Impact of Metabolically Healthy Obesity vs. Non-Obese but Metabolic Syndrome on CVD

Seong Hwan Kim, MD, PhD

Division of Cardiology

Korea University Ansan Hospital

Presenter Disclosure Information

Seong Hwan Kim, MD, PhD

Impact of Metabolically Healthy Obesity vs. Non-Obese but Metabolic Syndrome on CVD

DISCLOSURE INFORMATION:

No relationship exists related to this presentation

C…of CV risk factors…ease?

nature
International weekly journal of science

NATURE | OUTLOOK

Perspective: Obesity is not a disease

D. L. Katz

Nature **508**, S57 (17 April 2014) | doi:10.1038/508S57a
Published online 16 April 2014

The misguided urge to pathologize this condition reflects society's failure to come to terms with the need for prevention, says D. L. Katz.

Subject terms: Obesity · Disease prevention

Doctors are historically ill-prepared to address the problem of obesity — with a tendency either to ignore it, or to ineffectually wag an admonishing finger[1, 2, 3]. To focus physicians' attention on this prevalent health issue, the American Medical Association (AMA) recently declared obesity to be a disease. This well-intentioned move by the AMA is misguided in that it implies that tens of millions of people must now have bodies or minds, or both, that are not working properly. Even seemingly healthy, but heavy, people — adults and children alike — are now, by definition, diseased[4]. Imposing such a status has broad ramifications for society and requires careful reflection.

had stud…

"Recognizing obesity a…

Editors' pick

Image credit: Denis Carrier

LGBT in science: Gay rights is civil rights issue of the year in the US; but even in liberal academia, there are enormous barriers for this community. ▸

Science jobs | Science events

nature events directory

3rd Max Planck Freiburg Epigenetics Meeting

European Heart Journal
doi:10.1093/eurheartj/ehv509

REVIEW

Controversies in cardiovascular medicine

Obesity and cardiovascular disease: friend or foe?

Seong Hwan Kim[1], Jean-Pierre Després[2], and Kwang Kon Koh[3,4]*

[1]Division of Cardiology, Korea University Ansan Hospital, Ansan, Republic of Korea; [2]Department of Kinesiology, Faculty of Medicine, Quebec Heart and Lung Institute, Université Laval, Quebec, Canada; [3]Division of Cardiology, Department of Cardiovascular Medicine, Heart Center, Gachon University Gil Medical Center, 774 Beongil 21, Namdongdaero, Namdong-Gu, Incheon 405-760, Republic of Korea; and [4]Gachon Cardiovascular Research Institute, Incheon, Republic of Korea

Received 23 May 2015; revised 26 August 2015; accepted 7 September 2015

Obesity is currently one of the greatest public health issues worldwide. However, despite its known deleterious effects on the cardiovascular system and its association with numerous cardiovascular diseases (CVD), recent findings leading to the development of concepts such as metabolically healthy obesity, the obesity paradox, and protective subcutaneous fat depots have raised a lively debate on the disparate effects of obesity on health outcomes. Regarding the concept of metabolically healthy obesity, by presumably labelling a subset of obese people as metabolically healthy, physicians may not feel pressed to curb the current obesity epidemic and prevent the next generation of people from becoming obese. Another issue is that the most commonly used anthropometric index to define obesity, the body mass index, is at the core of the controversy because of its limitations including its inability to discriminate between fat mass and muscle mass. Many recent epidemiological and metabolic studies have used other indices such as waist–hip ratio, waist circumference, and imaging (computed tomography or magnetic resonance imaging) measurements of visceral adiposity and of ectopic fat depots. In addition, emerging evidence supports the importance of cardiorespiratory fitness, skeletal muscle mass and strength in patients with obesity as useful variables to predict CVD risk beyond adiposity. In this review, we will discuss the complex and disparate effects of obesity on CVD, particularly focusing on whether, under given circumstances, it could be harmful, potentially harmless or neutral, or even possibly protective.

Keywords Obesity • Metabolically healthy obesity • Obesity paradox • Cardiovascular disease • Cardiometabolic syndrome

Eur Heart J. 2015 Dec 18. [Epub ahead of print]

Obesity diagnosis

WHO BMI cut-off points

	International Classification	Asian Population
Severe Underweight	< 16 kg/m^2	
Moderate Underweight	16.0 – 16.9 kg/m^2	
Mild Underweight	17.0 – 18.4 kg/m^2	≤ 18.4 kg/m^2
Normal Weight	18.5 – 24.9 kg/m^2	18.5 – 23.0 kg/m^2
Overweight	25.0 – 29.9 kg/m^2	23.0 – 27.4 kg/m^2
Obese Class I	30.0 – 34.9 kg/m^2	≥ 27.5 kg/m^2
Obese Class II	35.0 – 39.9 kg/m^2	
Obese Class III	> 40.0 kg/m^2	

WHO Expert Consultation. Lancet 2004;363:157-163

Obesity diagnosis

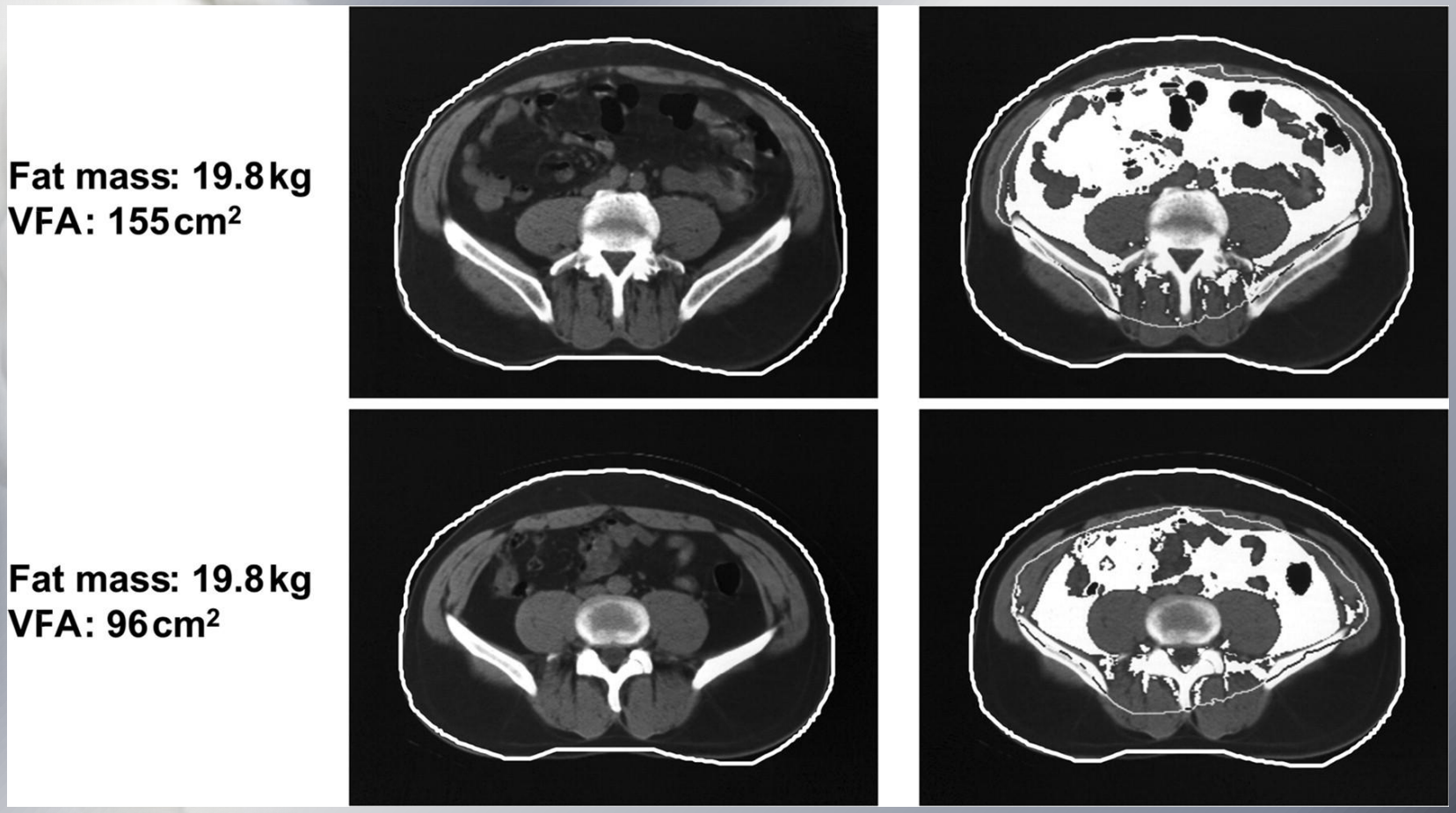
Waist circumference cut-off values

IDF criteria		
	Male	Female
European	94 cm	80 cm
South Asians	90 cm	80 cm
Chinese	90 cm	80 cm
Japanese	85 cm	90 cm
AHA/NHLBI criteria		
	Male	Female
Non-Asian Americans	102	88 cm
Asian Americans	90	80 cm
Korean Society for the Study of Obesity		
	Male	Female
Korean	90 cm	85 cm

Obesity diagnosis

Visceral fat

CT scans from two subjects with comparable BMI illustrating adiposity phenotypes characterized mainly by intra-abdominal adiposity (top panels) and subcutaneous adiposity (bottom panels).



