight loss as a predictor of all-cause and cardiovascular disease mortality in older Korean men

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Abstract

Background and objective: Little is known regarding the prognostic role of unintentional weight loss (UWL) in mortality risk among older Korean men. This study examined the associations of UWL and unhealthy behaviors with all-cause and cardiovascular disease (CVD) mortality in Korean men aged 60 years and older.

Material and Methods: Data (n = 2,309) obtained from the Korean longitudinal study of aging were analyzed. Exposures were UWL, smoking, alcohol abuse, underweight/obesity, and physical inactivity. Primary outcomes were all-cause mortality and CVD mortality. Covariates included parameters of sociodemographics and health conditions.

Results: Individuals with three or more risk factors had significantly higher risks of all-cause mortality (hazard ratio [HR] = 1.536, 95% confidence interval [CI] = 1.084∼2.175, *P* = 0.016) and CVD mortality (HR = 2.925, 95% CI = 1.386∼6.174, *P* = 0.005) even after adjustments for parameters of sociodemographics, health conditions, and UWL compared to individuals with zero risk factors (HR = 1). Additionally, individuals with UWL had a significantly higher risk of all-cause mortality (HR = 1.307, 95% CI = 1.052∼1.623, *P* = 0.016) even after adjustments for the covariates and lifestyle risk factors compared to individuals with normal weight (HR = 1).

Conclusion: The current findings show that exposure to three or more lifestyle risk factors is an independent predictor of all-cause mortality and CVD mortality, and UWL was a predictor of all-cause mortality in older Korean men.

Keywords

Premature death; Behavioral risk factors; Unintentional weight loss; Koreans

1. Introduction

A large proportion of global illness and death has been attributed to behavioral risk factors such as smoking, heavy alcohol consumption, physical inactivity, sitting time, overweight/obesity, and unhealthy diet (https://www.who.int/gho/ncd/risk_factors/en/). In South Korea, smoking, heavy alcohol consumption, overweight/obesity, and physical inactivity are behavioral risk factors associated with morbidity [1] and mortality [2]. For example, several of the risk factors were significantly associated with an increased risk of premature death from all and specific causes in a population-based cohort study involving 59,941 Korean men and women aged 30-84 years [3] and in a Seoul male cohort study involving 12,538 men aged 40 to 59 years [4].

Findings from recent studies showed that unintentional weight loss (UWL) might be a novel risk factor of cardiovascular diseases (CVDs) such as myocardial infarction [5] and heart failure [6]. In a meta-analysis involving a total of 178,644 participants from 15 previous cohort studies, UWL was significantly associated with all-cause mortality,

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and the association was stronger in older adults [7]. Although the exact pathology of UWL in relation to morbidity and mortality is unclear, the most common etiologies are malignancy [8], nonmalignant gastrointestinal disease [9], mental health [10], and medication use and polypharmacy [11]. Social factors such as poverty, alcoholism, isolation, financial constraints, and physical barriers to obtaining food also can contribute to UWL [12].

From a public health perspective, UWL is an important issue that should be carefully monitored, especially in geriatric populations. Furthermore, the impact of lifestyle risk factors on mortality might be modulated by UWL. To the best of our knowledge, no previous study has examined the prognostic role of UWL in mortality among older Korean men. This study aimed to investigate whether or not UWL has an influence on the association between lifestyle risk factors and all-cause and CVD mortality in older Korean men.

2. Materials and methods

2.1 Study design and participants

Men aged 60 years and older (n = 2,309) for whom all information regarding demographics, socioeconomic status, health behaviors, health conditions, and causes of death was available were retrospectively selected from male participants (n = 4,345) in the Korean longitudinal study of aging (KLoSA), a nationwide survey study conducted in the Republic of Korea that launched in 2006. In brief, the KLoSA survey was conducted using multi-stage, stratified sampling based on geographical area and housing type across the nation. A detailed description of the KLoSA is provided elsewhere [13, 14].

