Body weight fluctuation and the risk of incident atrial fibrillation

Hyun-Jung Lee[1], MD, Eue-Keun Choi[1], MD, PhD, Kyung-Do Han[2], PhD, Euijae Lee[1], MD, Inki Moon[1], MD, You-Jung Choi[1], MD, So-Ryoung Lee[1], MD, Myung-Jin Cha[1], MD, Seil Oh[1], MD, PhD, Gregory Y. H. Lip[1,3,4], MD

[1] Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

[2] Department of Medical Statistics, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

[3] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Chest & Heart Hospital, Liverpool, United Kingdom; and [4] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Running title: Body weight fluctuation and atrial fibrillation

Table xx; Figure xx

Total word count: xx

Keywords:

Address for correspondence:

Eue-Keun Choi, MD, PhD

Professor, Department of Internal Medicine, Seoul National University Hospital

101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea

Phone: +82-2-2072-0688, Fax: +82-2-762-9662, E-mail: choiek17@snu.ac.kr

Abstract

Background: Obesity and weight gain are established risk factors for atrial fibrillation (AF). Whether body weight variability is also a risk factor for AF development is unclear.

Methods: A nationwide population-based cohort of 8,091,401 adults from the Korean National Health Insurance Service database without previous history of AF and with at least 3 measurements of body weight over a 5-year period were followed up for incident AF. Intra-individual body weight variability was calculated using variability independent of mean, and high body weight variability was defined as the quartile with highest body weight variability (Q4) with Q1-3 as reference.

Results: During a median of 8.1 years follow-up, AF was newly diagnosed in 158,347 (2.0%). After adjustment for baseline body weight, height, age, sex, lifestyle factors and comorbidities, each increase of 1-SD in body weight variability was associated with a 5% increased risk of AF development, and the quartile with the highest body weight variability showed a 14% increased risk of AF development compared to the quartile with lowest body weight variability (HR 1.14, 95% CI 1.12-1.15). High body weight variability was significantly associated with AF development in all BMI groups except the very obese (BMI≥30), and this association was stronger in subjects with lower body weight. In underweight subjects, high body weight variability was associated with a 16% increased risk of AF development. High body weight variability was associated with a 7~12% increased risk of AF in all weight change groups.

Conclusions: Body weight fluctuation was independently associated with an increased risk of AF development, especially in individuals with low body weight, and regardless of overall weight change. Avoiding substantial fluctuations in body weight may confer protection against the future risk of AF.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population[1]. Body weight and AF are closely related. Obesity is an established risk factor for AF, explaining 3.4% and 17.9% of all AF cases in Korea and US, respectively[2, 3]. In a meta-analysis, each 5-unit increase in body mass index (BMI) was associated with a 28% increase in the risk of incident AF, and different measures of adiposity were also associated with AF development[4]. On the other hand, underweight was also shown to increase the risk for incident AF[5]. AF patients with underweight had an increased risk of ischemic stroke and major bleeding, but direct oral anticoagulants showed better effectiveness and safety compared to warfarin as in patients with normal weight[6, 7]. Meanwhile, there is an 'obesity paradox' in patients with established AF, in which overweight and obese patients show lower all-cause mortality[8].

However, most studies are based on BMI measurements recorded at baseline and do not take into account body weight changes that occur throughout follow-up. Importantly, body-mass index (BMI) criteria developed by WHO may not be suitable for Asian populations, since such individuals have different associations between BMI, percentage of body fat, and health risks, from European populations [ref]. There is no recommendation, however, for new clear BMI cut-off points for all Asians; however, weight changes may be a simple and practical assessment in everyday practice.

Indeed, some studies have shown that *weight gain* is associated with a higher risk of AF[9, 10], and that interventions for weight loss can lower the risk of incident AF[11] or AF burden[12, 13]. Individuals often oscillate in weight over time, and body weight fluctuation may also have negative consequences. Body weight variability is a risk factor for cardiovascular events and death in previous research[14-16]. Whether body weight fluctuation (rather than BMI variability [ref]) is also a risk factor for the development of AF is unclear.

To address this, we aimed to find whether body weight fluctuation affects the development of

incident AF, independent of baseline body weight or overall weight change in the general population.

