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Implications of the dynamic nature of metabolic health status and obesity on risk of incident cardiovascular events and mortality: a nationwide population-based cohort study

Yun Kyung Cho [a,b], Yu Mi Kang [c], Jee Hee Yoo [a], Jiwoo Lee [a], Joong-Yeol Park [a], Woo Je Lee [a], Ye-Jee Kim [d,*], Chang Hee Jung [a,**]

[a] Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[b] Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, Republic of Korea
[c] International Healthcare Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[d] Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Aims: We hypothesized that transitions in metabolic health status and obesity affect the cardiovascular (CV) risk and mortality in population with metabolically healthy obesity (MHO).
Methods: This study enrolled 514,866 participants from the Korean National Health Insurance Service–National Sample Cohort. Changes in metabolic health status and obesity from the baseline examination in 2009–2010 to the next biannual health examination in 2011–2012 were determined. Study participants were categorized into four groups: (1) metabolically healthy, non-obese (MHNO), defined as BMI < 25 kg/m^2 and no or one metabolic risk factor; (2) metabolically unhealthy, non-obese (MUNO), defined as BMI < 25 kg/m^2 and ≥2 metabolic risk factors; (3) MHO, defined as BMI ≥ 25 kg/m^2 and no or one metabolic risk factor; and (4) metabolically unhealthy, obese (MUO), defined as BMI ≥ 25 kg/m^2 and ≥2 metabolic risk factors. The study subjects were followed-up from 2011 to 2015 for cardiovascular events, CV mortality and all-cause mortality.
Results: Among the subjects classified as MHO in 2009–2010, 45.6% were classified as MHO in 2011–2012, whereas 11.6%, 6.0%, and 36.8% were classified as MHNO, MUNO, and MUO, respectively. The risk of CV events was higher in baseline MHO group than MHNO group (HR, 1.14; 95% CI, 1.05–1.24). However, in baseline MHO group, CV mortality was not increased (HR, 0.85; 95% CI, 0.69–1.06) and all-cause mortality was even lower than that of MHNO group (HR, 0.86; 95% CI, 0.79–0.93). Compared to the stable MHO subjects, the risk of CV events was significantly higher in the subjects who transitioned from MHO to MUO with multivariate-adjusted HRs of 1.24 (95% CI: 1.00–1.54). When weight loss and progression to metabolic unhealthy phenotype occur simultaneously in the MHO population, the all-cause mortality was increased compared to the stable MHO group (HR, 1.96; 95% CI, 1.45–2.65).
Conclusions: **S**ubjects with MHO constitute a heterogeneous group. Our finding supports that evolving to a metabolically unhealthy status and losing weight simultaneously is associated with the adverse outcome in the MHO population.

Abbreviations: ATP III, Adult Treatment Panel III; BMI, body mass index; BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; ICD, International Classification of Diseases; KCD, Korean Standard Classification of Diseases and Causes of Death; LDL-C, low-density lipoprotein cholesterol; MHNO, metabolically healthy, non-obese; MHO, metabolically healthy obesity; MUNO, metabolically unhealthy non-obesity; MUO, metabolically unhealthy obesity; NHIS, National Health Insurance Service; NHIS-HEALS, National Health Insurance Service-National Health Screening Cohort; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

* Correspondence to: Y-J. Kim, Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea.
** Correspondence to: C. H. Jung, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea.
E-mail addresses: kimyejee@amc.seoul.kr (Y.-J. Kim), chjung0204@gmail.com (C.H. Jung).

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1. Introduction

Obesity is a major risk factor for cardiovascular (CV) morbidity [1]. Recent studies suggest, however, that the prognoses of obese subjects depend significantly on the presence of cardiometabolic risk factors [2,3]. Some obese subjects have a normal metabolic profile, a condition referred to as metabolically healthy obesity (MHO) [4]. Although CV risk is higher in individuals with MHO than in metabolically healthy individuals of normal weight, the risk is substantially lower in individuals with MHO than in those with metabolically unhealthy obesity (MUO) [2,5,6].

MHO is a dynamic concept that changes over time [7]. A subject's health status can switch from metabolically healthy to metabolically unhealthy and vice versa. For example, one-third to one-half of subjects with MHO have been reported to progress to a metabolically unhealthy state [7–11]. This may alter CV risk over time, suggesting that the initial determination of MHO may not be reliable.

Non-obese, unfit subjects were found to have a higher CV risk and a poorer prognosis than individuals with MHO [12]. These subjects, referred to as having metabolically unhealthy non-obesity (MUNO), were reported to have a CV risk similar to that of subjects with MUO [5,6,13,14]. However, it remains unclear how changes in obesity status as well as metabolic health in subjects with MHO affect CV risk and mortality.

This study was therefore designed to assess the effects of metabolic health and obesity state on CV events, CV mortality, and all-cause mortality in a large number of subjects who participated in a national health screening examination. In addition, this study evaluated the impact of changes in metabolic health and obesity states among participants with MHO on CV events, CV mortality, and all-cause mortality.