Després JP. Can J Cardiol 2015;31:216-222

Obesity & Mortality

The NEW ENGLAND JOURNAL of MEDICINE

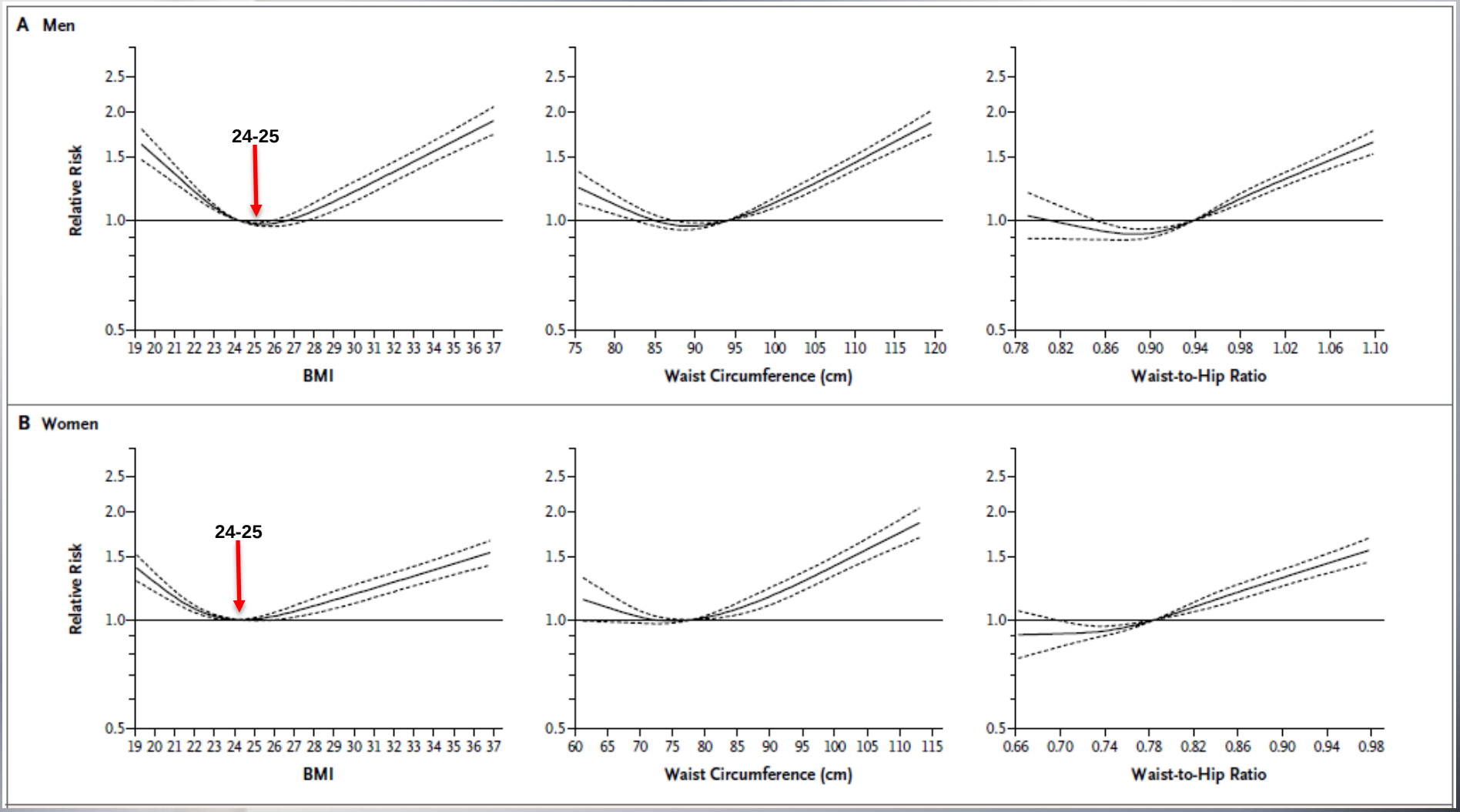
N Engl J Med 2008;359:2105-2120

ORIGINAL ARTICLE

General and Abdominal Adiposity and Risk of Death in Europe

T. Pischon, M.D., M.P.H., H. Boeing, Ph.D., M.S.P.H., K. Hoffmann, Ph.D.,*
M. Bergmann, Ph.D., M.B. Schulze, Dr.P.H., K. Overvad, M.D., Ph.D.,
Y.T. van der Schouw, Ph.D., E. Spencer, Ph.D., K.G.M. Moons, Ph.D.,
A. Tjønneland, M.D., Ph.D., Dr.Med.Sci., J. Halkjaer, Ph.D., M.K. Jensen, Ph.D.,
J. Stegger, M.D., F. Clavel-Chapelon, Ph.D., M.-C. Boutron-Ruault, Ph.D.,
V. Chajes, Ph.D., J. Linseisen, Ph.D., R. Kaaks, Ph.D., A. Trichopoulou, M.D., Ph.D.,
D. Trichopoulos, M.D., Ph.D., C. Bamia, Ph.D., S. Sieri, Ph.D., D. Palli, M.D.,
R. Tumino, M.D., P. Vineis, M.D., M.P.H., S. Panico, M.D., M.Sc.,
P.H.M. Peeters, M.D., Ph.D., A.M. May, Ph.D.,
H.B. Bueno-de-Mesquita, M.D., Ph.D., M.P.H., F.J.B. van Duijnhoven, Ph.D.,
G. Hallmans, M.D., L. Weinehall, M.D., Ph.D., J. Manjer, M.D., Ph.D.,
B. Hedblad, M.D., Ph.D., E. Lund, M.D., Ph.D., A. Agudo, Ph.D., L. Arriola, Ph.D.,
A. Barricarte, Ph.D., C. Navarro, M.D., Ph.D., C. Martinez, M.D., J.R. Quirós, M.D.,
T. Key, D.Phil., S. Bingham, Ph.D., K.T. Khaw, M.B., B.Chir., P. Boffetta, M.D., M.P.H.,
M. Jenab, Ph.D., P. Ferrari, Ph.D., and E. Riboli, M.D., M.P.H., Sc.M.

Obesity & Mortality



N Engl J Med 2008;359:2105-2120

Obesity & Mortality

ORIGINAL ARTICLE

Body-Mass Index and Mortality in Korean Men and Women

Sun Ha Jee, Ph.D., Jae Woong Sull, Ph.D., Jungyong Park, Ph.D., Sang-Yi Lee, M.D., Heechoul Ohrr, M.D., Eliseo Guallar, M.D., Dr.P.H., and Jonathan M. Samet, M.D.

ABSTRACT

BACKGROUND

Obesity is associated with diverse health risks, but the role of body weight as a risk factor for death remains controversial.

METHODS

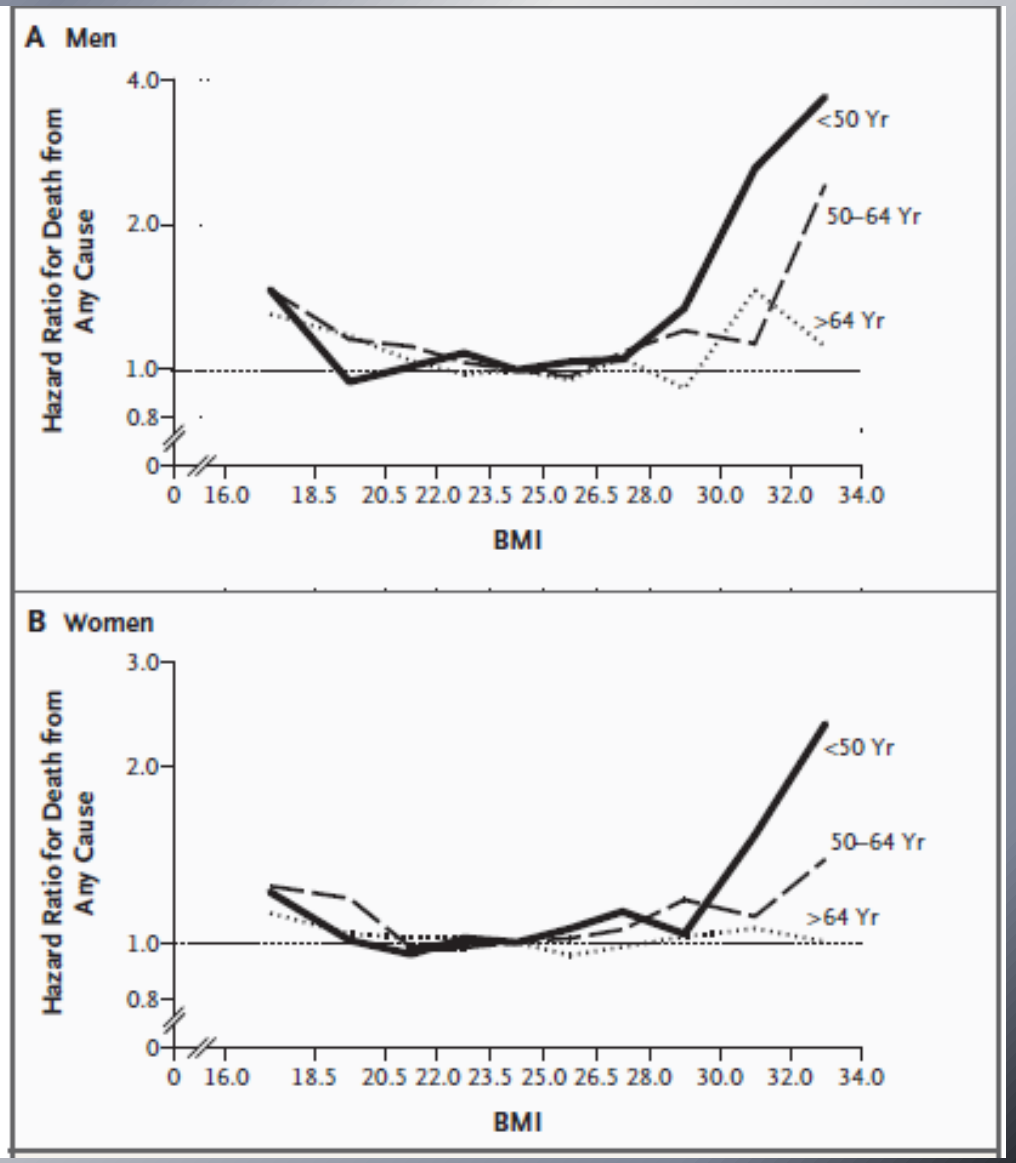
We examined the association between body weight and the risk of death in a 12-year prospective cohort study of 1,213,829 Koreans between the ages of 30 and 95 years. We examined 82,372 deaths from any cause and 48,731 deaths from specific diseases (including 29,123 from cancer, 16,426 from atherosclerotic cardiovascular disease, and 3362 from respiratory disease) in relation to the body-mass index (BMI) (the weight in kilograms divided by the square of the height in meters).