The KLoSA protocol was reviewed and approved by the Institutional Review Board of Statistics Korea (approval number: 336052). All of the participants provided written informed consent. Descriptive statistics of study participants are provided in Table 1. The mean age and body mass index (BMI) of study participants at study entry were 69.4 ± 6.7 years and 22.8 ± 3.0 kg/m^2, respectively. Education, employment, religion, type of housing, impaired cognition, depressive symptoms, impaired activities of daily living (ADL), fall experience, hospitalization, comorbidity, and medications were included as covariates. The prevalence of individual risk factors was 58.2% for smoking, 16.2% for at-risk alcohol consumption, 66.5% for physical inactivity, and 23.5% for underweight/obesity, in conjunction with a 12% prevalence for UWL. Data from the KLoSA are accessible via the national public database (https://www.kli.re.kr/kli/index.do).

TABLE 1. Description of study participants at baseline (n = 2,309).

Measured parameters	
Age (years)	69.4 ± 6.7
BMI (kg/m^2)	22.8 ± 3.0
Household income (10,000 won/month)	120 ± 182
Education, n (%)	
Elementary or less	1,109 (48.0)
Middle or high school	924 (40.0)
College or higher	276 (12.0)
Employment status, n (%)	
Yes	823 (35.6)
No	1,486 (64.4)
Religion, n (%)	
No religion	1,282 (55.5)
Protestant	377 (16.3)
Catholic	168 (7.3)
Buddhist	461 (20.0)
Others	21 (0.9)
Type of housing, n (%)	
General house	1,560 (67.6)
Apartment	749 (32.4)
Impaired cognition, n (%)	619 (26.8)
Depressive symptoms, n (%)	723 (31.3)
Impaired ADL, n (%)	130 (5.6)
Falls, n (%)	64 (2.8)
Hospitalization, n (%)	302 (13.1)
Unintentional weight loss, n (%)	290 (12.1)
Comorbidity, n (%)	
0	1,038 (45.0)
1	786 (34.0)
≥ 2	485 (21.0)
Medications, n (%)	
0	1,215 (52.6)
1	714 (30.9)
≥ 2	380 (16.5)
Lifestyle risk factors	
Past/current smoking, n (%)	1,344 (58.2)
At-risk alcohol consumption, n (%)	375 (16.2)
Physical inactivity, n (%)	1,535 (66.5)
Underweight/obesity, n (%)	543 (23.5)

ADL, activities of daily living; BMI, body mass index.

2.2 Measured variables

2.2.1. Exposures

UWL and lifestyle risk factors were included as primary exposures. Lifestyle risk factors were smoking (current or past smoker) [15], heavy alcohol use (≥ 5 drinks per week) [16], underweight (< 18.5) or obesity (body mass index ≥ 25), and physical inactivity (fewer than 2 times per week). A binary score (yes = 1 or no = 0) was given for each risk factor. A possible risk score obtained by summing each of the four risk factors ranged from 0 (heathiest) to 4 points (least healthy). The sum of the four risk factors was classified as low risk (0 points), moderate risk (1-2 points), or high risk (3-4 points). UWL was defined as a loss of 5 kg or more in the past year [17].

2.2.2 Primary outcomes

The primary outcomes were all-cause and CVD mortality. Mortality data for this study were derived from the KLoSA from 2006, 2008, 2010, 2012, 2014, and 2016. Mortality outcomes in the acquired information were cross-checked

TABLE 2. Descriptive statistics of study participants according to severity of lifestyle risk factors.