Methods

Study population

This study utilized the database of National Health Insurance Service, a government corporation that provides health care benefits and regular health check-ups for the total Korean population, which can be used for population-based studies. Details of the database and health examinations are available in previous studies[17, 18]. Briefly, of 17,539,992 subjects (≥20 years) from the general population who underwent health examinations in 2009 to 2010 (year of health examination as index year), those who underwent at least 3 examinations during the previous 5 years (including the index year) were included (n=8,376,754). Of the remaining subjects, those with missing parameters (n=165,191), and those with the previous history of AF (n=120,162) were excluded. A total of 8,091,401 subjects were included in the final study population. The study population was followed from the index year until censoring by new-onset AF, death, or until 31 December 2017 (end of study), whichever came first. This study was approved by the Institutional Review Board of Seoul National University Hospital [E-1811-130-987], and informed consent was waived.

Definition of body weight variability

Intra-individual body weight variability can be measured by various indices, including standard deviation (SD), coefficient of variation (CV), average successive variability (ASV), and variability independent of the mean (VIM) (Supplementary Figure 2). A CV is calculated as the ratio of the SD to the mean. ASV is defined as the average absolute differences between successive body weight measurements and reflects the order of measurements. SD, CV or ASV are partially dependent on mean body weight level and its changes over time, and this may not be resolved even if adjusted for mean body weight. VIM is a measure of variability designed not to correlate with mean levels[19, 20], and is calculated as $100 \times SD/mean^{beta}$, where beta is the

regression coefficient based on the natural logarithm of the SD over the natural logarithm of the mean. VIM was used as the primary variability measure in this study. Subjects were classified into quartiles of body weight variability (Q1, lowest quartile; Q4, highest quartile). High body weight variability was defined as Q4 with reference body weight variability as Q1-3; the rationale for this classification was that subjects in Q4 showed a steep increase in AF risk compared to those in the lower three quartiles (Q1-3) (Figure 1).

Baseline body weight and characteristics were those collected in the index year. BMI was calculated as the weight in kilograms divided by the height in meters squared. Subjects were categorized into 5 groups according to BMI: underweight (BMI<18.5), normal weight (BMI 18.5-22.9), overweight (BMI 23-24.9), obese stage I (BMI 25-29.9), and obese stage II (BMI≥30). The association between AF development and high body weight variability was compared within each BMI group.

Overall body weight change was that between the first and last health exams; subjects were categorized according to total body weight change into 3 groups: weight loss (weight decrease of -5% or more), stable weight (weight change within 5%), and weight gain (weight increase of 5% or more), and the AF risk associated with high body weight variability was compared within each group.

Definition of diseases

Comorbidities and outcomes were defined using either diagnosis codes from the tenth revision of *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) with healthcare usage and medication or health examination results, as in previous studies[7, 21, 22]. The endpoint was incident nonvalvular AF (ICD-10 code I48, with ≥1 diagnosis during admission or at the outpatient clinic, with the exclusion of rheumatic mitral stenosis or prosthetic heart valves). The definitions for comorbidities are described in Supplementary

Table 1.

Statistical analysis

The relation between body weight variability and risk of AF development was evaluated with body weight variability as a continuous variable and a categorical variable. Baseline characteristics are presented as mean ± SD for continuous variables and n (%) for categorical variables. The incidence rates of AF were calculated per 1,000 person-years. Cox proportional hazards regression was used to calculate unadjusted and adjusted hazard ratios (HR) and 95% CI values for the risk of developing AF. The proportional hazards assumption was evaluated graphically by the analysis using log-log plots, and there was no significant departure from proportionality in hazards over time. To control for confounding, we adjusted for baseline body weight, baseline height, age, sex, smoking, drinking, exercise, low income, diabetes mellitus, hypertension, dyslipidemia, and chronic kidney disease. Health examination results such as glucose, blood pressure, and creatinine clearance levels were not adjusted for due to collinearity with comorbidities.

The risk of developing AF was calculated for each 1-SD increase and quartiles of body weight variability. Analyses were performed to assess the relationship between high body weight variability and AF risk based on baseline BMI categories and overall body weight change. Subgroup analyses for high body weight variability and AF risk were conducted for age strata, sex, and presence of comorbidities. Sensitivity analyses were performed using other indices of variability: SD, CV, and ASV.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and p-value<0.05 was considered to indicate statistical significance.