RESULTS

In both sexes, the average baseline BMI was 23.2, and the rate of death from any cause had a J-shaped association with the BMI, regardless of cigarette-smoking history. The risk of death from any cause was lowest among patients with a BMI of 23.0 to 24.9. In all groups, the risk of death from respiratory causes was higher among subjects with a lower BMI, and the risk of death from atherosclerotic cardiovascular disease or cancer was higher among subjects with a higher BMI. The relative risk of death associated with BMI declined with increasing age.

CONCLUSIONS

Underweight, overweight, and obese men and women had higher rates of death than men and women of normal weight. The association of BMI with death varied according to the cause of death and was modified by age, sex, and smoking history.



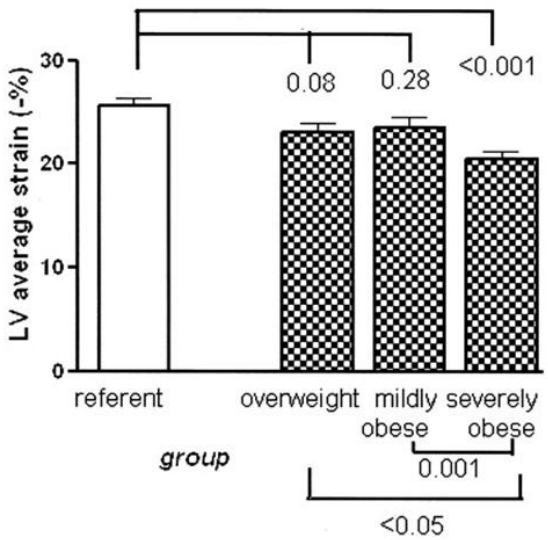
N Engl J Med 2006;355:779-789

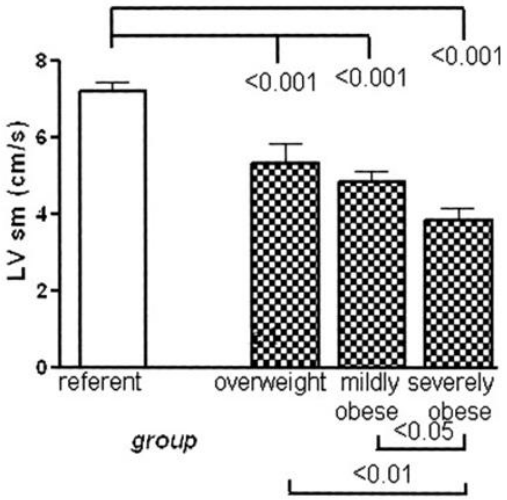
Obesity & the Heart

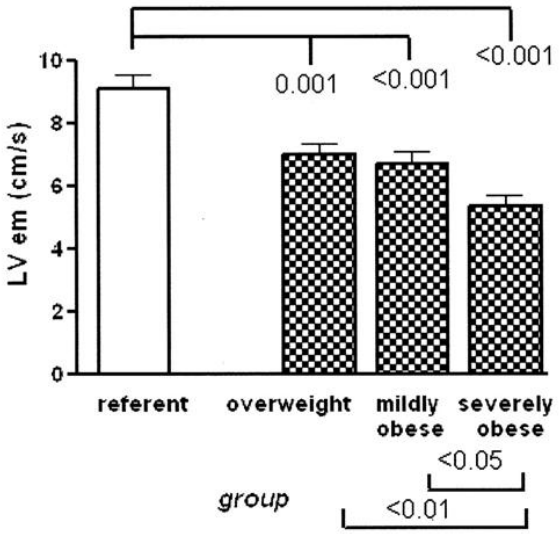
Heart Failure

Alterations of Left Ventricular Myocardial Characteristics Associated With Obesity

Chiew Y. Wong, MBBS, FRACP; Trisha O'Moore-Sullivan, MBBS, FRACP; Rodel Leano, BS; Nuala Byrne, PhD; Elaine Beller, PhD; Thomas H. Marwick, MBBS, PhD, FRACP







Based on BMI

Wong CY et al. Circulation 2004;110;3081-3087

Obesity & the Heart

Association of visceral fat area (VFA) tertiles with cardiac structure and function: multivariate analysis.

	Tertiles of VFA		
	T1 (lowest)	T2	T3 (highest)
LA size, cm	3.58 ± 0.02	3.71 ± 0.02*	3.86 ± 0.02*,†
LV mass index, g/m$^{2.7}$	40.0 ± 0.3	40.9 ± 0.3	43.5 ± 0.3*,†
LV ejection fraction, %	63.5 ± 0.2	63.6 ± 0.2	64.1 ± 0.2
Mitral E/A ratio	1.09 ± 0.01	1.01 ± 0.01*	1.01 ± 0.01*
TDI Sa, cm/s	7.51 ± 0.04	7.45 ± 0.04	7.32 ± 0.04*
TDI Ea, cm/s	7.56 ± 0.05	6.95 ± 0.05*	6.67 ± 0.05*,†
E/Ea ratio	9.08 ± 0.08	9.38 ± 0.08*	9.93 ± 0.08*,†

Based on VFA

Kim SH et al. Int J Cardiol 2014;176;951-955

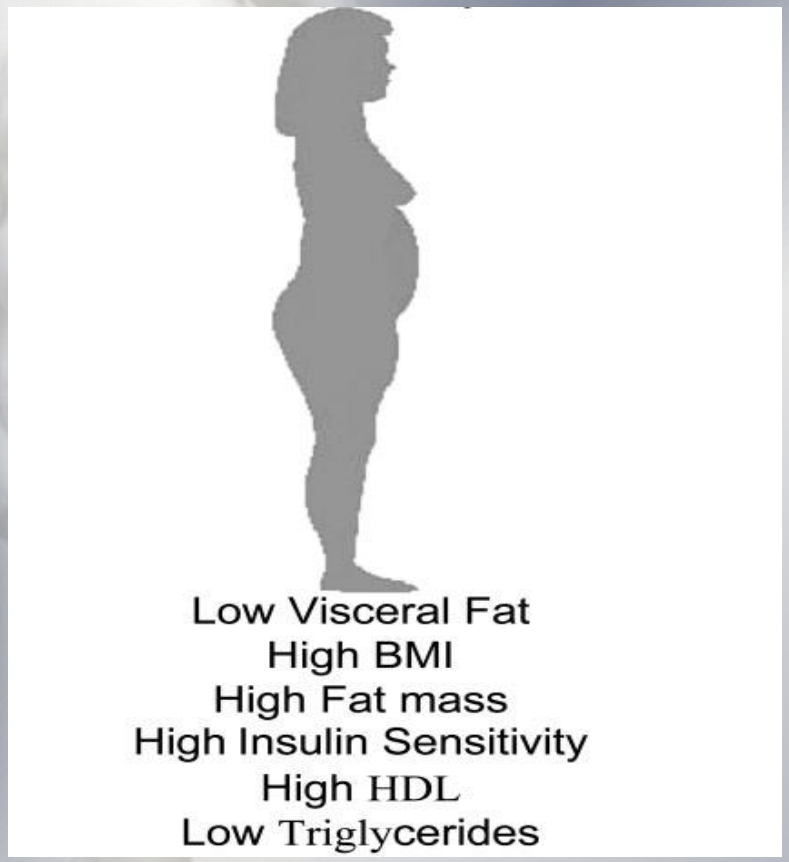
Definition of benign obesity or healthy obesity or metabolically healthy obesity (MHO)

Healthy obesity vs. at risk obesity

- Based on body mass index (BMI)
- Based on levels of insulin resistance (IR)
- Based on clustering of cardiometabolic risk factors

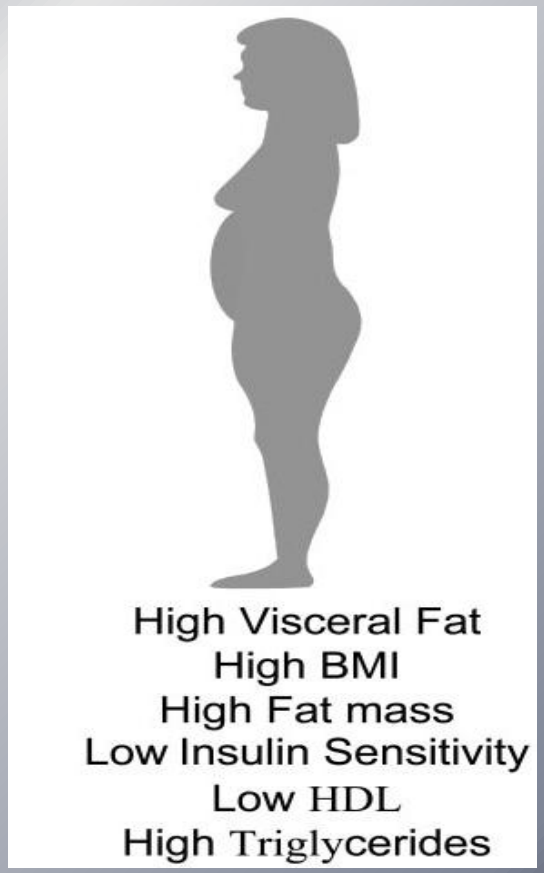
(BP, TG, CRP, HOMA, DM, HDL…)