Variables	Classification of lifestyle risk factors			*P* for trend
	Low risk (10.1%)	Moderate risk (74.7%)	High risk (15.2%)	
Age (years)	68.7 ± 6.5	69.6 ± 6.6	69.2 ± 6.9	0.164
BMI (kg/m^2)	22.6 ± 1.6	22.8 ± 2.7	23.1 ± 4.6	0.072
Income (10,000 won/month)	140 ± 215	121 ± 189	101 ± 107	0.045
Education, n (%)				< 0.001
Elementary or less	67 (28.8)	838 (48.6)	204 (58.0)	
Middle or high school	104 (44.6)	692 (40.1)	128 (36.4)	
College or greater	62 (26.6)	194 (11.3)	20 (5.7)	
Occupation, n (%)				< 0.001
Yes	71 (30.5)	597 (34.6)	155 (44.0)	
No	162 (69.5)	1,127 (65.4)	197 (56.0)	
Religion, n (%)				0.001
No religion	93 (39.9)	962 (55.8)	227 (64.5)	
Protestant	62 (26.6)	282 (16.4)	33 (9.4)	
Catholic	20 (8.6)	126 (7.3)	22 (6.3)	
Buddhist	57 (24.5)	333 (19.3)	68 (19.3)	
Other	1 (0.4)	21 (1.2)	2 (0.6)	
Type of housing, n (%)				< 0.001
General house	119 (51.1)	1,175 (68.2)	266 (75.6)	
Apartment	114 (48.9)	549 (31.8)	86 (24.4)	
Impaired cognition, n (%)	45 (19.3)	467 (27.1)	107 (30.4)	0.001
Depressive symptoms, n (%)	60 (25.8)	542 (31.4)	121 (34.4)	0.033
Impaired ADL, n (%)	11 (4.7)	98 (5.7)	21 (6.0)	0.552
Falls, n (%)	6 (2.6)	47 (2.7)	11 (3.1)	0.667
Hospitalization, n (%)	23 (9.9)	236 (13.7)	43 (12.1)	0.585
UWL, n (%)	32 (11.4)	211 (75.4)	37 (13.2)	0.230
Comorbidity, n (%)				0.728
0	107 (45.9)	768 (44.5)	163 (46.3)	
1	77 (33.0)	590 (34.2)	119 (33.8)	
> 2	49 (21.0)	366 (21.2)	70 (19.9)	
Medications, n (%)				0.406
0	121 (51.9)	896 (52.0)	198 (56.3)	
1	76 (32.6)	539 (31.3)	99 (28.1)	
> 2	36 (15.5)	289 (16.8)	55 (15.6)	

Lifestyle risk factors include smoking, heavy alcohol consumption, physical inactivity, and underweight or obesity. A binary score (yes = 1 or no = 0) was given for each risk factor. A possible risk score obtained by summing across the four risk factors ranged from 0 (heathiest) to 4 points (least healthy). The sum of risk scores was classified as low risk (0 points), moderate risk (1-2 points), or high risk (3-4 points). ADL, activities of daily living; BMI, body mass index; UWL, unintentional weight loss.

against the death records from the national statistical office in Korea.

2.2.3 Covariates

Covariates were age, household income, educational level, employment status, religion, type of housing, falls, comorbidity, and medications. Cognitive function and depressive symptoms were assessed with the Mini-mental Status Examination (K-MMSE) and Center for Epidemiological Studies of Depression 10 (CES-D 10), respectively [18]. Activities of Daily Living (ADL) were used to assess impairment [18].

2.3 Statistical analyses

Physical characteristics of the study participants at baseline are presented as mean ± standard deviation (SD) or percentage. Pearson's χ^2 test and analysis of variance were used to compare categorical and continuous variables, respectively. Absence of multicollinearity among the 4 risk factors was assessed by variance inflation factors (VIFs). Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality according to classification of lifestyle risk factors (i.e., low risk, moderate risk, and high risk) and stratified by weight status (i.e., normal weight vs. UWL). Additionally, the Kaplan-Meier procedure with log-rank test was used to estimate mortality functions. Survival time was measured as the time from the baseline survey to death or the censor point (November 30, 2016). Alpha was set at 0.05. All statistical analyses were performed using the SPSS-PC statistical software (version 27.0, SPSS Inc., Chicago, IL, USA).

3. Results

The final sample for analysis comprised 2,309 participants with an average follow-up of 8.9 ± 2.6 years, for a total of 20,530 person-years. During the follow-up period, there were a total of 692 cases of death from all causes, of which 179 cases were due to CVD.

Table 2 presents descriptive statistics of study participants according to classification of lifestyle risk factors. With respect to sociodemographics, significant linear trends in household income (P = 0.045), education (P < 0.001), occupation (P < 0.001), religion (P = 0.001), and type of housing (P < 0.001) were found according to classification of lifestyle risk factors (from low to high risk). The linear trends were interpreted as follows: individuals with moderate or high risk were economically less stable and less educated and were more likely to have no religion and be a resident of a general house compared to individuals with low risk. With respect to health conditions, significant linear trends in impaired cognition (P = 0.001) and depressive symptoms (P = 0.033) were found according to classification of lifestyle risk factors (from low to high risk); individuals with moderate or high risk had higher prevalence of impaired cognition and depression compared to individuals with low risk.

