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Association Between Body Weight Changes and Subsequent Development of Out-of-Hospital Cardiac Arrest: A Population-Based Nested Case-Control Study

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ABSTRACT

Background: Body weight is a modifiable demographic factor. Although the association of body mass index (BMI) categories with sudden cardiac death was reported, dynamic changes of BMI and the risk of cardiac arrest remain unknown. This study aimed to evaluate the association between the out-of-hospital cardiac arrest (OHCA) occurrence within a year and the percent changes of BMI preceding the OHCA.
Methods: This population-based nested case-control study used the National Health Insurance Service Data of Korea. In all, 24,465 patients with non-traumatic OHCA between 2010 and 2018, who underwent national health check-up twice (one within a year and the other within 2–4 years before OHCA) and 32,434 controls without OHCA, were matched for age and sex. The association between the risk of OHCA and BMI percent change stratified by sex was investigated.
Results: All the BMI percent changes of ≥ 5% significantly increased the OHCA occurrence with a reverse J-shaped association. Compared to individuals with a stable weight, those with severe (> 15%) BMI decrease had the highest odds ratio (OR) of 4.29 (95% confidence intervals [CIs], 3.72–4.95) for OHCA occurrence followed by those with moderate (10–15%) weight loss (OR, 2.80; 95% CI, 2.55–3.08) and those with severe (> 15%) weigh gain (OR, 2.24; 95% CI, 1.96–2.57), respectively. The impact of weight loss on the cardiac arrest occurrence was more prominent in men, while the impact of weight gain was more prominent in women.
Conclusion: Significant weight changes increase the risk of OHCA within a year with a reverse J-shaped association. Significant weight loss might be a warning sign for OHCA especially for men.

Keywords: Body Weight; Out-of-Hospital Cardiac Arrest; Body Mass Index; Weight Loss; Weight Gain

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Author Contributions
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INTRODUCTION

Cardiac arrest is a leading cause of mortality and morbidity worldwide. Despite the advances in cardiac arrest resuscitation, less than 8% of the out-of-hospital cardiac arrest (OHCA) patients survive to discharge and regain their cognitive and activity function as before cardiac arrest.[1] From this point of view, optimizing medical resources and treatment strategies for OHCA patients is not sufficient to improve public health.[2] Identifying people at high risk and implementing prevention strategies would contribute to a lower incidence of cardiac arrest and ultimately enhance public health.

Body weight and body composition have attracted much attention because of their long-term clinical impact on lifetime, and abnormal body weight is a modifiable condition with adequate interventions such as nutrition and physical activities.[3,4] Obesity is a highly prevalent risk factor for cardiovascular disease and has been a well-known risk factor for cardiovascular events and mortality. However, recent systemic studies examining the association between abnormal weight status including underweight, overweight and obesity, defined by body mass index (BMI) and sudden cardiac death or cardiovascular disease have shown conflicting results.[5,6] Overweight patients exhibit lower mortality after cardiac arrest in the presence of a shockable rhythm, known as obesity paradox; however, mortality rates in other studies were reported to be higher for obese patients following therapeutic hypothermia.[7] Additionally, a single measurement of BMI is not informative enough to reflect the dynamic features of body weight, and thus would contribute to conflicting findings.[5,6,8]

An enhanced understanding the link of OHCA occurrence to body weight and weight changes would help in establishing effective preventive strategies including lifestyle habits and goals. This population-based nested case-control study aimed to investigate the association between OHCA occurrence and changes in BMI over a period of less than 4 years.

METHODS

Study design and population

This population-based nested case-control study used the claims data from Korean National Health Information Database collected between 2009 and 2018. The cases were defined as adult non-traumatic OHCA patients who received cardiopulmonary resuscitation (CPR) at an emergency department (ED) between 2010 and 2018 and who underwent national health check-ups twice, one within a year and the other within 2 to 4 years prior to cardiac arrest. The controls were defined as adults who did not experience an OHCA and underwent national health check-ups twice in similar manner as the cases.