Metabolically Healthy Obesity (MHO)



Low Visceral Fat
High BMI
High Fat mass
High Insulin Sensitivity
High HDL
Low Triglycerides

Metabolically Abormal Obesity (MAO)



High Visceral Fat
High BMI
High Fat mass
Low Insulin Sensitivity
Low HDL
High Triglycerides

V Primeau et al. Int J Obes 2011;35:971-981

Various criteria of MHO

	Meigs et al. 2006	Stefan et al. 2008	Aguilar-Salinas et al. 2008	Karelis et al. 2008	Wildman et al. 2008	Park et al. 2011
Study population	US (n=2,902, M=45%)	Germany (n=314, M=38.5%)	Mexico (n=716, M=26.4%)	Canada (n=154, M=0%)	US (n=5,440, M=47.9%)	Korea (n=2,540, M=49.6%)
Metabolic components						
WC, cm	≥102 (M) ≥88 (F)					<90 (M) <80 (F)
BP, mmHg	≥130/85 or treatment		<140/90 and no treatment		≥130/85 or treatment	<130/85 and no treatment
FPG, mg/dL	≥100 or treatment		<126 and no treatment		≥100 or treatment	<100 and no treatment
TG, mg/dL	≥150			<150	≥150	<150
HDL, mg/dL	<40 (M) <50 (F)		≥40	≥50	<40 (M) <50 (F)	≥40 (M) ≥50 (F)
HOMA-IR				<1.95	>90th percentile	
Others		WBISI >75th percentile		TC <200 mg/dL LDL <100 mg/dL	hsCRP >90th percentile	
MH criteria	<3 of the above	All of the above	All of the above	≥4 of the above	<2 of the above	All of the above

Kim SH et al. Eur Heart J. 2015 Dec 18.

MHO and Cardiovascular disease (CVD)

MHO does not associated with target organ change?

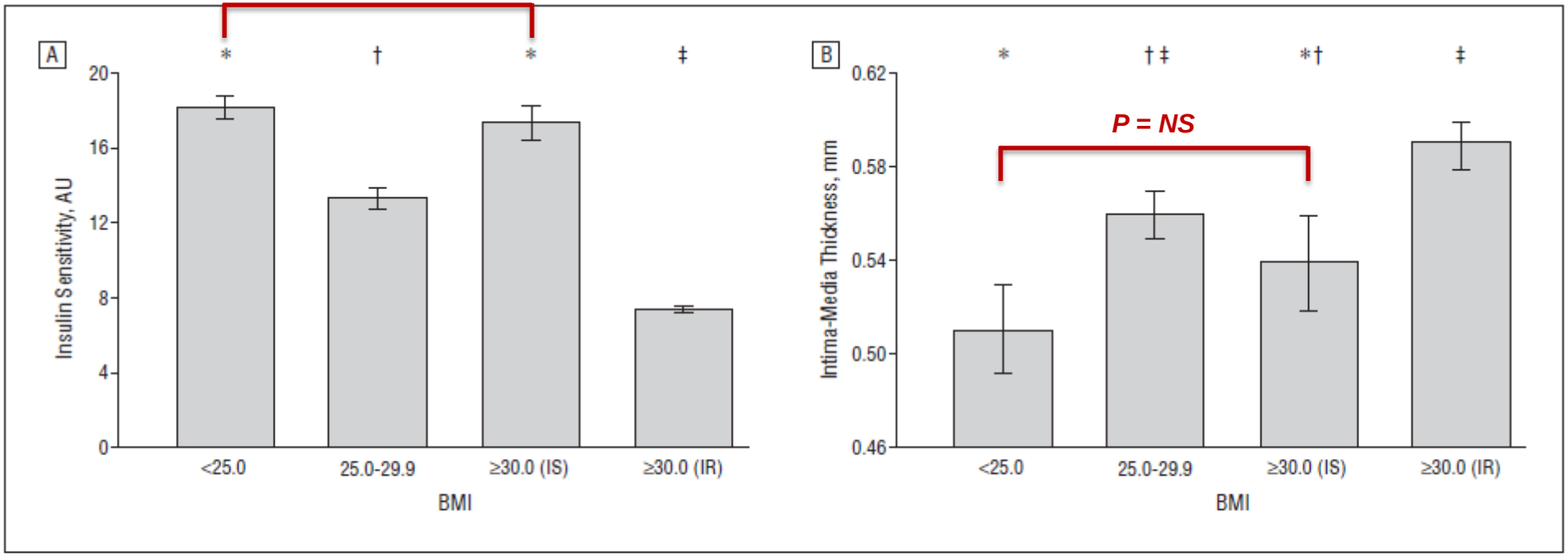
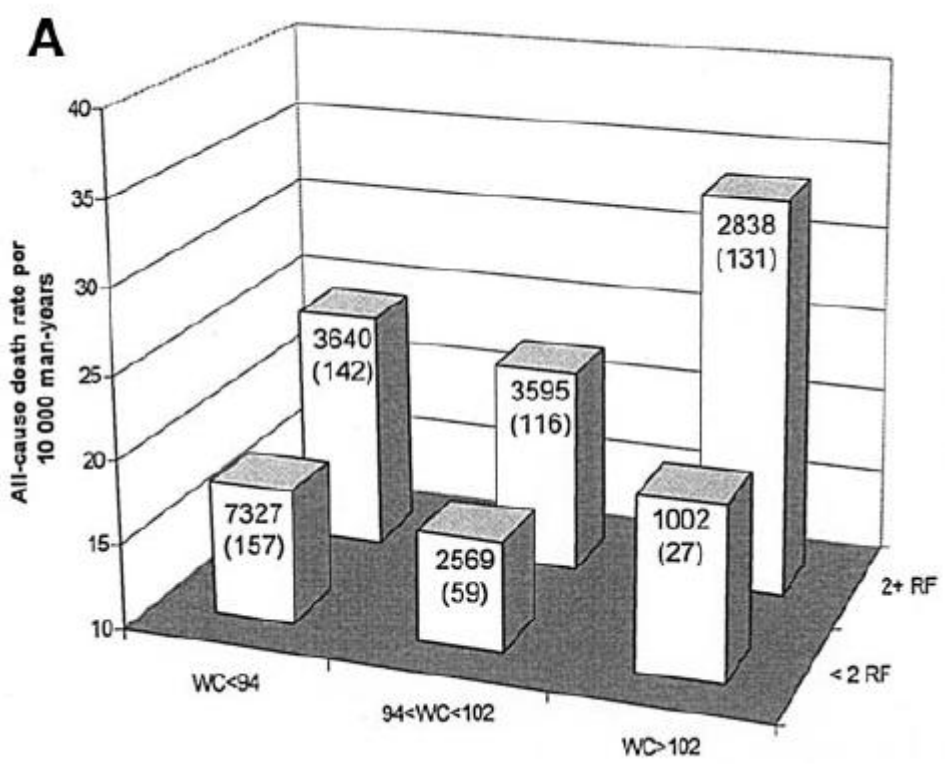


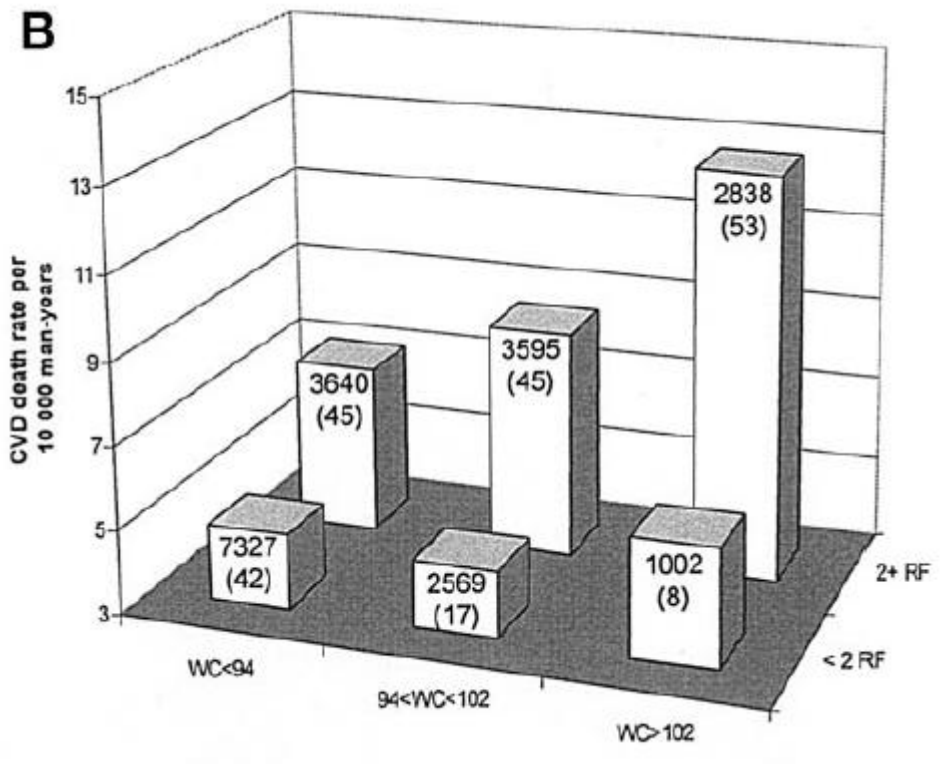
Figure 2. Insulin sensitivity (A) and intima-media thickness of the carotid artery (B) among subjects characterized for body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) and insulin sensitivity (obese individuals). Obese individuals were divided into those who were insulin sensitive (IS) (defined as being in the upper quartile of insulin sensitivity) and those who were insulin resistant (IR) (defined as being in the lower 3 quartiles of insulin sensitivity). Bars and limit lines represent mean and standard error values, respectively. Values that are not connected by the same symbol are statistically different from each other at $P < .05$ after correction for multiple comparisons.