Table 3 presents descriptive statistics of study participants by weight category. With respect to sociodemographics, individuals with UWL were older (P < 0.001), lighter (P < 0.001), less educated (P = 0.020), more likely to be unemployed (P < 0.001), and more often residents of a general house compared to individuals with normal weight. With respect to health conditions, individuals with UWL had higher prevalence of impaired cognition, depression, impaired ADL, and hospitalization, in conjunction with higher comorbidities and medications, compared to individuals with normal weight. By contrast, no such group differences were found in prevalence of individual risk factors.

Table 4 presents all-cause and CVD mortality according to classification of lifestyle risk factors and weight category. With respect to lifestyle risk factors, the crude HR for all-cause mortality was 1.442 (95% CI, 1.082∼1.923, P = 0.013) for moderate risk and 1.854 (95% CI, 1.341∼2.563, P < 0.001) for high risk. The HR for high risk remained statistically significant (HR = 1.536, 95% CI, 1.084∼2.175, P = 0.016) even after adjustments for all the covariates. Likewise, the crude HR for CVD mortality was 2.055 (95% CI, 1.046∼4.039, P = 0.037) for moderate risk and 3.290 (95% CI, 1.599∼6.770, P = 0.001) for high risk. The adjusted HR for high risk remained statistically significant (HR = 2.925, 95% CI, 1.386∼6.174, P = 0.005) after adjustment.

With respect to weight category, the crude HR for all-cause mortality was 1.665 (95% CI, 1.364∼2.032, P < 0.001) for UWL compared to normal weight. The HR of UWL remained statistically significant even after adjustments for all the covariates. The crude HR for CVD mortality was 1.790 (95% CI, 1.221∼2.624, P = 0.001) for UWL compared to normal weight. However, the HR of UWL was no longer significant when adjusted for all the covariates.

Finally, the Kaplan-Meier mortality functions, as illustrated in Fig. 1, showed dose-response associations between classification of risk factors and all-cause and CVD mortality. Cumulative hazard ratios of all-cause and CVD mortality were incremental according to classification of risk factors (from low to high risk). As shown in Fig. 2, UWL was associated with higher cumulative hazard ratios of all-cause and CVD mortality compared to normal weight.

TABLE 3. Descriptive statistics of study participants by weight category.

Variables	Normal weight	UWL	*P* value
Age (years)	69.2 ± 6.6	70.7 ± 6.9	< 0.001
BMI (kg/m^2)	23.0 ± 3.0	21.7 ± 2.7	< 0.001
Income (10,000 won/month)	122 ± 189	102 ± 129	0.100
Education, n (%)			0.020
Elementary or less	951 (46.9)	158 (56.4)	
Middle or high school	834 (41.4)	90 (32.1)	
College or greater	244 (12.0)	32 (11.4)	
Occupation, n (%)			< 0.001
Yes	753 (37.1)	70 (25.0)	
No	1,276 (62.9)	210 (75.0)	
Religion, n (%)			0.929
No religion	1,120 (55.2)	162 (57.9)	
Protestant	344 (17.0)	33 (11.8)	
Catholic	142 (7.0)	26 (9.3)	
Buddhist	400 (19.7)	58 (20.7)	
Other	23 (1.1)	1 (0.4)	
Type of housing, n (%)			0.041
General house	1,356 (66.8)	204 (72.9)	
Apartment	673 (33.2)	76 (27.1)	
Impaired cognition, n (%)	512 (25.2)	107 (38.2)	< 0.001
Depressive symptoms, n (%)	587 (28.9)	136 (48.6)	< 0.001
Impaired ADL, n (%)	91 (4.5)	39 (13.9)	< 0.001
Falls, n (%)	52 (2.6)	12 (4.3)	0.123
Hospitalization, n (%)	236 (11.6)	66 (36.6)	< 0.001
Comorbidity, n (%)			< 0.001
0	941 (46.4)	97 (34.6)	
1	681 (33.6)	105 (37.5)	
> 2	407 (20.1)	78 (27.9)	
Medications, n (%)			< 0.001
0	1,097 (54.1)	118 (42.1)	
1	616 (30.4)	98 (35.0)	
> 2	316 (15.6)	64 (22.9)	
Classification of risk scores, n (%)			
Low risk	201 (9.9)	32 (11.4)	0.230
Moderate risk	1,513 (74.6)	211 (75.4)	
High risk	315 (15.5)	37 (13.2)	

A binary score (yes = 1 or no = 0) was given for each risk factor (i.e., smoking, heavy drinking, physical inactivity, and underweight/obesity). A possible risk score obtained by summing across the four risk factors ranged from 0 (heathiest) to 4 points (least healthy). The sum of risk scores was classified as low risk (0 points), moderate risk (1-2 points), or high risk (3-4 points). ADL, activities of daily living; BMI, body mass index; UWL, unintentional weight loss.