2. Materials and methods

2.1. Study population

This study used data from the Korean National Health Insurance Service (NHIS). The Korean NHIS was launched in 1963 in response to the National Health Insurance Act, which mandated that all Korean citizens participate in this program [15]. Currently, the Korean NHIS maintains and manages databases on the use of all health services throughout Korea. The present study utilized data from the NHIS-National Health Screening Cohort (NHIS-HEALS) 2002–2015, which were released by the Korean NHIS in 2017. The NHIS-HEALS comprises a random sample of 514,866 individuals throughout the population who underwent NHIS health screening examinations between 2002 and 2003 [15]. This cohort represents approximately 10% of the source population who underwent NHIS health screening examinations between 2002 and 2003, and who were followed up to disqualification from health services due to death or emigration or the end of the study period in 2015 [15]. Importantly, this cohort contains the general health examination data of subjects who participated in biannual examinations. The detailed structure and function of NHIS-HEALS have been described elsewhere [15].

Demographic and biochemical databases were analyzed for the index period, defined as the period between January 1, 2009, and December 31, 2010. This index period was chosen because the NHIS-HEALS started to include some biochemical parameters, including triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) concentrations, in 2009 [15]. To evaluate changes in metabolic health status and obesity over time, data were collected from the next set of biannual health examinations, performed between January 1, 2011, and December 31, 2012. This study was approved by the NHIS inquiry commission. As this study was based on the results of the NHIS-HEALS, in which all data were fully anonymized and de-identified for all analyses, specific informed consent was not obtained from each participant. This study was approved by the Institutional Review Board of Asan Medical Center (IRB-No 2017-1337).

2.2. Definitions of metabolic health and obesity states

Obesity (body mass index [BMI] ≥ 25 kg/m^2) and non-obesity (BMI < 25 kg/m^2) were defined according to Asia-Pacific criteria, established by the World Health Organization Western Pacific Region [16] and officially adopted by the Korean Centers for Disease Control and Prevention and other Korean governmental organizations [17]. Metabolically healthy subjects were defined according to the Adult Treatment Panel III (ATP III) criteria as having none or one of the following risk factors [18]: (1) systolic blood pressure (BP) ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg and/or taking antihypertensive treatment; (2) TG ≥ 150 mg/dl and/or taking antidyslipidemic medications; (3) fasting plasma glucose (FPG) ≥ 100 mg/dl and/or taking antidiabetic medications; and (4) HDL-C < 40 mg/dl in men and < 50 mg/dl in women. Based on these criteria, all study participants were categorized into one of four groups: (1) metabolically healthy, non-obese (MHNO), defined as BMI < 25 kg/m^2 and no or one metabolic risk factor; (2) MUNO, defined as BMI < 25 kg/m^2 and ≥2 metabolic risk factors; (3) MHO, defined as BMI ≥ 25 kg/m^2 and no or one metabolic risk factor; and (4) MUO, defined as BMI ≥ 25 kg/m^2 and ≥2 metabolic risk factors. Waist circumference (WC) was not included because of its collinearity with BMI. Subjects with MHO at baseline examination were categorized into four subgroups, based on their metabolic health and obesity in 2011–2012.

2.3. Mortality data

Information on mortality and cause of death was available for all subjects in the cohort. Cause of death was classified according to the Korean Standard Classification of Diseases and Causes of Death [KCD-7], based on the tenth revision of the International Classification of Diseases (ICD)-10, as provided by the Korean National Statistical Office. Diseases or conditions directly leading to death were regarded as specific causes of death. Deaths due to diseases of the circulatory system (I00-99) were defined as CV deaths.

2.4. Definition of incident CV events

CV events were defined as admissions for MI and stroke (ischemic or hemorrhagic) between January 1, 2011, and December 31, 2015. All events were identified using hospital discharge records. Subjects were included if their ICD-10 codes for a principal or subsidiary diagnosis included I21 (ST and non-ST elevation MI), I22 (subsequent ST elevation and non-ST elevation MI), I23 (certain concurrent complications following ST and non-ST elevation MI), I63 (cerebral infarction), I64 (stroke, not specified as hemorrhage or infarction), I693 (sequelae of cerebral infarction), I694 (sequelae of stroke, not specified as hemorrhage or infarction), G45 (transient cerebral ischemic attacks and related syndromes), I60 (subarachnoid hemorrhage), I61 (intracerebral hemorrhage), I62 (other nontraumatic intracranial hemorrhage), I690 (sequelae of subarachnoid hemorrhage), I691 (sequelae of intracerebral hemorrhage), and I692 (sequelae of nontraumatic intracranial hemorrhage).

Of the total 514,866 subjects in NHIS-HEALS, those who died or who had any history of admission due to a CV event before the end of the index period were excluded, as were subjects with missing values for baseline BMI, systolic BP, diastolic BP, FPG, TG, and HDL-C. The final study cohort consisted of 362,863 subjects; of these, 31,488 subjects were categorized as MHO during the baseline examination and were followed up in 2011–2012. The study design and subject flow are shown in Fig. S1.

2.5. Definitions of type 2 diabetes, hypertension, and dyslipidemia

Subjects prescribed antidiabetic drugs and with ICD-10 codes E11 (noninsulin-dependent diabetes mellitus), E12 (malnutrition-related

diabetes mellitus), E13 (other specified diabetes mellitus), and E14 (unspecified diabetes mellitus) as either principal or secondary diagnosis were defined as having type 2 diabetes. Eight classes of antidiabetic drugs were dispensed by pharmacies in Korea during the study period: sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinediones, meglitinide, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and insulin.