OHCA patients were those who received CPR at ED (Korean classification of health intervention code: a combination of M1583-M1587, M5873-M5877, and last digit 020 based on the national insurance claims data). We counted the first OHCA as our case during the study period. After excluding the patients previously counted as OHCA cases (n = 7,077) and those with missing demographic variables such as age and sex (n = 596), a total of 210,327 OHCA cases were identified between 2010 and 2018. The identified cases accounted for 80.8% of the total OHCA cases (n = 260,183) reported by Korea Disease Control and Prevention Agency during the same period. Each case was matched with two controls of the same sex, age, and alive status at the particular age of cardiac arrest. The traumatic OHCA patients with a diagnosis of International Classification of Diseases (ICD) 10th codes S00-T98 were also excluded from the study.

Data sources

The Medical Insurance Act enacted in 1963 requires all Korean citizens to register for national healthcare insurance, managed by the National Health Insurance Service (NHIS).[9] The NHIS maintains a comprehensive database including health service utilization, prescription or procedure records, and diagnosis codes from the 10th revision of the ICD. This database covers clinical data from all health-care facilities in Korea due to the obligatory nature of the national health insurance system. The NHIS also provides national health screening examinations biannually for all registered individuals and Koreans aged > 20 years who are employed by a company.[10] The health screening dataset includes anthropometric measurements, comorbidities, family history, self-reported health behavior, and results of laboratory investigations.[9] In this study, demographic information, disease histories based on diagnostic codes, medical services provided, medical prescriptions, and the national health screening program results within 4 years before cardiac arrest were extracted from the de-identified database.

Data definitions

Anthropometric measurements, including body weight, height, and degree of physical activity, alcohol consumption, and tobacco use were retrieved from the recent national health check-up results measured within one year before the cardiac arrest. The BMI was calculated as weight in kilograms divided by height squared in meters (kg/m^2). We categorized the participants into five groups based on the BMI according to the World Health Organization criteria for Asian populations: underweight (< 18.5 kg/m^2); normal weight (18.5–22.9 kg/m^2); overweight (23.0–24.9 kg/m^2); obese I (25.0–29.9 kg/m^2); and obese II (≥ 30.0 kg/m^2).[11] The closest body weight and height measured in national health check-up within 2–4 years prior to the cardiac arrest were also retrieved to calculate the earlier BMI. The average annual BMI change over the study period was calculated, as well the percent change in BMI using the equation: $(BMI_{\text{within a year}} - BMI_{\text{previous 4 years}})/BMI_{\text{previous 4 years}} \times 100$. We defined seven groups describing percent change in BMI around these cut-offs: 1) severe weight loss as a BMI decrease over 15%, 2) moderate weight loss as a 10–15% BMI decrease, 3) mild weight loss as a 5–10% decrease, 4) stable weight as the absolute value of BMI percent change value < 5%, 5) mild weight gain as 5–10% increase, 6) moderate weight gain as a 10–15% increase, and 7) severe weight gain as a BMI increase over 15%.

Statistical analysis

Descriptive analyses were conducted to evaluate the characteristics of cases and controls. Cases and controls were matched for age and sex at a 1:2 ratio. During the matching process, individuals with a history of trauma were excluded, and participants without a suitable match were also excluded from the study. Duplicates were not permitted during the matching process. Conditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of each variable for risk of OHCA using Enterprise Guide (version 7.1; SAS Institute Inc., Cary, NC, USA). The association between the risk of OHCA and BMI percent change was investigated. All tests of significance used two-sided P values < 0.05.

Ethics statement

This study was approved by the Institutional Review Board of Asan Medical Center (approval No. 2021-0291) and by the Korean NHIS inquiry commission. No informed consent was required from patients due to the nature of public data from NHIS. The privacy of the study subjects was protected through the de-identification of the national insurance claims data.

RESULTS

From 2010 to 2018, a total of 210,327 adult patients received CPR in ED for the first time in their lifetime, and 40,591 (19.3%) nontraumatic adult OHCA patients underwent national health check-up more than two times, with one check-up conducted within a year and the other within 2 to 4 years prior to the cardiac arrest. Controls were matched to cases at a 1:2 ratio by age and sex, resulting in the identification of 81,046 controls. Among the controls, 36,578 participants underwent national health check-up more than twice. After excluding the traumatic OHCA patients and their controls, this study finally included 24,465 nontraumatic adult OHCA cases and 32,434 control participants (**Fig. 1**).