Stefan N et al. Arch Intern Med. 2008

MHO and CVD

MHO does not increase the risk of all cause/CVD mortality?





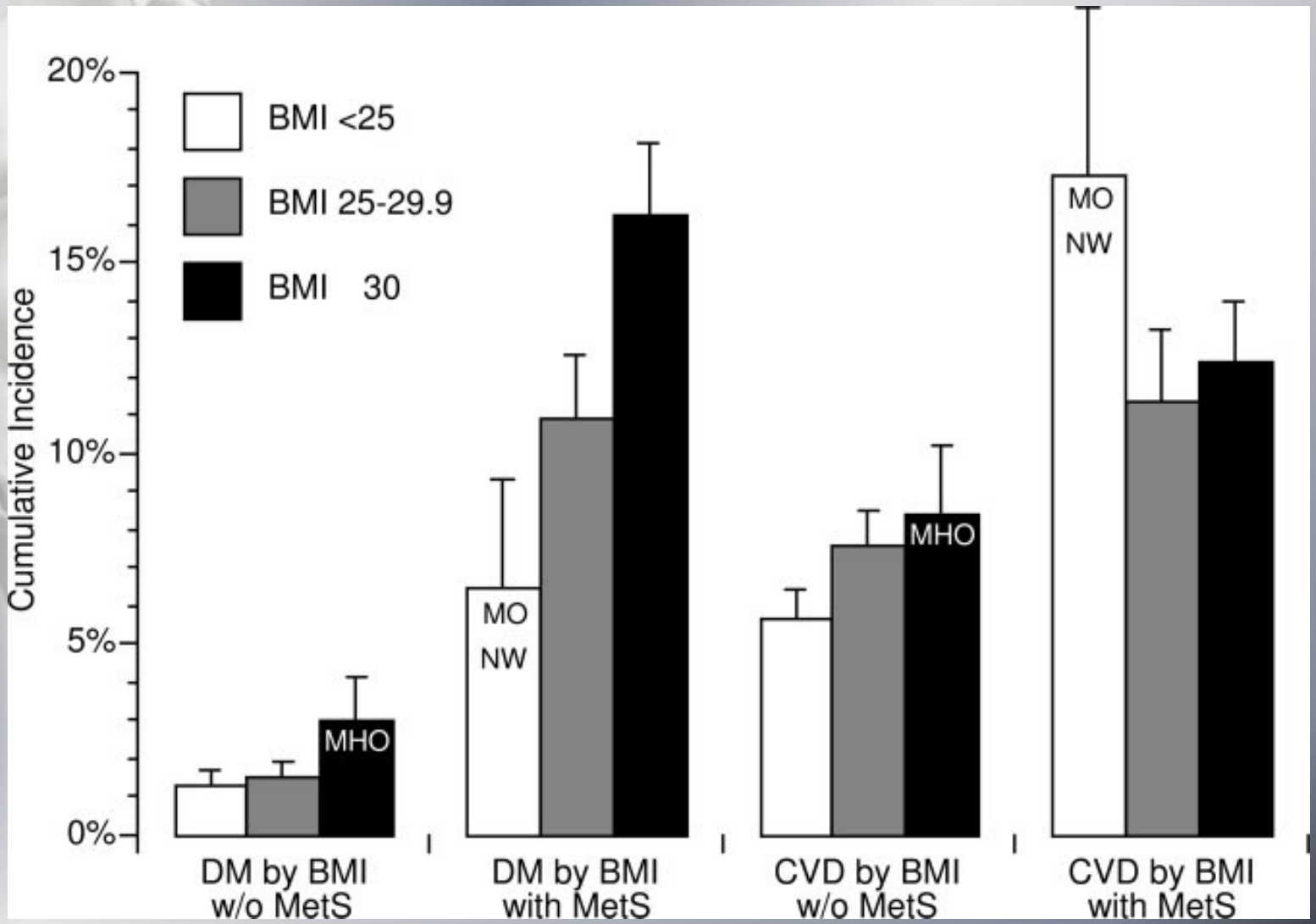
The Aerobics Center Longitudinal Study (ACLS) - 10 yrs of follow-up

Katzmarzyk PT et al. Diabetes Care 2006;29:404-409

MHO and CVD

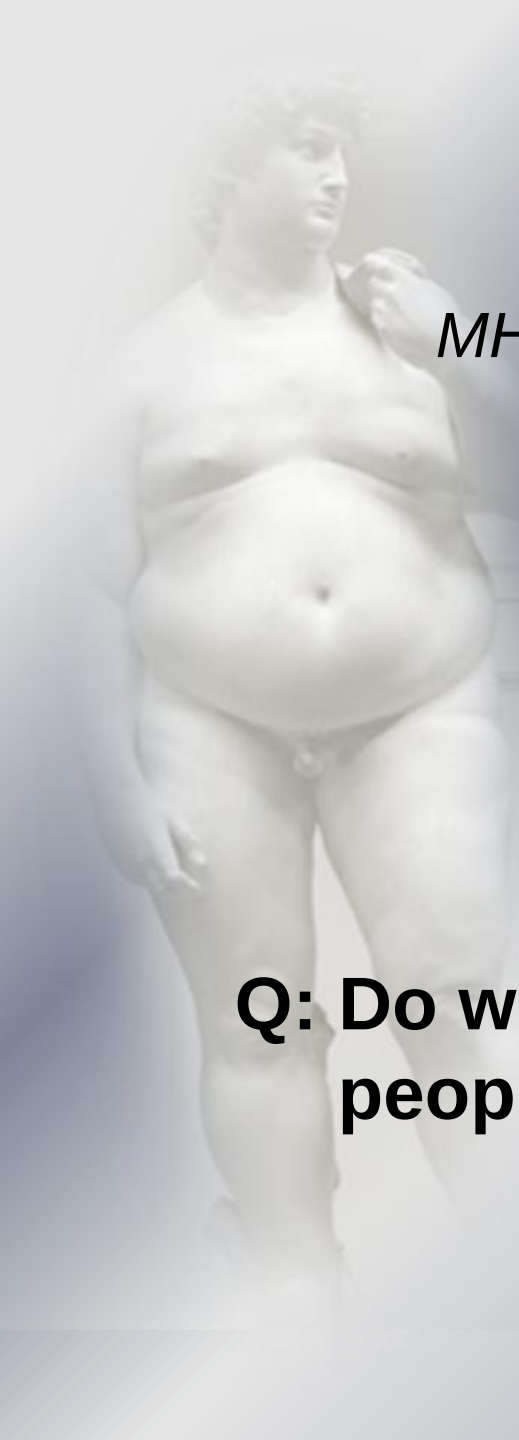
MHO does not increase the risk of DM & CVD?

11 yrs of follow-up



Meigs JB et al. J Clin Endocrinol Metab 2006;91:2906-2912

MHO and CVD



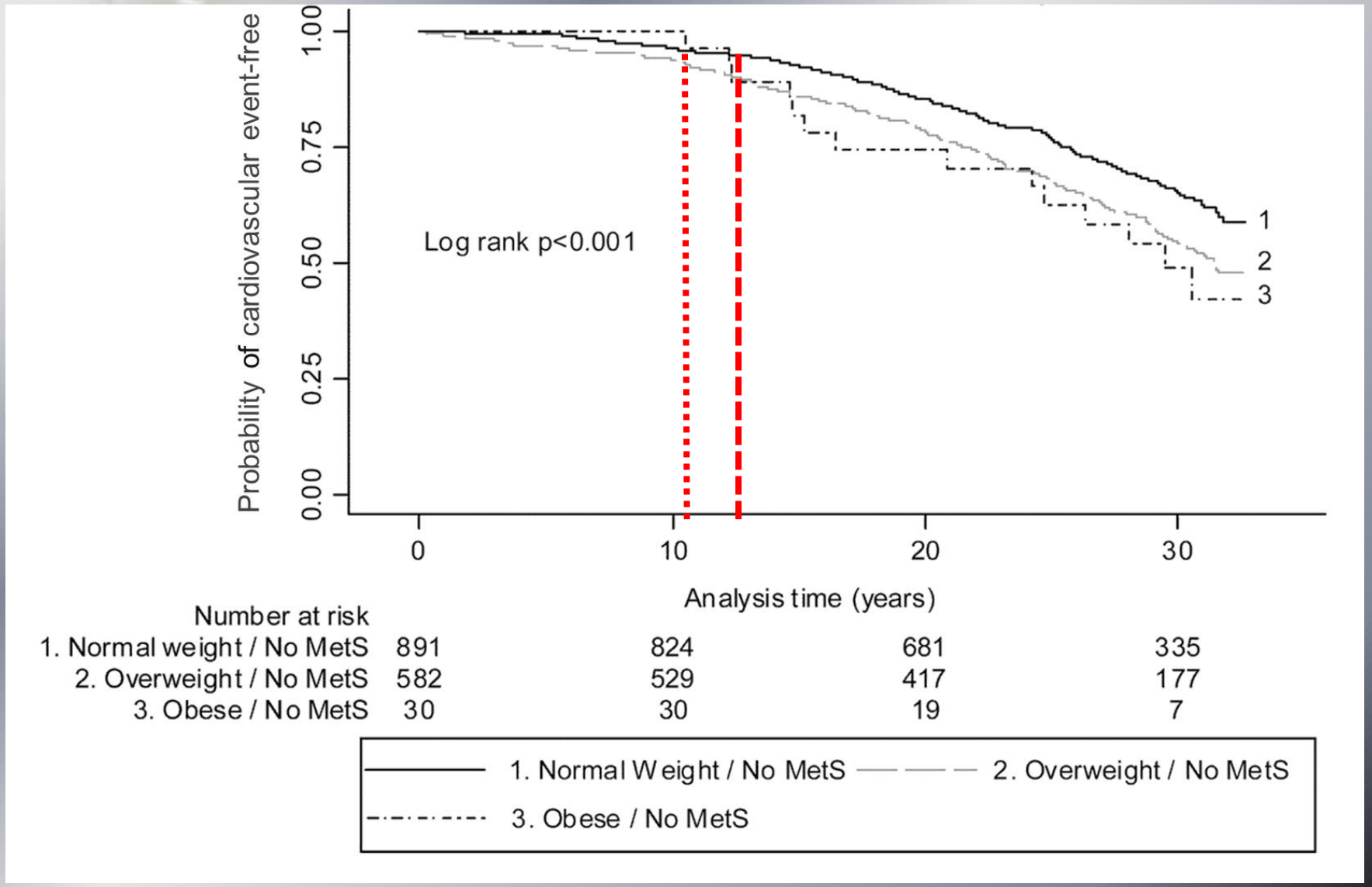
MHO does increase the risk of CVD?