Subjects prescribed antihypertensive medications and with ICD-10 codes I10 (essential [primary] hypertension), I11 (hypertensive heart disease), I12 (hypertensive chronic kidney disease), I13 (hypertensive heart and chronic kidney disease), and I15 (secondary hypertension) as either principal or secondary diagnosis were defined as having hypertension. Five classes of antihypertensive medications were dispensed by pharmacies in Korea during the study period: angiotensin receptor blockers, angiotensin converting enzyme inhibitors, beta blockers, calcium channel blockers, and diuretics. Subjects prescribed lipid-lowering medications and with ICD-10 code E78 (disorders of lipoprotein metabolism and other lipidemias) as either a principal or secondary diagnosis were defined as having dyslipidemia. Lipid-lowering medications dispensed by pharmacies in Korea during the study period included statins, ezetimibe, and fibrates.

2.6. Covariates

Covariates from the baseline health examination included smoking habits (non-, ex-, or current smoker), drinking habits (none, mild, moderate, or heavy drinking), and physical activity (0, 1–2, 3–4, or ≥5 times per week), and low-density lipoprotein cholesterol (LDL-C) concentrations. Heavy drinkers were defined as individuals who consumed seven or more drank on the same occasion and drinking >5 days per week, whereas mild and moderate drinkers were those who consumed <7 drinks on any single day and drank 1–2 or 3–4 days per week, respectively.

2.7. Statistical analysis

Continuous data were expressed as means ± standard deviation (SD), and categorical data as percentages. ANOVA or the chi-square test was used to compare the baseline characteristics of study participants according to their metabolic health and obesity status. The multiple imputation procedure was applied to impute missing variables. Time to death or CV event was estimated by the Kaplan-Meier method and compared by log-rank tests.

Cox proportional-hazard analyses were performed to estimate the hazard ratio (HR) and 95% confidence intervals (CI) of all-cause mortality, CV mortality, CV event, and incident metabolically unhealthy status during three follow-up periods. We used Cox regression method with age as the time-scale. Multivariate-adjusted models were adjusted for age, sex, smoking, alcohol drinking, physical activities, and LDL-C level. Among subjects with MHO at baseline, the relationships between changes in metabolic and obesity status and all-cause mortality, CV mortality, and CV events were analyzed. The MHNO group at baseline and the each stable group at follow-up (i.e., stable MHNO, MHO, MUNO and MUO) were regarded as the reference group. All statistical analyses were performed using SAS Enterprise Guide software (version 7.1, SAS Institute, Inc., Cary, NC).

3. Results

3.1. Baseline characteristics of the entire cohort

Overall, 10.0% of the subjects were categorized as MHO. Compared with the MHNO group, the MHO group had a less favorable risk profile, including elevated TG, LDL-C, and total cholesterol (TC) concentrations and reduced HDL-C concentrations. Compared with the MUO group, the MHO group tended to be younger and to display a more favorable risk profile. Compared with the MUNO group, the MHO group had a less insulin-resistant profile, including higher HDL-C and lower FPG and TG levels, despite their higher BMI and WC. The baseline clinical and biochemical characteristics of the entire cohort population are shown in Table S1.

3.2. Prognosis relative to baseline metabolic health and obesity state

Table 1 presents the HRs for incident CV events, CV deaths, and all-cause mortality according to baseline metabolic health and obesity. The risk of CV event was significantly higher in the MHO than in the MHNO group (HR, 1.14; 95% CI, 1.05–1.24) after full adjustment. However, the CV mortality was not higher in the MHO than in the MHNO group (HR, 0.85; 95% CI, 0.69–1.06). By contrast, metabolically unhealthy individuals, regardless of obesity status, had significantly higher risks of CV event and CV mortality than the lean healthy population. Compared with the MHNO group, the MUNO group had multivariate-adjusted HRs of 1.48 (95% CI: 1.41–1.55) for CV events and 1.38 (95% CI: 1.23–1.55) for CV mortality, whereas the MUO group had multivariate-adjusted HRs of 1.55 (95% CI: 1.47–1.63) for CV events and 1.32 (95% CI: 1.16–1.50) for CV mortality. All-cause mortality was higher in the MUNO than in the MHNO group (multivariate-adjusted HR, 1.20; 95% CI, 1.15–1.25). By contrast, all-cause mortality in the MUO group was not significantly different from that in the MHNO group (multivariate-adjusted HR, 0.96; 95% CI, 0.91–1.01). Furthermore, MHO group showed significantly lower all-cause mortality than the MHNO group having multivariate-adjusted HRs of 0.86 (95% CI: 0.79–0.93).

3.3. Changes in the metabolic health and obesity status of the MHO cohort and their prognosis

Among the subjects with MHO at baseline, 11.6% lost weight and were metabolically healthy without obesity (MHO to MHNO) at follow-up, 6.0% lost weight but transitioned to a metabolically unhealthy status (MHO to MUNO), 45.6% remained in the MHO group (MHO to MHO), and 36.8% remained obese and transitioned to a metabolically unhealthy status (MHO to MUO). Obesity and the presence of risk factors at baseline were significantly associated with the risk of incident unhealthy metabolic status (Table S2).

Table 2 and Fig. 1 present the crude and multivariate-adjusted HRs for incident CV events, CV deaths, and all-cause mortality according to follow-up metabolic health and obesity state in the baseline MHO cohort using the stable MHO group as the reference category. Compared to the stable MHO group, the risk of CV events was significantly higher in the MHO to MUO group with multivariate-adjusted HRs of 1.24 (95% CI: 1.00–1.54). In the MHO to MUNO group, the HR for CV events was 1.23, however, the difference was not statistically significant (95% CI: 0.86–1.78). There was a no significant difference of CV mortality among groups. The all-cause mortality was significantly higher in the MHO to MUNO group than in the stable MHO group (multivariate-adjusted HR, 1.61; 95% CI, 1.24–2.09).