Characteristics of the participants and the risk of OHCA

The mean age of the study patients was 65 years, and 72.1% were male. There were significant differences in comorbidities and physical activity between the OHCA cases and controls (**Table 1**). The prevalence of normal BMI group (36.3%) was highest in OHCA cases, followed by obese I (30.2%), overweight (23.6%), underweight (5.6%), and obese II (4.3%) groups, with BMI being measured within a year before OHCA occurrence (**Table 2**). The risk of OHCA by BMI categorization showed a similar pattern regardless of BMI measurement timing. The highest risk of OHCA was observed in the underweight group, followed by the obese II group, while the risk was lowest in the overweight and obese I groups. Between the maximum 4 years before cardiac arrest and within a year before cardiac arrest, 43.9% of OHCA cases experienced weight loss of > 0.10 kg/m^2/year, and 36.3% experienced weight gain of > 0.10 kg/m^2/year. Only 19.8% of OHCA cases had stable weight (weight changes < ± 0.10 kg/m^2/year) during the period. In the control group, 39.2% experienced weight gain of > 0.10 kg/m^2/year.

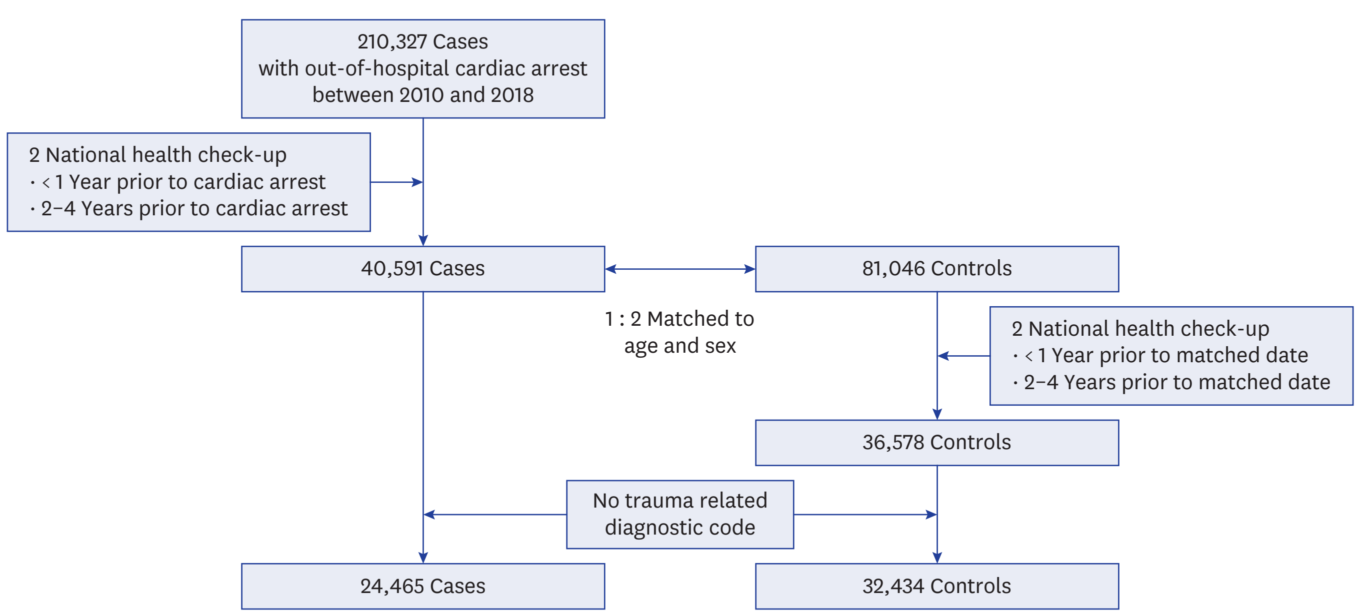

Fig. 1. Flow diagram of the patient selection process. Participants without a suitable match were excluded from the study. Duplicates were not permitted during the matching process.