Absolutely NOT

Q: Do we need to treat a subset of obese people labelled as MH differently?

MHO and CV events

Without metabolic syndrome



Arnlöv J et al. Circulation 2010;121:230-236

MHO and CVD

MHO does increase the risk of CVD?

Table 3. Deaths and Major Cardiovascular Events in Groups With Different Combinations of BMI and IR

	Normal Weight Without IR	Normal Weight With IR	Overweight Without IR	Overweight With IR	Obese Without IR	Obese With IR
Total death						
No. of events/No. at risk	290/681	137/277	196/408	154/296	17/24	51/72
Multivariable hazard ratio	Referent	1.06 (0.86–1.31)	1.22 (1.02–1.46)*	1.30 (1.06–1.59)†	2.04 (1.25–3.32)†	2.21 (1.64–2.99)‡
Cardiovascular death						
No. of events/No. at risk	112/681	65/277	86/408	91/296	6/24	26/72
Multivariable hazard ratio	Referent	1.23 (0.90–1.69)	1.36 (1.02–1.80)*	1.88 (1.42–2.50)‡	1.80 (0.79–4.08)	2.87 (1.87–4.42)‡
Major cardiovascular events						
No. of events/No. at risk	214/681	104/277	166/408	145/296	12/24	40/72
Multivariable hazard ratio	Referent	1.15 (0.90–1.46)	1.44 (1.18–1.77)‡	1.73 (1.39–2.14)‡	1.91 (1.07–3.41)*	2.56 (1.83–3.60)‡

30 yrs of follow-up

Arnlöv J et al. Circulation 2010;121:230-236

MHO and CV changes

Obesity phenotype and cardiovascular changes

Juri Park[a], Seong H. Kim[b], Goo-Yeong Cho[c], Inkyung Baik[d], Nan H. Kim[e], Hong E. Lim[f], Eung J. Kim[f], Chang G. Park[f], Sang Y. Lim[b], Yong H. Kim[b], Hyun Kim[g], Seung K. Lee[g] and Chol Shin[g]

Objective Healthy obese phenotype with favorable metabolic profiles is proposed. However, whether healthy obesity leads to target organ changes is controversial. We investigated the impact of a healthy obesity on cardiovascular structure and function.

Methods A total of 2540 participants without known cardiovascular disease were enrolled. According to BMI and the metabolic syndrome (MetS) component, the participants were divided into six groups: healthy (none of five MetS components) normal weight (BMI <23 kg/m^2), unhealthy (one or more of five MetS components) normal weight, healthy overweight (BMI 23–24.9 kg/m^2), unhealthy overweight, healthy obesity (BMI ≥25 kg/m^2), and unhealthy obesity. The cardiovascular changes were assessed by echocardiography, tissue Doppler imaging (TDI), carotid ultrasonography, and pulse wave velocity (PWV).

Results In a multivariate analysis after adjusting for age, sex, heart rate, high-sensitivity C-reactive protein, and medication for hypertension and diabetes mellitus, the unhealthy overweight and obese groups showed statistically significant changes in the left ventricular mass index, mitral E/A ratio, E/Ea ratio, TDI Ea velocity, common carotid artery intima–media thickness (CCA-IMT), and brachial-ankle PWV ($P<0.001$), compared with the healthy normal weight individuals. In the healthy overweight and obese groups, CCA-IMT and brachial-ankle PWV values were similar, but left-ventricular mass index and TDI Ea velocity were significantly different ($P<0.001$).

Conclusion Healthy obesity was associated with subtle changes in left ventricular structure and function. These data provide evidence that metabolically healthy phenotypes with excess weight may not be a benign condition. *J Hypertens* 29:1765–1772 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Journal of Hypertension 2011, 29:1765–1772

Keywords: arterial stiffness, carotid intima-media thickness, echocardiography, left ventricle, metabolic syndrome, obesity

Abbreviations: CCT-IMT, common carotid artery intima-media thickness; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment Insulin Resistance Index; hs-CRP, high-sensitivity C-reactive protein; LV, left ventricle; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; MetS, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; PWV, pulse wave velocity; TDI, tissue Doppler imaging

[a]Division of Endocrinology, Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, [b]Division of Cardiology, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, [c]Division of Cardiology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, [d]Department of Foods and Nutrition, Kookmin University, Seoul, [e]Division of Endocrinology, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, [f]Division of Cardiology, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul and [g]Institute of Human Genomic Study, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea

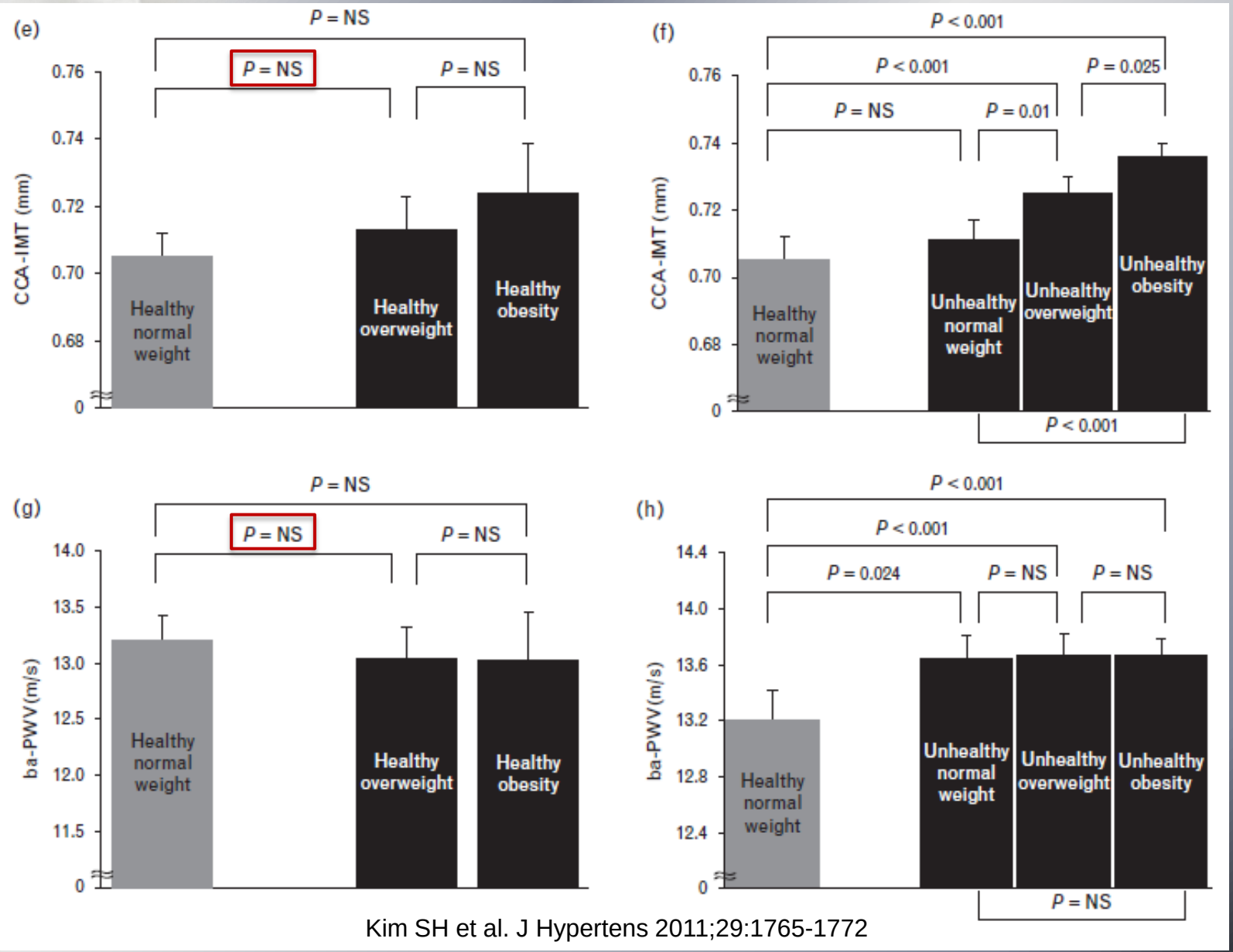
Correspondence to Seong H. Kim, MD, PhD, Division of Cardiology, Department of Medicine, Korea University Ansan Hospital, Korea University College of Medicine, 516 Gojan-1-dong, Danwon-gu, Ansan-si, Gyeonggi-do 425-707, Korea
Tel: +82 31 412 5546; fax: +82 31 412 5594; e-mail: cardioguy@korea.ac.kr