3.4. Changes in the metabolic health and obesity status of the MHNO, MUNO and MUO cohort and their prognosis

Fig. 2 shows the HRs for incident CV events, CV deaths, and all-cause mortality according to follow-up metabolic health and obesity state in the baseline MHNO, MUNO and MUO cohort. In subjects with MHNO at baseline, the transition from MHNO to MUNO was significantly related to the increased risks of incident CV events, CV deaths, and all-cause mortality [with multivariate-adjusted HR (95% CI) of 1.30 (1.15–1.46), 1.48 (1.16–1.88) and 1.24 (1.13–1.37), respectively; Fig. 2 and Table S3]. The subjects who transitioned from MHNO to MUO demonstrated the increased risk of CV event incidence (multivariate-adjusted HR, 1.60; 95% CI, 1.21–2.12; Fig. 2 and Table S3).

Table 1
Risk of CV events, CV mortality, and all-cause mortality according to baseline metabolic health and obesity status.

Baseline category	MHNO	MHO	MUNO	MUO
BMI	<25 kg/m^2	≥25 kg/m^2	<25 kg/m^2	≥25 kg/m^2
Metabolic health status	0–1 risk factors	0–1 risk factors	≥2 risk factors	≥2 risk factors
N (% of total)	115,750 (31.9)	36,378 (10.0)	116,816 (32.2)	93,919 (25.9)
CV event incidence				
Number of events (%)	2416 (2.1)	804 (2.2)	4492 (3.9)	3343 (3.6)
HR (95% CI)	1 (ref)	1.12 (1.04–1.22)	1.49 (1.42–1.56)	1.54 (1.46–1.62)
Multivariate-adjusted HR (95% CI)[a]	1 (ref)	1.14 (1.05–1.24)	1.48 (1.41–1.55)	1.55 (1.47–1.63)
CV mortality				
Number of events (%)	459 (0.4)	97 (0.3)	876 (0.8)	510 (0.5)
HR (95% CI)	1 (ref)	0.78 (0.63–0.97)	1.32 (1.18–1.48)	1.20 (1.06–1.36)
Multivariate-adjusted HR (95% CI)[a]	1 (ref)	0.85 (0.69–1.06)	1.38 (1.23–1.55)	1.32 (1.16–1.50)
Mortality				
Number of events (%)	3186 (2.8)	689 (1.9)	5095 (4.4)	2562 (2.7)
HR (95% CI)	1 (ref)	0.77 (0.70–0.83)	1.15 (1.10–1.20)	0.86 (0.82–0.91)
Multivariate-adjusted HR (95% CI)[a]	1 (ref)	0.86 (0.79–0.93)	1.20 (1.15–1.25)	0.96 (0.91–1.01)

[a] Adjusted for baseline age, sex, smoking, alcohol drinking, physical activities, and LDL-cholesterol level.

In the baseline MUNO subjects, the transition from MUNO to MHNO was significantly related to the decreased risk for incident CV events (multivariate-adjusted HR, 0.72; 95% CI, 0.64–0.81; Fig. 2 and Table S4).

In the baseline MUO group, the transition to MHO significantly decreased the all-cause mortality (multivariate-adjusted HR, 0.77; 95% CI, 0.64–0.93; Fig. 2 and Table S5). In contrast, the transition from MUO to MUNO was related to the increased all-cause mortality (multivariate-adjusted HR, 1.31; 95% CI, 1.15–1.49; Fig. 2 and Table S5).

4. Discussion

The present study data showed that MHO subjects were at a higher risk of developing CV events than the lean healthy population, although their CV mortality was similar. By contrast, the all-cause mortality was lower in the MHO than in the MHNO group. These results further demonstrate that metabolic health is transient in a large proportion of subjects with MHO. Finally, our data suggest that MHO subjects can vary widely, including individuals who progress to a metabolically unhealthy phenotype with higher CV and mortality risks than the stable MHO subjects.

Obesity is an established risk factor for CV diseases (CVDs) and a major public health problem worldwide [1]. However, obesity not always entails metabolic abnormalities [19]. The concept of MHO was based on findings showing that a subgroup of obese individuals lack relevant cardiometabolic risk factors, putting these populations at reduced risk of CVD [12,20,21]. Many studies, however, report long-term adverse outcomes in MHO populations [6,21,22]. For example, individuals with MHO were found to be at higher risk of CVD than normal weight metabolically healthy individuals [6]. Similarly, we found that MHO status was associated with a high incidence of CV events, suggesting that MHO is not a benign condition in regard to CVD.

The clinical implications of MHO should also be considered in a context in which metabolic health is a transitory, not a permanent, state [7,23–25]. Approximately one-third to one-half of subjects originally identified as MHO were found to switch to a metabolically unhealthy state over time [7–11]. Similarly, only 57.2% of the initial MHO group in our NHIS cohort remained metabolically healthy after 2 years, whereas 42.8% progressed to a metabolically unhealthy status. These findings support the notion that MHO is a dynamic concept. Our MHO group, with higher BMI and 0–1 metabolic risk factors, was found to be at risk of developing an unhealthier state, putting them at higher risk for CVD (Table S2).