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Table 1. Baseline characteristics and risk of OHCA among participants in the nested case-control study

Characteristics	OHCA case patients (n = 24,465)	Controls (n = 32,434)	Conditional logistic regression analysis		
			Matched OR	95% CI	*P* value
Age, yr	65.0 ± 11.5	65.0 ± 11.2	-	-	-
Male	17,644 (72.1)	23,263 (71.7)	-	-	-
Comorbidities					
Hypertension	9,179 (37.5)	10,738 (33.1)	1.24	1.19–1.28	< 0.001
Diabetes mellitus	5,183 (21.2)	4,179 (12.9)	1.87	1.79–1.96	< 0.001
Dyslipidemia	1,320 (5.4)	2,059 (6.3)	0.85	0.79–0.92	< 0.001
Myocardial infarction	1,662 (6.8)	492 (1.5)	4.73	4.26–5.26	< 0.001
Heart failure	4,394 (18.0)	1,626 (5.0)	4.36	4.09–4.65	< 0.001
Renal failure	1,626 (6.6)	389 (1.2)	6.07	5.34–6.82	< 0.001
CVD	4,436 (18.1)	3,129 (9.6)	2.14	2.03–2.25	< 0.001
Physical activity	(N = 24,446)	(N = 32,411)			
Active (≥ 5 days/wk)	2,838 (11.6)	4,701 (14.5)	Reference		< 0.001
Mild to moderate (1–4 days/wk)	7,514 (30.7)	12,012 (37.0)	1.03	0.97–1.09	0.296
None	14,094 (57.6)	15,698 (48.4)	1.50	1.42–1.59	< 0.001

Age is presented as mean ± standard deviation. Other categorical variables are presented as number (%).
OHCA = out-of-hospital cardiac arrest, OR = odds ratio, CI = confidence interval, CVD = cerebrovascular disease.

Table 2. Association between longitudinal body mass index percent changes and risk of OHCA among participants in the nested case-control study

Characteristics	OHCA case patients (n = 24,465)	Controls (n = 32,434)	Conditional logistic regression analysis		
			Matched OR	95% CI	*P* value
Recent BMI category[a]					
Underweight	1,369 (5.6)	817 (2.5)	1.96	1.78–2.15	< 0.001
Normal	8,885 (36.3)	10,504 (32.4)	Reference		< 0.001
Overweight	5,785 (23.6)	8,956 (27.6)	0.77	0.73–0.80	< 0.001
Obese I	7,386 (30.2)	11,112 (34.3)	0.79	0.76–0.82	< 0.001
Obese II	1,040 (4.3)	1,045 (3.2)	1.18	1.08–1.30	< 0.001
Previous BMI category[a]					
Underweight	1,012 (4.1)	748 (2.3)	1.67	1.51–1.85	< 0.001
Normal	8,658 (35.4)	10,758 (33.2)	Reference		< 0.001
Overweight	6,005 (24.5)	8,986 (27.7)	0.84	0.80–0.88	< 0.001
Obese I	7,781 (31.8)	10,998 (33.9)	0.89	0.85–0.93	< 0.001
Obese II	1,009 (4.1)	944 (2.9)	1.34	1.22–1.47	< 0.001
BMI change during recent 4 years					
Stable	4,852 (19.8)	8,108 (25.0)	Reference		< 0.001
Weight loss > 0.10 kg/m^2/yr	10,737 (43.9)	11,608 (35.8)	1.54	1.47–1.61	< 0.001
Weight gain > 0.10 kg/m^2/yr	8,876 (36.3)	12,718 (39.2)	1.16	1.10–1.21	< 0.001

Data are presented as number (%).
OHCA = out-of-hospital cardiac arrest, OR = odds ratio, CI = confidence interval, BMI = body mass index.
[a]The participants were categorized into five groups based on the BMI: underweight (< 18.5 kg/m^2); normal weight (18.5–22.9 kg/m^2); overweight (23.0–24.9 kg/m^2); obese I (25.0–29.9 kg/m^2); and obese II (≥ 30.0 kg/m^2) according to the World Health Organization criteria for Asian populations.

Individuals with weight loss of > 0.10 kg/m^2/year were more likely to develop OHCA (OR, 1.54; 95% CI, 1.47–1.61; *P* < 0.001) compared to those who gained weight of > 0.10 kg/m^2/year (OR, 1.16, 95% CI, 1.10–1.21; *P* < 0.001).