Results

Characteristics of the study population

A total of 8,091,401 subjects were followed up for a median of 8.1 years (mean 7.8±1.0 years), and 158,347 (2.0%) developed AF. Mean age was 48.1 years, and 58.7% were men. Mean baseline body weight was 64.4±11.5 kg. Body weight of each subject was measured 3 (n=5,352,333; 66.2%), 4 (n=1,287,666; 15.9%), or 5 (n=1,451,402; 17.9%) times. Mean ASV was 2.2 kg, and mean VIM was 1.9%. The characteristics of the study population divided into quartiles of body weight variability by VIM are summarized in Table 1.

Subjects with high body weight variability were younger, less likely to be male, less likely to exercise regularly, more likely to have a lower income, had a higher proportion of diabetes mellitus and heart failure, and a lower proportion of hypertension and dyslipidemia. P-values for trend were <0.001 for most variables because of the large study population, but there were little numerical differences among the groups for the rest of the variables.

Body weight variability as a continuous variable and AF risk

Risk of AF development increased significantly with each 1-SD increase in body weight variability (Table 2). Each 1-SD increase in body weight variability (VIM) was independently associated with a 5% increase in the risk of AF development (hazard ratio [HR] 1.049, 95% confidence interval [CI] 1.044-1.053).

Quartiles of body weight variability and AF risk

Incidence rates of AF were greatest in subjects with the highest quartile of body weight variability. Risk of AF development increased with each higher quartile of body weight variability after multivariable adjustment (Figure 1), significantly for Q3 and Q4 compared to Q1. There was a steep increase of AF risk in subjects in the highest quartile of body weight

variability (Q4) compared to those in the lower three quartiles (Q1-3). Subjects in the highest quartile of body weight variability (VIM) showed a 14% increase in the risk of AF development compared to the lowest quartile (HR 1.14, 95% CI 1.12-1.15).

Body weight variability and AF risk according to baseline body mass index

While crude incidence rates increased with BMI, the risk of AF showed a J-shaped relationship with BMI in the fully adjusted model (Table 3). AF risk was lowest in the normal weight group, and there was a graded increase in AF risk with higher BMI in overweight and obese patients, while underweight subjects also showed an increased risk of AF.

Subjects with high body weight variability (Q4) showed a shallow U-shaped relationship of BMI with AF incidence, with the highest incidence rate of AF in the underweight group (2.98 per 100 person-years [PY], Figure 2A). On the other hand, subjects with reference body weight variability (Q1-3) showed a proportional increase of AF incidence with BMI, with the highest AF incidence in the obese group. After multivariable adjustment, high body weight variability was significantly associated with AF development in all BMI groups except for the extreme obese stage II group (BMI≥30). The association of high body weight variability with AF became stronger with lower BMI (p for interaction<0.001), and in underweight subjects, high body weight variability was associated with 16% increased risk of AF development (HR 1.16, 95% CI 1.08-1.24). Obese subjects with high body weight variability showed lower crude AF incidence rates compared to those with reference variability, but after multivariable analysis, AF risk was increased (obese stage I) or comparable (obese stage II).

Body weight variability and AF risk according to the overall weight change

AF incidence was highest in subjects who lost the most weight, and lowest in those who gained the most weight between the first and last measurements (Table 3). In the fully adjusted model,

overall weight change showed a reversed J-shaped relation with the risk of AF development; AF risk was highest in subjects with greatest overall weight loss, lowest in those who gained a small amount of weight (3-7%), and slightly increased in those with overall weight gain≥10%. Subjects with high body weight variability (Q4) showed higher AF incidence compared to those with lower variability in all weight change groups (Figure 2B). High body weight variability was independently associated with an elevated AF risk in all weight change groups, and this association became stronger with greater weight loss (p for interaction<0.001). Subjects with overall weight loss (≥-5%) and high body weight variability showed the highest AF incidence (3.57 per 100 PY) and AF risk (HR 1.12, 95% CI 1.09-1.15).

Body weight variability and AF risk in subgroup analyses

Incidence rates of AF were higher for subjects with high body weight variability in all subgroups by age strata, sex, and presence of comorbidities, except in the subgroup of young age adults (20-39 years). High body weight variability was consistently associated with AF development in subgroup analyses with multivariable adjustment as well, except for showing similar AF risk in the young age subgroup (Figure 3). This association was consistent in those with cardiac disease predisposing towards AF development such as heart failure or ischemic heart disease. P for interaction was significant in nearly all subgroups due to the large population.