By updating metabolic health status and BMI 2 years after the baseline study, we found that the CV outcomes of the MHO group were highly variable. The present analysis showed that the incidence of CV events was higher in the MHO than in the MHNO group. However, the 2 year follow-up of the MHO cohort showed that the MHO subjects had variable prognosis according to their transition of the metabolic healthy and obesity status. When we compared the risk of each transition in the MHO cohort in reference with stable MHO group, the subjects who evolved to MUO had a higher risk of CV events than those who remained MHO status (Table 2). Three recent studies reported

Table 2
Risks of CV events, CV mortality, and all-cause mortality in participants with MHO at baseline according to 2 year metabolic health and obesity status using the stable MHO group as a reference group.

Baseline category	MHO			
Follow-up category	MHO	MHNO	MUNO	MUO
Follow-up BMI	≥25 kg/m^2	<25 kg/m^2	<25 kg/m^2	≥25 kg/m^2
Follow-up metabolic health status	0–1 risk factors	0–1 risk factors	≥2 risk factors	≥2 risk factors
N (% of baseline MHO)	14,318 (45.8)	3642 (11.7)	1837 (5.9)	11,468 (36.7)
CV event incidence				
Number of events (%)	165 (1.2)	50 (1.4)	36 (2.0)	180 (1.6)
R (95% CI)	1 (ref)	1.04 (0.76–1.43)	1.28 (0.89–1.84)	1.25 (1.01–1.54)
Multivariate-adjusted HR (95% CI)[a]	1 (ref)	1.02 (0.74–1.40)	1.23 (0.86–1.78)	1.24 (1.00–1.54)
N (% of baseline MHO)	14,365 (45.6)	3658 (11.6)	1876 (6.0)	11,589 (36.8)
CVD mortality				
Number of events (%)	23 (0.2)	7 (0.2)	9 (0.5)	29 (0.3)
HR (95% CI)	1 (ref)	0.97 (0.42–2.28)	1.92 (0.88–4.18)	1.33 (0.77–2.30)
Multivariate-adjusted HR (95% CI)[a]	1 (ref)	0.98 (0.42–2.29)	1.90 (0.87–4.14)	1.32 (0.76–2.29)
Mortality				
Number of events (%)	153 (1.1)	56 (1.5)	59 (3.1)	169 (1.5)
HR (95% CI)	1 (ref)	1.21 (0.89–1.65)	1.97 (1.45–2.67)	1.18 (0.94–1.47)
Multivariate-adjusted HR (95% CI)[a]	1 (ref)	1.18 (0.87–1.61)	1.96 (1.45–2.65)	1.19 (0.96–1.48)

[a] Adjusted for baseline age, sex, smoking, alcohol drinking, physical activities, and LDL-cholesterol level.