Associations between longitudinal BMI changes and OHCA risk

During the study period, 59.1% of OHCA patients classified in the stable BMI percent change group (**Supplementary Table 1**). The highest proportion of stable BMI percent change was observed in those with the previous overweight and obese I group (62.3%). The association between OHCA and longitudinal BMI percent change was reverse J-shaped (**Fig. 2**), with a significant increase in OHCA risk for all BMI percent changes ≥ 5%. The severe weight loss (BMI decrease > 15%) during the study period showed the highest OR of 4.29 (95% CI, 3.72–4.95) for the OHCA occurrence. Moderate weight loss (BMI decrease 10–15%) and severe weight gain (BMI increase > 15%) were also significantly associated with increased

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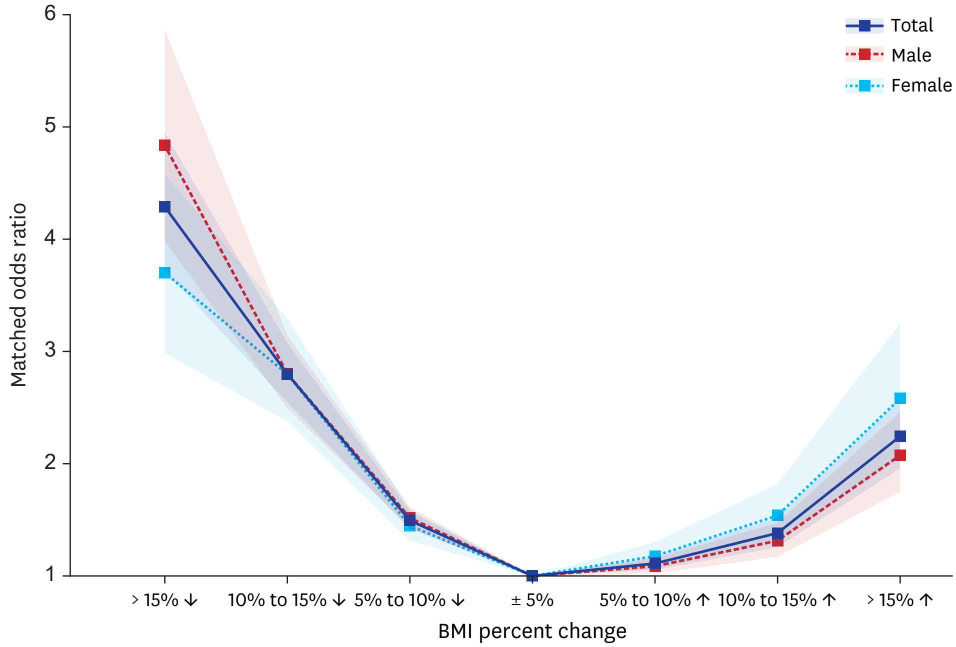

BMI change (%)	> 15% decrease	10% to 15% decrease	5% to 10% decrease	± 5% (Stable)	5% to 10% increase	10% to 15% increase	> 15% increase
Total	4.29 (3.72–4.95)	2.80 (2.55–3.08)	1.49 (1.42–1.57)	Reference	1.11 (1.05–1.17)	1.38 (1.26–1.52)	2.24 (1.96–2.57)
Male	4.84 (3.98–5.87)	2.80 (2.50–3.15)	1.52 (1.43–1.61)	Reference	1.09 (1.02–1.16)	1.31 (1.17–1.48)	2.08 (1.75–2.46)
Female	3.70 (2.99–4.58)	2.80 (2.38–3.29)	1.45 (1.31–1.59)	Reference	1.18 (1.06–1.30)	1.54 (1.30–1.82)	2.58 (2.05–3.25)

Fig. 2. Association between percent changes in BMI and out-of-cardiac arrest.
BMI = body mass index.

risk of OHCA, with ORs (95% CI) of 2.80 (2.55–3.08) and 2.24 (1.96–2.57), respectively. The association between weight loss and OHCA was more prominent in males, while the association between BMI increase and OHCA tended to be attenuated. In females, the reverse J-shape curve remained unchanged, although the OR for OHCA in severe BMI decrease (> 15%) was decreased, and the ORs for BMI increase were noted to have increased.

Our subgroup analyses focusing on individuals with a previous normal weight (BMI, 18.5–29.9 kg/m^2) revealed findings that were consistent with our main results. A strong graded association between BMI percent decrease and OHCA was observed, whereas the association between BMI percent increase and OHCA was substantially attenuated, with only severe BMI increase (> 15%) significantly increasing the risk of OHCA (**Fig. 3**).