TABLE 4. All-cause and cardiovascular disease mortality according to lifestyle risk factors and weight category.

	Stratification of lifestyle risk factors					Weight category		
	Low risk	Moderate risk	*P* value	High risk	*P* value	Normal weight	UWL	*P* value
All-cause mortality								
Death (n, %)	51 (21.9)	511 (29.6)		130 (36.9)		576 (28.4)	116 (41.4)	
Crude HR (95% CI)	1	1.442 (1.082∼1.923)	0.013	1.854 (1.341∼2.563)	< 0.001	1	1.665 (1.364∼2.032)	< 0.001
[a] Adjusted HR (95% CI)	1	1.121 (0.828∼1.517)	0.461	1.536 (1.084∼2.175)	0.016	1	1.307 (1.052∼1.623)	0.016
CVD mortality								
Death (n, %)	9 (3.9)	129 (7.5)	41 (11.6)			147 (7.2)	32 (11.4)	
Crude HR (95% CI)	1	2.055 (1.046∼4.039)	0.037	3.290 (1.599∼6.770)	0.001	1	1.790 (1.221∼2.624)	0.003
[b] Adjusted HR (95% CI)	1	1.496 (0.752∼2.977)	0.251	2.925 (1.386∼6.174)	0.005	1	1.284 (0.839∼1.965)	0.250

[a] Adjusted HR for age, household income, education, occupation, religion, type of housing, UWL, cognition, depressive symptoms, comorbidity, medications, ADL condition, fall experience, and hospitalization.

[b] Adjusted HR for age, household income, education, occupation, religion, type of housing, lifestyle risk factors, cognition, depressive symptoms, comorbidity, medications, ADL condition, fall experience, and hospitalization.

ADL, activities of daily living; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; UWL, unintentional weight loss.

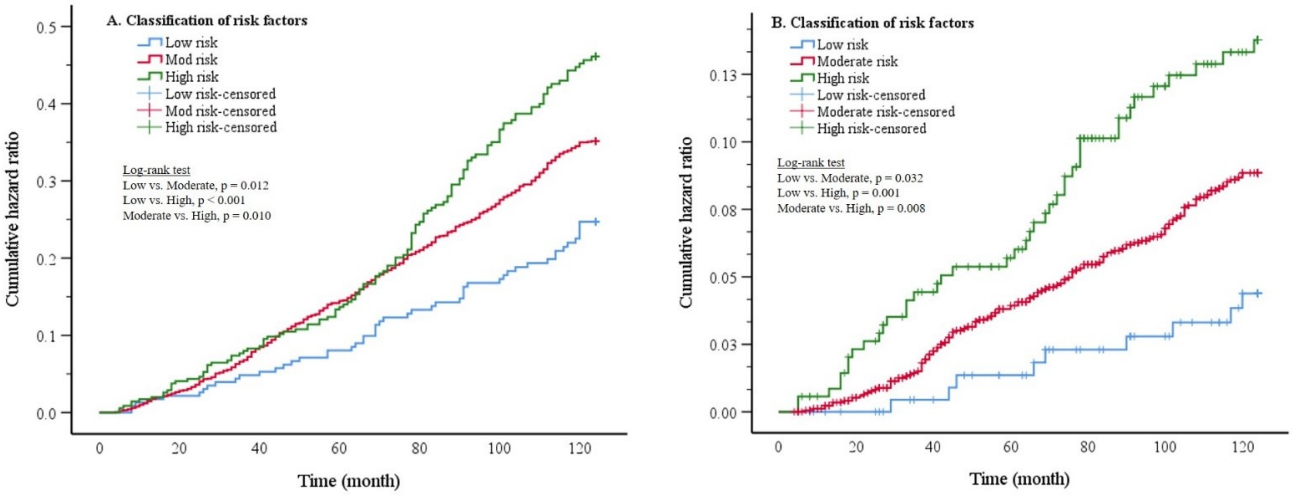

FIG. 1. The Kaplan-Meier survival curves for all-cause mortality (A) and cardiovascular disease mortality (B) according to classification of risk factors.