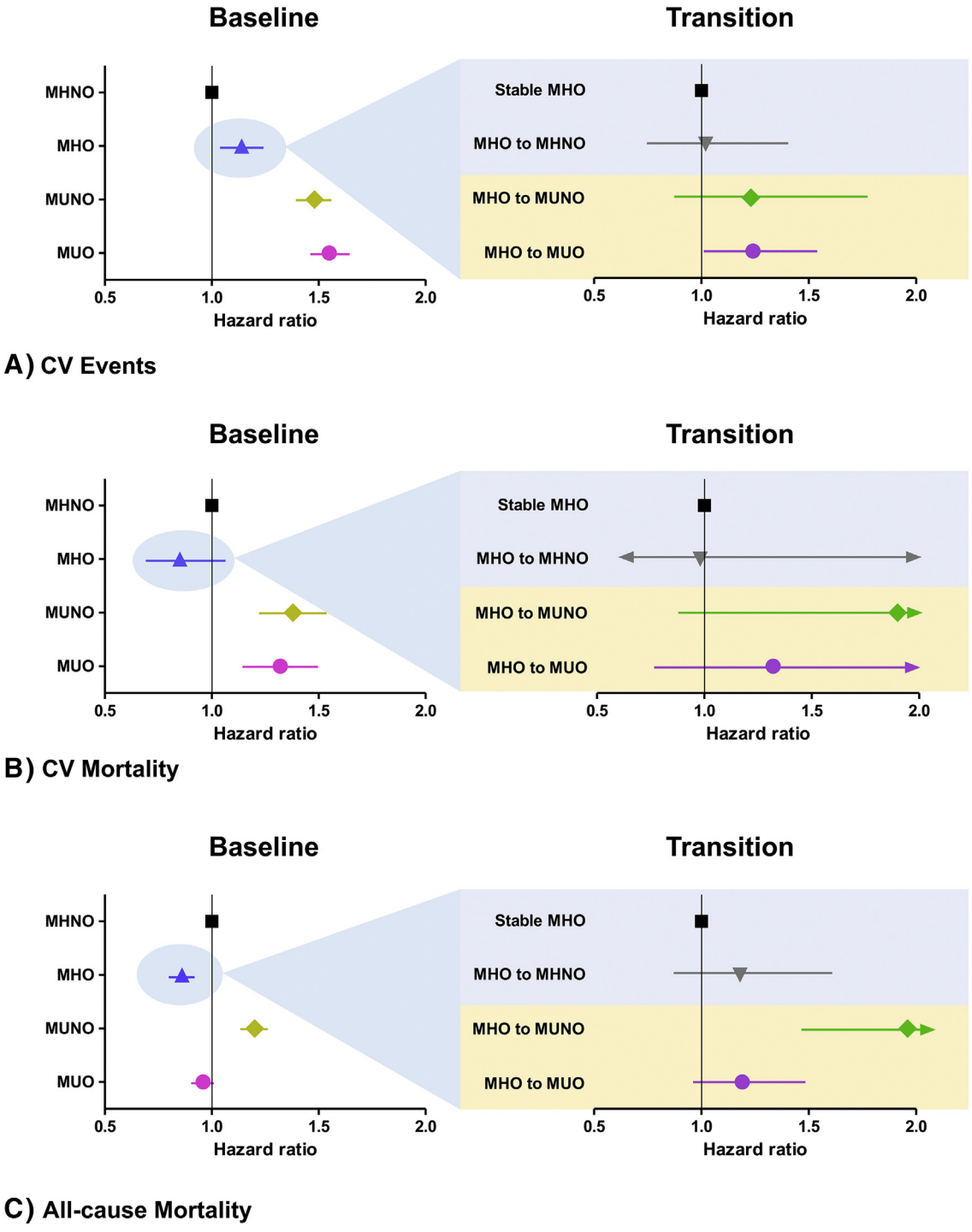

Fig. 1. Summarized figure of association of metabolically healthy obesity with CV events, CV mortality, and all-cause mortality.

adverse CV outcomes in a population who had progressed from MHO to a metabolically unhealthy phenotype [24–26]. In accordance with these previous studies, our results showed that MHO at baseline does not guarantee low CV risk for individuals, especially those who later transition to a metabolically unhealthy phenotype.

When we compared the outcomes among groups with the MHNO group as a reference, all of the risk of CV event, the CV mortality and all-cause mortality were significantly increased in the metabolically unhealthy groups (i.e. the subjects with the MUNO or the MUO at baseline; Table S6). Furthermore, in our additional analyses with the baseline MHNO subjects, the transition from metabolic healthy status to unhealthy phenotype was associated with adverse CV outcomes (Fig. 2 and Table S3). In the baseline MUNO subjects, the recovery of metabolic health was significantly related to decreased risk for incidence CV events (Fig. 2 and Table S4). Furthermore, in the baseline MUO group, the recovery of metabolic health significantly decreased all-cause mortality (Fig. 2 and Table S5). These findings strongly highlight the importance of metabolic health.

The term "obesity paradox" was introduced as a concept explaining that, although higher BMI is related to increased rates of hypertension, dyslipidemia, type 2 diabetes, and CVD, obese individuals with these conditions may have better outcomes than leaner individuals [27,28]. Similarly, individuals classified as normal weight or underweight may have a poorer prognosis than overweight persons with respect to CVD,