Sensitivity analysis

Sensitivity analyses with three other indices of variability, namely SD, CV, and ASV observed a consistent association between body weight variability and risk of AF development. Each 1-SD increase in SD, CV, and ASV was independently associated with a 4.8%, 4.8% and 4.4% increase in incident AF risk, respectively (Table 2). The study population was divided into

quartiles for each body weight variability index, and multivariable analysis showed that risk of AF incident increased in quartiles with higher body weight variability compared to Q1, significantly for Q3 and Q4 for all indices (Supplementary Table 2). There was a steep increase of AF risk for Q4 compared to the lower three quartiles (Q1-3), and subjects in Q4 showed approximately 14% higher AF risk compared to subjects in Q1 for all variability indices.

Discussion

In a large population-based cohort of more than 8 million Koreans, we found that (i) increasing body weight variability was independently associated with AF development; (ii) high body weight variability was significantly associated with AF development in all BMI groups except the very obese (BMI≥30), and this association was stronger in subjects with low body weight; (iii) high body weight variability was associated with an increased risk of AF regardless of the direction of overall weight change, though this association was stronger with weight loss; and (iv) underweight and obesity, weight loss and weight gain were all associated with AF development.

Body weight variability, weight change, and AF risk

Body weight influences the development of AF. Obesity is strongly associated with AF development[2, 4], and increases the risk of AF independently of metabolic comorbidities; metabolically healthy obesity was associated with a 30% higher risk for AF[21]. Obesity causes arrhythmogenic remodeling of the atria related to the development and progression of AF[23, 24]. Meanwhile, being underweight was also associated with an excess risk of AF independent of thyroid disease, chronic lung disease, malignancy, or health-related behaviors[5].

Previous studies have shown that weight change affects AF development, but data on the effect

of weight fluctuation on AF development are limited. Weight gain was demonstrated to be associated with an increased risk of AF in large prospective cohort studies[9, 10]. Weight loss may reverse AF risk associated with obesity according to data from the Women's Health Study[9]. Also, weight reduction in obese subjects with bariatric surgery was associated with a lower risk of AF development[11]. In obese patients with established AF, intentional weight reduction by lifestyle intervention was associated with a reduced burden of AF[12, 13].

We found that body weight variability is an independent risk factor for new-onset AF. The risk associated with AF development increased steeply in the fourth quartile of body weight variability, conferring a 14% increased risk of AF compared to the lowest quartile. Each 1-SD increase in body weight variability was associated with a 5% increase in risk for incident AF. This association was valid in most subgroup analyses.

Interestingly, the association between body weight variability and AF was especially stronger in subjects with low body weight. Incidence rates of AF were especially elevated in subjects with low BMI and high body weight variability; thus subjects with high body weight variability showed largely similar AF incidence rates regardless of BMI group, whereas subjects with reference body weight variability showed a proportional increase of AF incidence with BMI. The association between body weight variability and AF was attenuated with increasing BMI, becoming non-significant in the very obese (BMI≥30). We used VIM as the main measurement of body weight variability, which is designed to be uncorrelated to the mean levels and also adjusted for baseline body weight and height, so these findings are not driven by the lower baseline body weight. Subjects with lower BMI seem to be more vulnerable to fluctuations in body weight. This is supported by another study which found that BMI variability was associated with an increased risk of new-onset AF in underweight and normal weight individuals, but not in obese individuals (BMI≥25) in a much smaller cohort[25]. The latter focused on BMI variability but given that BMI may be less suited for Asian subjects, the present

analysis focuses on body weight variability. Weight is more relevant to recent studies focused on weight reduction as an intervention to reduce AF burden or its complications [ref]. Such efforts are also important in optimizing outcomes after catheter ablation [ref].

In the present study, body weight variability was also associated with an increased risk of AF regardless of the direction of overall weight change. High body weight variability was associated with a 12% higher AF risk in subjects with weight loss or stable body weight, and 7% higher AF risk in subjects with weight gain. This is in line with a previous study which found that weight fluctuation>5% attenuated the association between weight reduction and decreased AF burden in obese patients with AF[13]. While total weight change is important, weight fluctuation in the process is also an important factor to account for in the development of AF.