DISCUSSION

In this population-based nested case-control study, we found that a reverse J-shaped association between longitudinal BMI changes and OHCA risk within a year. Severe weight loss (BMI decrease > 15%) showed the highest risk of OHCA, followed by moderate weight loss (BMI decrease of 10% to 15%), and severe weight gain (BMI increase > 15%) over a period of less than 4 years. Even mild weight loss (BMI decrease of 5% to 10%) was significantly

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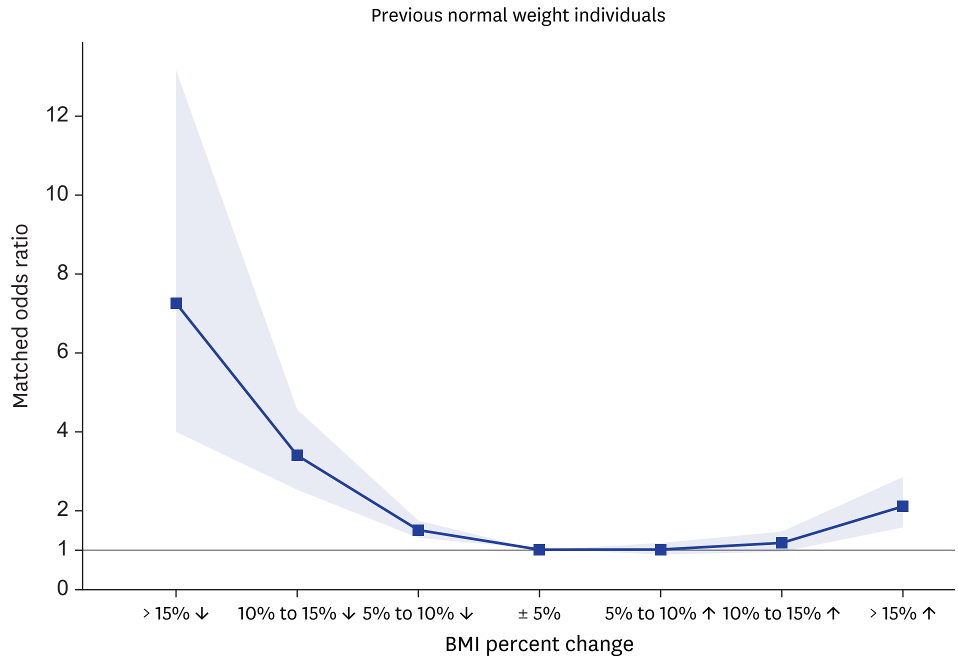

BMI change (%)	> 15% decrease	10% to 15% decrease	5% to 10% decrease	± 5% (Stable)	5% to 10% increase	10% to 15% increase	> 15% increase
Previous normal	7.24 (3.98–13.17)	3.39 (2.52–4.55)	1.51 (1.30–1.75)	Reference	1.03 (0.90–1.18)	1.18 (0.95–1.47)	2.12 (1.57–2.87)

Fig. 3. Association between percent changes in BMI and out-of-cardiac arrest in individuals with previous normal weight status.
BMI = body mass index.

related to increased OHCA risk in all participants. Our findings highlight the importance of maintaining a stable weight to reduce the risk of cardiac arrest and suggest that significant weight loss would be considered a warning sign for OHCA.

Understanding triggering factors of OHCA is crucial for developing appropriate public strategies to decrease its incidence and improve clinical outcomes. Previous investigations have demonstrated a positive association between obesity and the risk of cardiovascular disease mortality and sudden cardiac death.[5,12] Obesity contributes to the exacerbation of systemic inflammation and alterations in neurohormonal systems and circulatory physiology, thereby resulting in increased risk of cardiovascular disease and mortality, including coronary heart disease, heart failure and even sudden cardiac death. Even the metabolically healthy obese people have an increased risk of cardiovascular disease and mortality.[13-15] Weight loss for adults with overweight and obesity is an important lifestyle intervention to prevent cardiovascular disease.[4,16] However, many observational studies have demonstrated a U-shaped association between BMI levels and the risk of cardiovascular disease mortality and sudden cardiac death.[5,6] The underweight patients had worse outcomes compared to those with overweight or obese state.[6] For survival after sudden cardiac arrest, despite higher prevalence of cardiovascular comorbidities in obese patients, a higher BMI was associated with lower mortality (hazard ratio of 0.86).[17] Consistent with these previous studies, our population-based study identified a higher risk of OHCA development in underweight and severely obese people, while overweight and mildly obese individuals had a lower risk compared to those with a normal BMI.