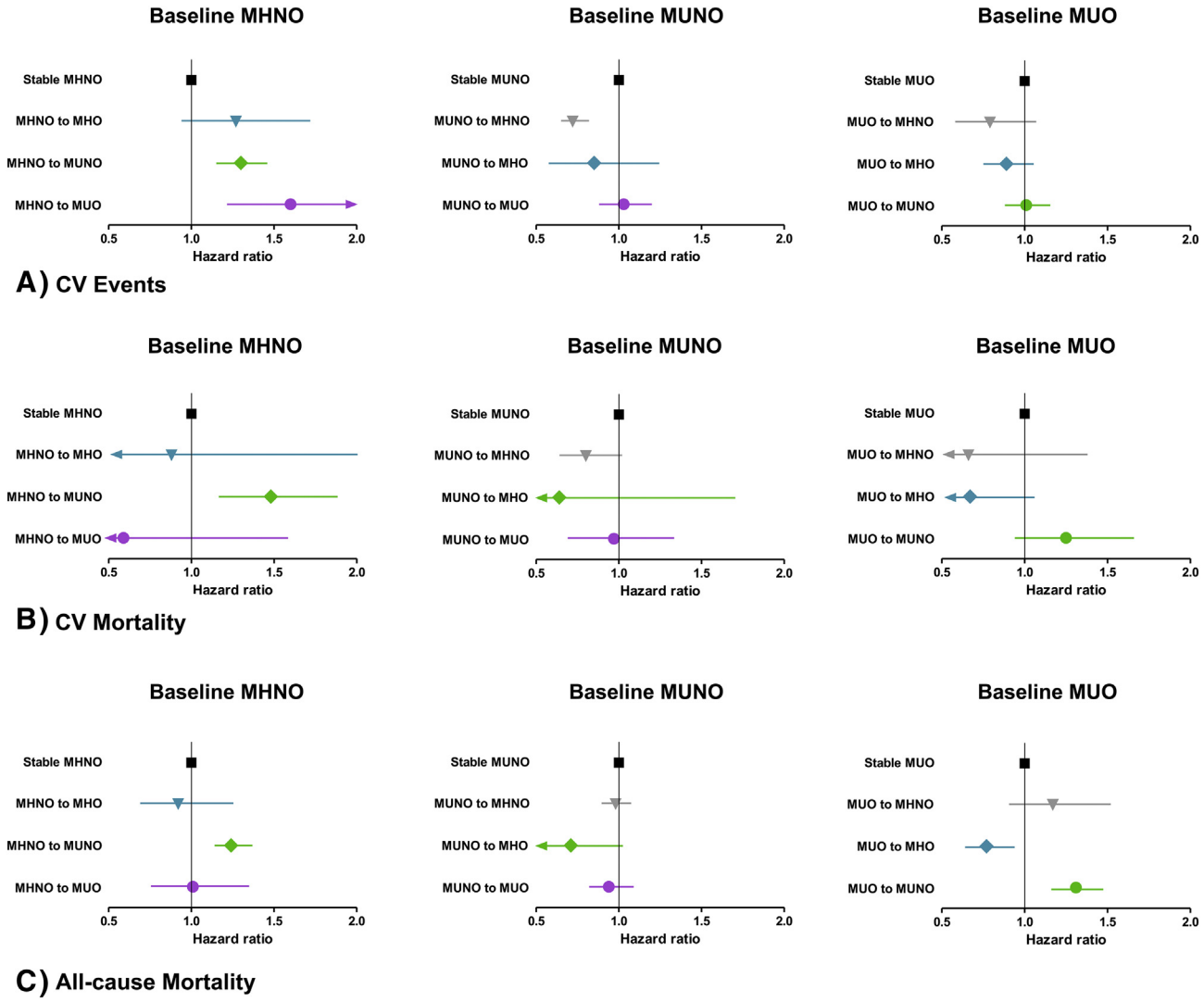

Fig. 2. Risks of CV events, CV mortality, and all-cause mortality in participants with MHNO, MUNO and MUO at baseline according to 2 year metabolic health and obesity status.

a condition termed the "lean paradox" [29]. Better outcomes in obese populations, or poorer prognoses in lean subjects, may result from a progressive catabolic state and loss of lean mass [29]. Additionally, as obesity is well known as a cardiometabolic risk factor, higher pretest probability for CVD and earlier diagnostic testing in obese individuals could lead to earlier testing and earlier diagnosis, which could result in increased survival [29,30]. Previous studies have reported that obesity is associated with a better prognosis for coronary heart disease patients in secondary care, on the contrary to that in the primary care [30–32]. This discrepancy could be attributed to earlier diagnosis and earlier medical intervention for CVD in obese population, which could be coined the obesity paradox. Similarly, the present study found that, although CV event incidence was higher in obese subjects regardless of their metabolic health status, all-cause mortality in obese subjects was similar to or lower than in non-obese healthy individuals. Moreover, the comparison of the all-cause mortality using the MHO group as a reference showed the higher mortality in the MHNO group than in the MHO group, which provides additional evidence of "lean paradox" (Table S6).

All-cause mortality in the baseline MHO cohort varied widely and was dependent on changes in metabolic status and body weight. Having MHO at baseline was not associated with increased mortality compared to having MHNO. However, these results may have obscured the heterogeneity of the MHO group. Individuals who transitioned from the MHO to the MUNO group, thus transitioning to a metabolically unhealthy status and losing weight simultaneously, had higher all-cause mortality than the stable MHO group (Table 2). Our additional analyses setting the MHO to MHNO group as a reference also showed that evolving to metabolically unhealthy phenotype with weight loss in subjects is significantly associated with increased mortality (Table S7). This finding supports the "lean paradox", as well as highlighting the highly heterogeneous nature of the MHO population. Moreover, the transition from obesity to non-obesity, or weight loss, was related to poor prognosis in the baseline MUO subjects, as well as the baseline MHO group. Interestingly, the transition to MUNO was associated with significantly increased all-cause mortality while the transition to MHO decreased all-cause mortality (Fig. 2 and Table S5). These results additionally support the "lean paradox".

This study had several limitations. Our definition of metabolic health was based on ATP III criteria; therefore, stricter or broader criteria of MHO may have yielded different results. Secondly, this study may not be powered to fully assess interactions, due to the small numbers of events and short duration of follow-up. As our study population mainly consisted of Koreans, generalizability to other ethnic groups is limited. Finally, although we adjusted for CV risk factors, there may have been other confounding variables. For example, all-cause mortality was increased although CV event incidence and CV mortality were not increased in subjects who transitioned from MHO to MUNO. Therefore,

particularly in this group, additional, non-CVD factors may have been associated with mortality; identification of these factors may be necessary to understand why estimates of these outcomes differed. Additionally, in lean subjects, it has been reported that cardimetabolic risk factors such as high glucose or dyslipidemia are more strongly associated with a relatively low leg fat mass than with central obesity [33]. Therefore, in the MUNO subjects, a disproportionate body fat distribution such as low extremity fat mass could have contributed to the poor prognosis of the group. However, we could not assess the body composition in our study subjects.

However, the aforementioned limitations are compensated for several strengths including a novel approach we used. For the first time in Asia, to our knowledge, we demonstrated the heterogeneity of MHO population using a large and national sample of subjects. Secondly, we focused on the separate implications of transition to metabolically unhealthy status and weight change in individuals with MHO at baseline. This approach showed that catabolic state, as represented by weight loss, may be a powerful predictor of poor patient prognosis. Further research on the therapeutic intervention against progression to metabolically unhealthy phenotype would help to improve the health outcomes of obesity.

In conclusion, our findings suggest that subjects with MHO are a heterogeneous group. Subjects with MHO can convert to a metabolically unhealthy phenotype over time, a transition associated with an increased incidence of CV events. Furthermore, weight loss is a predictor of increased mortality in MHO patients who develop a metabolically unhealthy phenotype.

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Disclosure of interest

The authors declare that they have no conflicting interest.

Author contributions

CHJ conceived this study. YKC and CHJ contributed to the design of the study. YKC, YMK, JHY and JL conducted data collection. YKC and YJK conducted the analysis. JYP, WJL, YKC, YJK and CHJ interpreted the results. YKC wrote the initial draft of the manuscript, with revisions by all authors. The final manuscript was approved by all authors. YKC, YJK and CHJ are the guarantors of this work.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2019.05.002.