Of interest was the finding that weight loss was associated with a greater increase in incident AF than weight gain. Weight gain of less than 10% did not increase AF risk; furthermore, weight gain of 3-7% was associated with the lowest AF risk, while weight gain of more than 10% was associated with a 3% increase in AF development. Meanwhile, weight loss from small amounts was associated with a graded increase in AF risk, and weight loss of more than 10% was associated with a 34% increase in incident AF. This was an unexpected trend observed in a general population receiving health examinations, and we had no information on the reasons for weight loss. Similar findings have been found in the ARIC study, in which weight loss>5% was associated with a marked increase in incident AF[10]. This may be explained by the difference between intentional and unintentional weight loss. While intentional weight loss is associated with favorable outcomes regarding AF[11-13], unintentional weight loss may be related to cachexia, decreased muscle mass, chronic diseases which can negatively affect AF development.

Strengths and Limitations

Strengths of this study include its large sample size of 8 million comprised from the whole Korean population who received health examinations, the long follow-up period of more than 8 years, and completeness of data including all healthcare usage of subjects. Several limitations should also be considered. First, the diagnosis of AF was based on claims data. Therefore, AF events without healthcare usage may be undetected. Second, electrocardiograms or information on the duration of arrhythmic episodes were unavailable in the database, and we could not specify the types of AF. Third, the study population is subject to selection bias. Despite the fact that all Korean residents are entitled to health examinations by the government, only three-fourths actually receive it because it is voluntary rather than obligatory. According to the Korean Statistical Information Service, 76.1% of total 17,633,406 subjects took the scheduled health examinations in 2015. Thus, the individuals in the present study may have healthier lifestyles and visit healthcare services more frequently than those who did not receive regular checkups. Fourth, we cannot exclude the presence of unadjusted confounding factors. Fifth, while this study found a statistically significant relationship between body weight variability and AF, there is insufficient evidence for a causal relationship. It needs to be tested in future prospective studies whether avoiding fluctuations in body weight is protective for AF.

Conclusions

Body weight variability was independently associated with an increased risk of AF development, especially in individuals with low body weight, and regardless of overall weight change. Avoiding substantial fluctuations in body weight may confer protection against future risk of AF.

References

1. Joung B, Lee JM, Lee KH, Kim TH, Choi EK, Lim WH, et al. 2018 korean guideline of atrial fibrillation management. *Korean Circ J*. 2018;48:1033-1080
2. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: The atherosclerosis risk in communities (aric) study. *Circulation*. 2011;123:1501-1508
3. Son MK, Lim NK, Cho MC, Park HY. Incidence and risk factors for atrial fibrillation in korea: The national health insurance service database (2002-2010). *Korean Circ J*. 2016;46:515-521
4. Aune D, Sen A, Schlesinger S, Norat T, Janszky I, Romundstad P, et al. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: A systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol*. 2017;32:181-192
5. Kang SH, Choi EK, Han KD, Lee SR, Lim WH, Cha MJ, et al. Underweight is a risk factor for atrial fibrillation: A nationwide population-based study. *Int J Cardiol*. 2016;215:449-456
6. Boriani G, Ruff CT, Kuder JF, Shi M, Lanz HJ, Rutman H, et al. Relationship between body mass index and outcomes in patients with atrial fibrillation treated with edoxaban or warfarin in the engage af-timi 48 trial. *Eur Heart J*. 2019
7. Lee SR, Choi EK, Park CS, Han KD, Jung JH, Oh S, et al. Direct oral anticoagulants in patients with nonvalvular atrial fibrillation and low body weight. *J Am Coll Cardiol*. 2019;73:919-931
8. Proietti M, Guiducci E, Cheli P, Lip GY. Is there an obesity paradox for outcomes in atrial fibrillation? A systematic review and meta-analysis of non-vitamin k antagonist