Received 16 March 2011 **Revised** 30 May 2011
Accepted 27 June 2011

Kim SH et al. J Hypertens 2011;29:1765-1772

MHO and CV changes

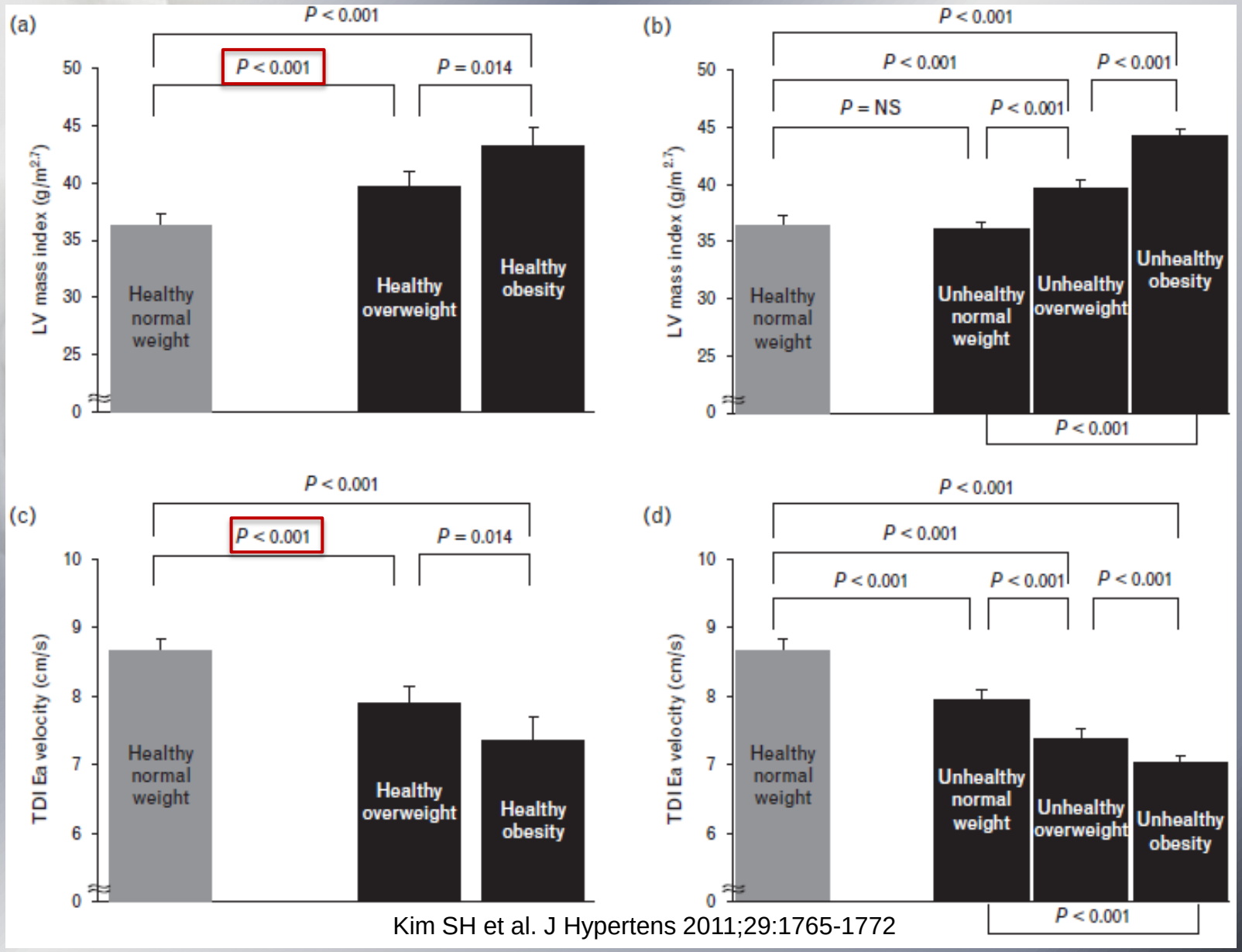
MHO is not associated with target organ changes?



Kim SH et al. J Hypertens 2011;29:1765-1772

MHO and CV changes

MHO is associated with target organ changes?



Kim SH et al. J Hypertens 2011;29:1765-1772

MHO and Hypertension

MHO increases the risk of hypertension incidence?

Obesity phenotype and incident hypertension: a prospective community-based cohort study

Seung Ku Lee[a], Seong Hwan Kim[b], Goo-Yeong Cho[c], Inkyung Baik[d], Hong Euy Lim[e], Chang Gyu Park[e], Jung Bok Lee[f], Yong Hyun Kim[b], Sang Yup Lim[b], Hyun Kim[a], and Chol Shin[a]

Objective The relationship betweens the healthy obese phenotype and the risk of cardiovascular events remains unclear. We prospectively investigated the association between the obesity phenotype and the incidence of hypertension.

Methods We studied 2352 participants, aged 40–69 years at baseline, with normal blood pressure (BP) from the Ansan cohort and the Ansung cohort of the Korean Genome Epidemiology Study. Participants were divided into six groups based on BMI and the metabolic syndrome (MetS) components: healthy (none of the five MetS components) normal weight (BMI <23 kg/m^2), unhealthy (one or more MetS component) normal weight, healthy overweight (BMI 23–24.9 kg/m^2), unhealthy overweight, healthy obesity (BMI ≥25 kg/m^2), and unhealthy obesity. The incidence of hypertension was identified by biennial health examinations during the 8-year follow-up.

Results After adjusting for age, sex, cohort, physical activity, smoking, alcohol consumption, and family history of hypertension and cardiovascular diseases, an increased risk for hypertension in combined cohort was observed in healthy obesity [hazard ratio (HR): 2.20, 95% confidence interval (CI):1.34–3.60], unhealthy overweight (HR: 1.47, 95% CI: 1.00–2.14), and unhealthy obesity (HR: 2.45, 95% CI: 1.79–3.37), compared with the healthy normal weight group. In each cohort, the healthy obesity was still associated with a higher incidence of hypertension (HR 2.20, 95% CI 1.11–4.36 for the Ansan cohort and HR 2.21, 95% CI 1.01–4.83 for the Ansung cohort).

Conclusion These findings provide evidence that the metabolically healthy obese phenotype may not be a benign condition.

INTRODUCTION

Obesity has become a major issue in both developing and developed countries, with 502 million adults globally being reported as obese [1,2]. The growing obesity epidemic is associated with a sharp increase in obesity-related cardiovascular disease (CVD), such as hypertension and type 2 diabetes mellitus, and consequently increases the risk of all-cause, coronary artery disease, and CVD mortality [3–5]. Even though obesity is a well established risk factor for CVD, recent studies have introduced a unique obesity phenotype known as 'healthy obesity' or 'metabolically normal obesity' based on data showing that some obese individuals with relatively favorable cardiometabolic profiles do not have increased risk of CVD morbidity and mortality compared with normal weight individuals [6–8]. The metabolic characteristics of healthy obese individuals including higher levels of insulin sensitivity and high-density lipoprotein (HDL) cholesterol as well as lower levels of fasting triglycerides and fasting glucose have been suggested as possible explanations for why healthy obesity may be a harmless condition. In contrast, more recent studies refute the existence of healthy obesity by demonstrating that healthy obesity is associated with all-cause and CVD mortality in longitudinal studies [9,10] as well as with target organ changes in cross-sectional studies [11,12].