References

[1] Kivimaki M, Kuosma E, Ferrie JE, Luukkonen R, Nyberg ST, Alfredsson L, et al. Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120 813 adults from 16 cohort studies from the USA and Europe. Lancet Public Health 2017;2:e277-e85.
[2] Stefan N, Haring HU, Schulze MB. Metabolically healthy obesity: the low-hanging fruit in obesity treatment? Lancet Diabetes Endocrinol 2018;6:249–58.
[3] Jung CH, Lee WJ, Song KH. Metabolically healthy obesity: a friend or foe? Korean J Intern Med 2017;32:611–21.
[4] Brochu M, Tchernof A, Dionne IJ, Sites CK, Eltabbakh GH, Sims EA, et al. What are the physical characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? J Clin Endocrinol Metab 2001;86:1020–5.
[5] Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. Eur J Prev Cardiol 2016;23:956–66.
[6] Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, et al. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. J Am Coll Cardiol 2017;70:1429–37.
[7] Soriguer F, Gutierrez-Repiso C, Rubio-Martin E, Garcia-Fuentes E, Almaraz MC, Colomo N, et al. Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study. J Clin Endocrinol Metab 2013;98:2318–25.
[8] Appleton SL, Seaborn CJ, Visvanathan R, Hill CL, Gill TK, Taylor AW, et al. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. Diabetes Care 2013;36:2388–94.
[9] Lee SH, Yang HK, Ha HS, Lee JH, Kwon HS, Park YM, et al. Changes in metabolic health status over time and risk of developing type 2 diabetes: a prospective cohort study. Medicine (Baltimore) 2015;94:e1705.
[10] Hamer M, Bell JA, Sabia S, Batty GD, Kivimaki M. Stability of metabolically healthy obesity over 8 years: the English Longitudinal Study of Ageing. Eur J Endocrinol 2015;173:703–8.
[11] Bell JA, Hamer M, Sabia S, Singh-Manoux A, Batty GD, Kivimaki M. The natural course of healthy obesity over 20 years. J Am Coll Cardiol 2015;65:101–2.
[12] Lavie CJ, De Schutter A, Milani RV. Healthy obese versus unhealthy lean: the obesity paradox. Nat Rev Endocrinol 2015;11:55–62.
[13] Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: a systematic review and meta-analysis. Ann Intern Med 2013;159:758–69.
[14] Lassale C, Tzoulaki I, Moons KGM, Sweeting M, Boer J, Johnson L, et al. Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis. Eur Heart J 2018;39:397–406.
[15] 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.
[16] Rutter MK, Meigs JB, Sullivan LM, D'Agostino Sr RB, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation 2004;110:380–5.
[17] Oh SW. Obesity and metabolic syndrome in Korea. Diabetes Metab J 2011;35:561–6.
[18] Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486–97.
[19] Iacobini C, Pugliese G, Blasetti Fantauzzi C, Federici M, Menini S. Metabolically healthy versus metabolically unhealthy obesity. Metabolism March 2019;92:51–60.
[20] Guo F, Garvey WT. Cardiometabolic disease risk in metabolically healthy and unhealthy obesity: stability of metabolic health status in adults. Obesity (Silver Spring) 2016;24:516–25.
[21] Morkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trondelag Health Study), Norway. J Am Coll Cardiol 2014;63:1071–8.
[22] Bell JA, Hamer M, Batty GD, Singh-Manoux A, Sabia S, Kivimaki M. Incidence of metabolic risk factors among healthy obese adults: 20-year follow-up. J Am Coll Cardiol 2015;66:871–3.
[23] Navarro-Gonzalez D, Sanchez-Inigo L, Fernandez-Montero A, Pastrana-Delgado J, Alfredo Martinez J. Are all metabolically healthy individuals with obesity at the same risk of diabetes onset? Obesity (Silver Spring) 2016;24:2615–23.
[24] Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. Lancet Diabetes Endocrinol 2018;6:714–24.
[25] Mongraw-Chaffin M, Foster MC, Anderson CAM, Burke GL, Haq N, Kalyani RR, et al. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol 2018;71:1857–65.
[26] Kouvari M, Panagiotakos DB, Yannakoulia M, Georgousopoulou E, Critselis E, Chrysohoou C, et al. Transition from metabolically benign to metabolically unhealthy obesity and 10-year cardiovascular disease incidence: the ATTICA cohort study. Metabolism April 2019;93:18–24.
[27] Goyal A, Nimmakayala KR, Zonszein J. Is there a paradox in obesity? Cardiol Rev 2014;22:163–70.
[28] Ma WQ, Sun XJ, Wang Y, Han XQ, Zhu Y, Liu NF. Does body mass index truly affect mortality and cardiovascular outcomes in patients after coronary revascularization with percutaneous coronary intervention or coronary artery bypass graft? A systematic review and network meta-analysis. Obes Rev 2018;19:1236–47.
[29] Elagizi A, Kachur S, Lavie CJ, Carbone S, Pandey A, Ortega FB, et al. An overview and update on obesity and the obesity paradox in cardiovascular diseases. Prog Cardiovasc Dis 2018;61:142–50.
[30] De Schutter A, Lavie CJ, Milani RV. The impact of obesity on risk factors and prevalence and prognosis of coronary heart disease-the obesity paradox. Prog Cardiovasc Dis 2014;56:401–8.
[31] Lavie CJ, Milani RV. Obesity and cardiovascular disease: the Hippocrates paradox? J Am Coll Cardiol 2003;42:677–9.
[32] Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363:2211–9.
[33] Stefan N, Schick F, Haring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab 2017;26:292–300.