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Considering the dynamic nature of body weight over time, the BMI calculated at a single time point would be insufficient to reflect the impact of the body weight on OHCA development. Our study revealed significant BMI changes increased OHCA risk and the association between BMI decrease and OHCA risk was stronger than that between BMI increase and OHCA risk, known as a reverse J-shaped association. A recent study has explored whether body weight fluctuation is more detrimental in overweight or obese individuals compared to those of normal weight, and among individuals with the highest variation in body weight, the risk of coronary and cardiovascular events was found to be 64% and 85% higher, respectively, with a 124% increased risk of death.[16] Zafir et al.[18] reported a reversed J-shaped association between BMI changes after cardiac catheterization and all-cause mortality, which BMI decrease was related to higher mortality rates than was an BMI increase. Such association was also observed in patients with chronic obstructive pulmonary disease and hemodialysis patients, which demonstrated a graded association between BMI decrease and worse clinical outcomes.[19,20] Longitudinal BMI decrease was independently associated with disease exacerbation and mortality in chronic obstructive pulmonary disease patients and with subsequent hospitalization hemodialysis patients, respectively.[19,20] To our knowledge, our study is the first to describe the association between BMI changes and subsequent development of cardiac arrest.

The positive association between weight loss and OHCA might appear paradoxical, considering the established risks of obesity and the proven benefits of intentional weight loss. This association was more robust in the male population. There can be several possible explanations for these associations. One possibility is that unintentional weight loss would be a later manifestation of an underlying systemic illness such as cancer.[21,22] However, a previous prospective cohort study using the US National Health and Nutrition Examination Survey data demonstrated no significant associations between weight changes and cancer mortality.[8] Also, this study cohort comprised middle-aged and older adults, and the body composition changes accompanied with weight loss in this cohort, including reduced muscle mass and redistribution of body fat, reduction of subcutaneous fat mass and increase of visceral fat, might be another possibility.[23,24] Interestingly, our previous studies found the sex-based differences in the impact of body composition on prognosis, and the association between weight loss following muscle depletion and poor outcome was stronger in men than that in women.[25,26] Consistent with this, the association between weight loss and OHCA risk was more prominent in men compared to that in women. Third, the body weight fluctuations might be another possible explanation. Body weight fluctuations is considered an independent risk factor of cardiovascular events and death, and more frequently occurs in people attempting intentional weight loss followed by weight gain.[16,27] Consistent with previous findings, our results confirmed the harmful effect of dramatic weight changes on OHCA and the importance of stabilizing weight status during middle and late adulthood.

Our study has several strengths. First, the population-based nested case-control study design helped to avoid potential recall and self-reported biases during the study period, as well as selection bias. Second, our detailed analysis stratified by weight status and sex allowed for a more nuanced understanding of our findings. Our findings suggest that public health strategies based on sex and weight status would be necessary to improve overall public health, and stabilizing weight status could be a simple and effective preventative strategy for OHCA. However, the limitations of this study need to be acknowledged. Firstly, this study did not document the cause of OHCA and the outcome. Secondly, we were unable to adjust the potential confounding factors, including the onset of new comorbid diseases or

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the exacerbation of pre-existing conditions, as well as diet habit, baseline health status and exercise, which may influence both weight change and OHCA development. Particularly, weight changes could be an initial presentation of certain diseases or could be associated with the worsening of pre-existing conditions. Another major limitation of this study is the definition of OHCA cohort, which was based on the intervention code. This definition excluded OHCA patients who had achieved return of spontaneous circulation (ROSC) before their ED arrival and did not undergo CPR at the ED due to sustained ROSC. According to the Korea Center for Disease Control and Prevention's announcement in 2019, the overall rate of ROSC before ED arrival was 4.9% during the study period. Also, this definition may include the patients who experienced cardiac arrest after presenting to the ED. Additionally, the generalizability of our findings to other countries and ethnicities requires further evaluation. Finally, we could not differentiate the intentional and unintentional weight changes, and consequently this study demonstrated an association, not the causation.

In conclusion, this study found that significant weight changes were associated with increased OHCA risk and revealed that weight loss affects more than weight gain, particularly pronounced in men. Monitoring weight and maintaining stable weight would be a reliable public health strategy to prevent OHCA occurrence. Further investigation is warranted to elucidate the underlying mechanisms about the relation between weight changes and OHCA risk.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Longitudinal percent changes in BMI according to sex and the previous weight status

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