oral anticoagulant trials. *Stroke*. 2017;48:857-866

9. Tedrow UB, Conen D, Ridker PM, Cook NR, Koplan BA, Manson JE, et al. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the whs (women's health study). *J Am Coll Cardiol*. 2010;55:2319-2327
10. Huxley RR, Misialek JR, Agarwal SK, Loehr LR, Soliman EZ, Chen LY, et al. Physical activity, obesity, weight change, and risk of atrial fibrillation: The atherosclerosis risk in communities study. *Circ Arrhythm Electrophysiol*. 2014;7:620-625
11. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Sjostrom L, Karason K. Bariatric surgery and the risk of new-onset atrial fibrillation in swedish obese subjects. *J Am Coll Cardiol*. 2016;68:2497-2504
12. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: A randomized clinical trial. *JAMA*. 2013;310:2050-2060
13. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: A long-term follow-up study (legacy). *J Am Coll Cardiol*. 2015;65:2159-2169
14. Lissner L, Odell PM, D'Agostino RB, Stokes J, 3rd, Kreger BE, Belanger AJ, et al. Variability of body weight and health outcomes in the framingham population. *N Engl J Med*. 1991;324:1839-1844
15. Bangalore S, Fayyad R, Laskey R, DeMicco DA, Messerli FH, Waters DD. Body-weight fluctuations and outcomes in coronary disease. *N Engl J Med*. 2017;376:1332-1340
16. Kim MK, Han K, Park YM, Kwon HS, Kang G, Yoon KH, et al. Associations of variability in blood pressure, glucose and cholesterol concentrations, and body mass

index with mortality and cardiovascular outcomes in the general population. *Circulation*. 2018;138:2627-2637

17. Song SO, Jung CH, Song YD, Park CY, Kwon HS, Cha BS, et al. Background and data configuration process of a nationwide population-based study using the korean national health insurance system. *Diabetes Metab J*. 2014;38:395-403

18. Seong SC, Kim YY, Park SK, Khang YH, Kim HC, Park JH, et al. Cohort profile: The national health insurance service-national health screening cohort (nhis-heals) in korea. *BMJ Open*. 2017;7:e016640

19. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895-905

20. Yano Y. Visit-to-visit blood pressure variability-what is the current challenge? *Am J Hypertens*. 2017;30:112-114

21. Lee H, Choi EK, Lee SH, Han KD, Rhee TM, Park CS, et al. Atrial fibrillation risk in metabolically healthy obesity: A nationwide population-based study. *Int J Cardiol*. 2017;240:221-227

22. Lee SR, Choi EK, Han KD, Jung JH, Oh S, Lip GYH. Edoxaban in asian patients with atrial fibrillation: Effectiveness and safety. *J Am Coll Cardiol*. 2018;72:838-853

23. Munger TM, Dong YX, Masaki M, Oh JK, Mankad SV, Borlaug BA, et al. Electrophysiological and hemodynamic characteristics associated with obesity in patients with atrial fibrillation. *J Am Coll Cardiol*. 2012;60:851-860

24. Abed HS, Samuel CS, Lau DH, Kelly DJ, Royce SG, Alasady M, et al. Obesity results in progressive atrial structural and electrical remodeling: Implications for atrial fibrillation. *Heart Rhythm*. 2013;10:90-100

25. Lim YM, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Body mass index variability

and long-term risk of new-onset atrial fibrillation in the general population: A korean nationwide cohort study. *Mayo Clin Proc*. 2019;94:225-235

Figure legends

Figure 1. Atrial fibrillation risk according to bodyweight variability (VIM) quartiles.

Bar graphs represent incidence rates per 1000 person-years with scales on the left. Line graphs with error bars represent atrial fibrillation risk in hazard ratios with 95% confidence intervals with scales on the right.Hazard ratios were adjusted for baseline bodyweight, baseline height, age, sex, smoking, drinking, exercise, low income, diabetes mellitus, hypertension, dyslipidemia, and chronic kidney disease.

VIM, variability independent of mean; Q, quartile.

Figure 2. Bodyweight variability and atrial fibrillation risk as a function of (A) baseline body mass index and (B) overall bodyweight change.

Bar graphs represent incidence rates per 1000 person-years with scales on the left. Line graphs with error bars represent atrial fibrillation risk in hazard ratios with 95% confidence intervals with scales on the right. Hazard ratios were adjusted for baseline bodyweight, baseline height, age, sex, smoking, drinking, exercise, low income, diabetes mellitus, hypertension, dyslipidemia, and chronic kidney disease.

AF, atrial fibrillation; Q, quartile.

Figure 3. Subgroup analysis for bodyweight variability and AF risk.

Incidence rates per 100 person-years. HRs were adjusted for baseline bodyweight, baseline height, age, sex, smoking, drinking, exercise, low income, diabetes mellitus, hypertension, dyslipidemia, and chronic kidney disease.

AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval; Q, quartile.