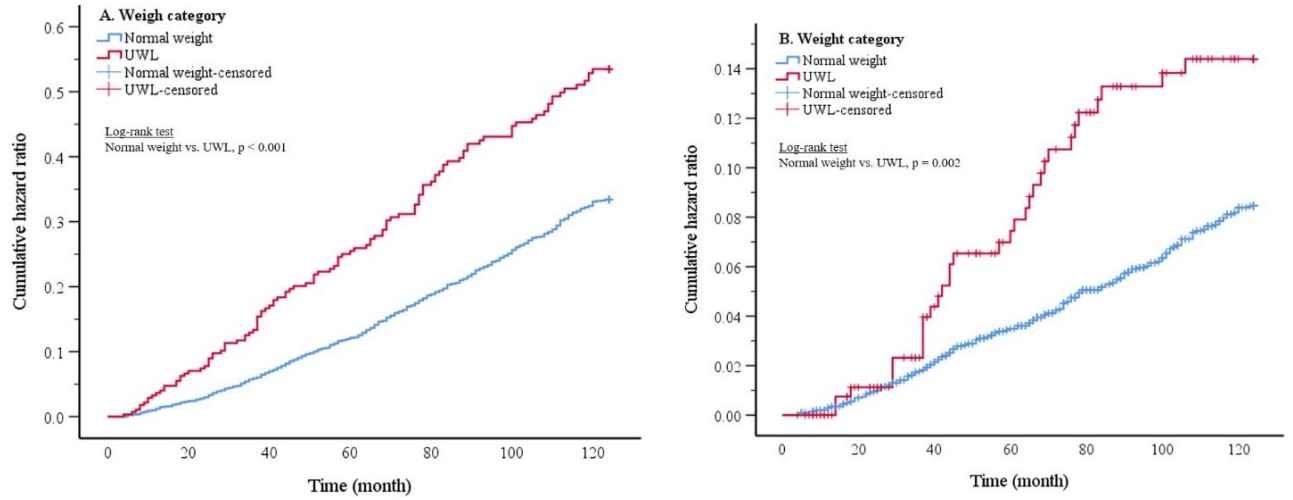

FIG. 2. The Kaplan-Meier survival curves for all-cause mortality (A) and cardiovascular disease mortality (B) by weight category. UWL, unintentional weight loss.

4. Discussion

This study examined the associations of lifestyle risk factors with all-cause and CVD mortality as well as the association between UWL and all-cause and CVD mortality in older Korean men. The current findings showed that exposure to

three or more lifestyle risk factors was a significant predictor of all-cause and CVD mortality, independent of UWL. Regardless of lifestyle risk factors, UWL was an independent predictor of all-cause mortality but not of CVD mortality, suggesting that weight status plays an important role in predicting mortality risk in older adults.

The current findings support and extend those of previous studies reporting the significant associations between behavioral risk factors and death risk from all and specific causes in Western populations, including the Nord-Trøndelag Health Study (HUNT) [19], a longitudinal study in Europe (HALE) study [20], and a nurses' health and health professionals follow-up study [21].

The associations between lifestyle risk factors and mortality have been reported in previous studies involving Korean populations. In the Severance Health Promotion Center visitors-based cohort study consisting of 59,941 Korean men and women aged 30-84 years, for example, Yun *et al.* [3] found that in men, the hazard ratio of having four risk factors (i.e., smoking, heavy alcohol intake, overweight or obesity, physical inactivity, and unhealthy diet) was 2.00 (95% CI, 1.58-2.52) for all-cause mortality, 2.04 (95% CI, 1.57-2.87) for cancer mortality, and 1.92 (95% CI, 1.39-2.64) for non-cancer mortality compared to having one or no risk factors (HR = 1). In women, the HR of four risk factors was 2.00 (95% CI, 0.93-4.29) for cancer mortality, 2.17 (95% CI, 1.01-4.67) for non-cancer mortality, and 2.09 (1.22-3.59) for all-cause mortality compared to having one or no risk factors (HR = 1). In the Seoul male cohort study involving 12,538 middle-aged and older men, Kim *et al.* [4] showed that the adjusted population attributable risk of the three combined risk factors (i.e., smoking, high blood pressure, and high fasting glucose) was 35.2% (95% CI, 21.7-47.4) for all-cause mortality and 52.8% (95% CI, 22.0-74.0) for CVD mortality.

Some explanations can be given for the impact of lifestyle risk factors on all-cause and CVD death risk observed in the current study. First, tobacco smoking is a well-established and leading cause of premature death worldwide [22]. Second, heavy alcohol consumption is associated with a higher risk of all-cause and cancer mortality [23]. Third, the findings from previous studies showed that unhealthy body weight was independently associated with increased risk of CVD and cancer mortality [24]. Lastly, physical inactivity is associated with higher risk of all-cause and cause-specific mortality [25].

In addition to lifestyle risk factors, we are the first to report that UWL might be an independent predictor of all-cause mortality in older Korean adults. In accordance with the current findings, UWL is known to be a novel risk factor for health conditions, such as morbidity and mortality, in elderly persons [26, 27]. By conducting a meta-analysis of 15 studies involving a total of 178,644 participants, for example, De Stefani *et al.* [7] showed that the adjusted risk ratio of UWL was 1.38 (95% CI, 1.23-1.53) for all-cause mortality. Another meta-analysis involving men and women aged 60 years and older showed that UWL was associated with increased all-cause mortality in older women (HR, 1.68; 95% CI, 1.20-2.35; $P < 0.001$) but not in older men [2].

As previously stated, the most common etiologies of morbidity and mortality from UWL in older adults include malignancy, nonmalignant gastrointestinal disease, and mental health conditions [28, 29]. For example, cancer cachexia is an excessive production of proinflammatory cytokines and other factors, which suppress the appetite, promote muscle and fat breakdown, and lead to a negative energy balance [30]. Consequently, UWL may reflect an advanced pathology of age-related diseases and other health conditions which increase all-cause mortality risk. In addition, there are a number of contributing factors to UWL in older adults, including medication use, polypharmacy, poor nutrition, social factors [31]. Together, the predictive role of UWL for all-cause mortality observed in the current study suggests that weight loss with an is an important health issue that should not be overlooked in older adults.

Unlike with all-cause mortality, however, we found that UWL was not an independent predictor of CVD mortality. In accordance with the current findings, previous studies found significant associations between UWL and mortality from all causes [32] but not between UWL and morbidity or mortality from CVD [7, 33]. Contrasting findings regarding the association between UWL and CVD mortality might stem from presence or absence of existing health conditions [7], sex or ethnicity differences [2], and others [29, 31]. The exact etiology of UWL in relation to morbidity and mortality of CVD remains to be determined in older adults.

The present study has some limitations. First, the cross-sectional nature of this study is a limitation in drawing conclusions about causation. Therefore, the current findings should be confirmed via a longitudinal study to establish causal relationships between unhealthy behaviors or UWL and premature deaths from all causes or CVD or non-CVD in Korean adults. Second, the current study did not include other significant risk factors, such as poor nutrition, prolonged sitting, and sleeping, which can affect existing health conditions including UWL. In particular, poor quality of diet (e.g., high-carbohydrate or high-fat) can contribute to an increased risk of mortality by triggering oxidative stress and subsequent inflammatory responses [34]. Considering the role(s) of those dietary factors will be necessary for better understanding the complexity of the relationships between weight status and mortality [35].

Despite the limitations, the findings of the current study support the independent role of UWL in all-cause mortality in older Korean men. Furthermore, these findings extend the existing literature regarding the prognostic role of traditional risk factors for mortality in Asian countries.

5. Conclusions

In this prospective cohort study, we examined the relationships of lifestyle risk factors and UWL with mortality in older Korean men and found that all-cause mortality was significantly associated with lifestyle risk factors as well as with UWL, while CVD mortality was associated with lifestyle risk factors only. Together, the current findings suggest the need for urgency in development of interventions targeting both

lifestyle risk factors and UWL in older Korean adults.

Author contributions

JK and HK contributed to the conception and design, data analyses, data interpretation, and writing of the manuscript. HH, MK, JK and HK contributed to statistical analyses, data interpretation, and writing of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All analyses were based on previous published studies. Therefore, no ethical approval and patient consent are required.

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Conflict of interest

The authors declare no conflict of interest.

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