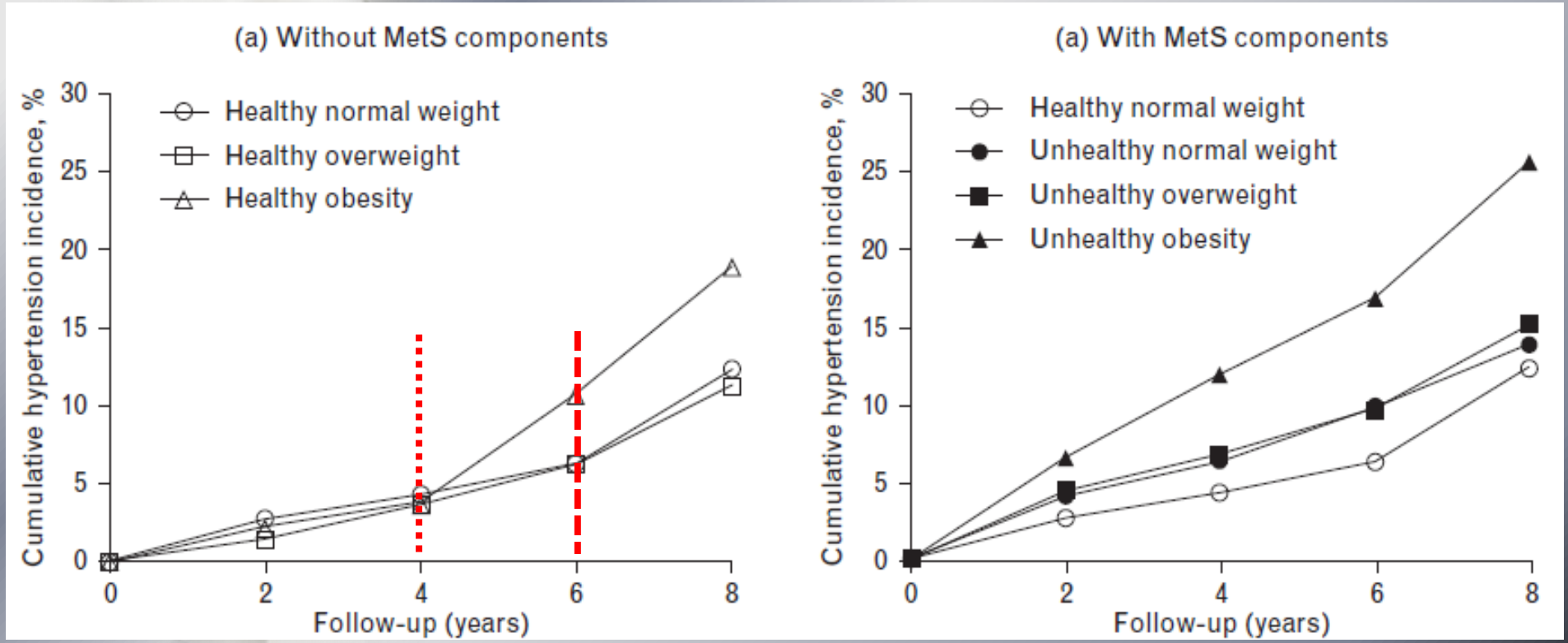
As the development of hypertension is a strong predictor of all-cause and CVD mortality, clarifying whether healthy obesity is associated with an increased risk of hypertension would bean essential step to solving the controversial issues related to mortality. However, no epidemiologic data up to

Kim SH et al. J Hypertens 2013;31:145-151

MHO and Hypertension

MHO increases the risk of hypertension incidence?

Cumulative 8-year hypertension incidence in different body mass index (BMI) without metabolic syndrome



Kim SH et al. J Hypertens 2013;31:145-151

MHO and CVD

REVIEW | Annals of Internal Medicine

Are Metabolically Healthy Overweight and Obesity Benign Conditions?

A Systematic Review and Meta-analysis

Caroline K. Kramer, MD, PhD; Bernard Zinman, CM, MD; and Ravi Retnakaran, MD

Background: Recent interest has focused on a unique subgroup of overweight and obese individuals who have normal metabolic features despite increased adiposity. Normal-weight individuals with adverse metabolic status have also been described. However, it remains unclear whether metabolic phenotype modifies the morbidity and mortality associated with higher body mass index (BMI).

Purpose: To determine the effect of metabolic status on all-cause mortality and cardiovascular events in normal-weight, overweight, and obese persons.

Data Sources: Studies were identified from electronic databases.

Study Selection: Included studies evaluated all-cause mortality or cardiovascular events (or both) and clinical characteristics of 6 patient groups defined by BMI category (normal weight/overweight/obesity) and metabolic status (healthy/unhealthy), as defined by the presence or absence of components of the metabolic syndrome by Adult Treatment Panel III or International Diabetes Federation criteria.

Data Extraction: Two independent reviewers extracted the data. Metabolically healthy people of normal weight made up the reference group.

Data Synthesis: Eight studies (n = 61 386; 3988 events) evaluated participants for all-cause mortality and/or cardiovascular events. Metabolically healthy obese individuals (relative risk [RR], 1.24; 95% CI, 1.02 to 1.55) had increased risk for events compared with metabolically healthy normal-weight individuals when only studies with 10 or more years of follow-up were considered. All metabolically unhealthy groups had a similarly elevated risk: normal weight (RR, 3.14; CI, 2.36 to 3.93), overweight (RR, 2.70; CI, 2.08 to 3.30), and obese (RR, 2.65; CI, 2.18 to 3.12).

Limitation: Duration of exposure to the metabolic–BMI phenotypes was not described in the studies and could partially affect the estimates.

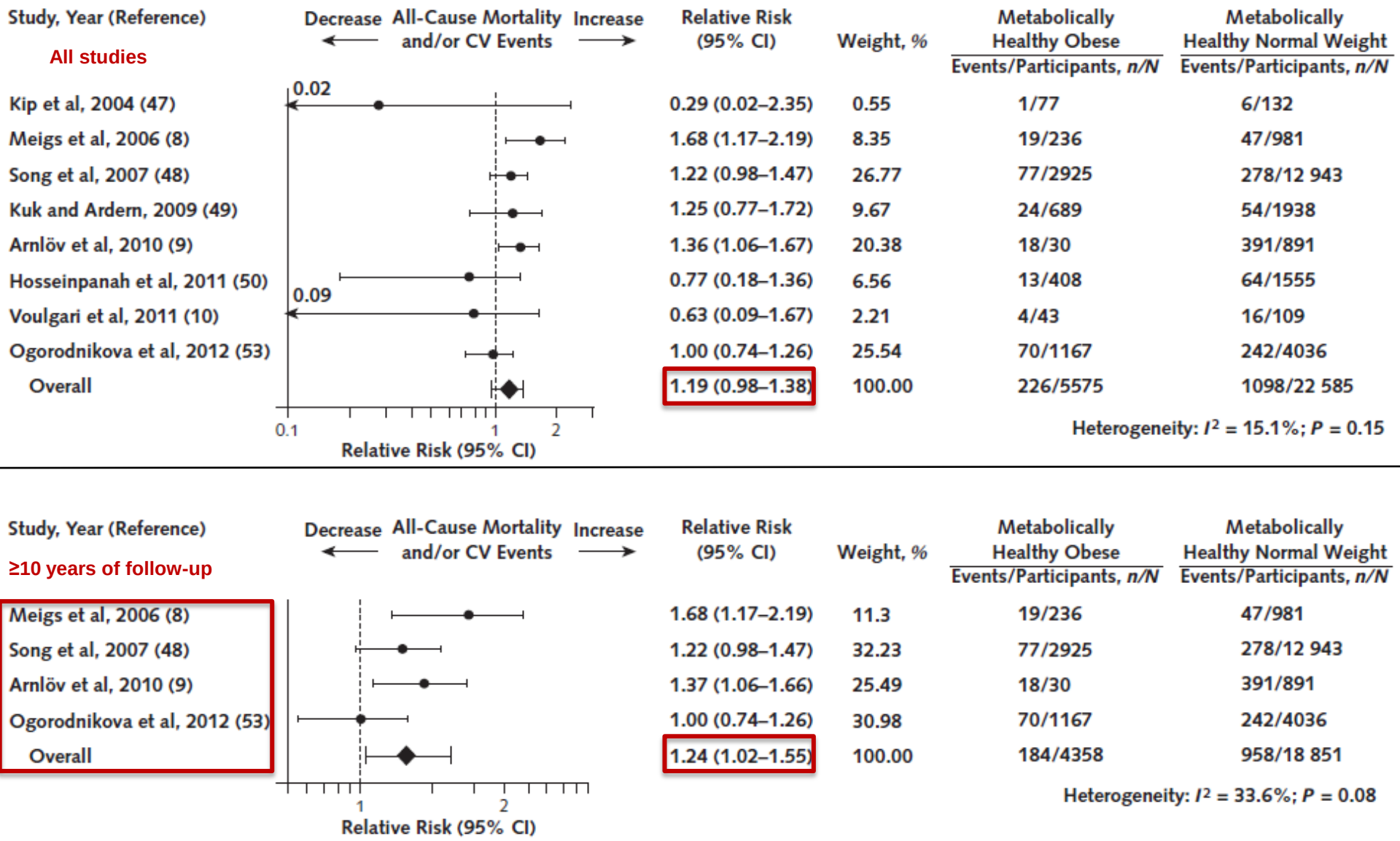
Conclusion: Compared with metabolically healthy normal-weight individuals, obese persons are at increased risk for adverse long-term outcomes even in the absence of metabolic abnormalities, suggesting that there is no healthy pattern of increased weight.

Primary Funding Source: Intramural funds from the Leadership Sinai Centre for Diabetes.

Ann Intern Med. 2013;159:758-769. www.annals.org

For author affiliations, see end of text.

MHO and CVD



Kramer CK et al. Ann Intern Med 2013;159:758-769

MHO and CVD

EDITORIAL COMMENT

Is it Finally Time to Dispel the Concept of Metabolically-Healthy Obesity?*

Rishi Puri, MB, BS

Cleveland, Ohio

Nevertheless, this has left many to ponder whether obesity per se or component metabolic abnormalities mediate cardiovascular risk.

With this in mind, in this issue of the *Journal*, Chang et al. (6) report a comparison of coronary artery calcium (CAC) scores between metabolically-healthy obese versus metabolically-healthy normal-weight Koreans (6). Their rationale was based on the notion that CAC scoring is a surrogate means of assessing subclinical coronary atherosclerosis, with known significant associations with incident major adverse cardiovascular events, and that this imaging method might illuminate the true relationship between obesity, metabolic health, and subclinical atherosclerotic cardiovascular disease. The overall population sample con-

"MHO" is simply a myth.

remains an ongoing debate regarding the impact of obesity on mortality rates. Fueling this debate has been the recent publication of 2 large-scale but somewhat conflicting meta-analyses. Although 1 analysis concluded that nearly one-fifth of total mortality within the United States is attributable to obesity (2), by contrast, the other uncovered possible protective effects of being overweight, with greater survival observed among people with body mass indexes (BMIs) between 25 and 30 kg/m^2 than among a normal-weight cohort (BMIs between 18.5 and 25 kg/m^2) (3). Even more controversial has been the concept of "metabolically-healthy obesity," defined as an obese (BMI >25 kg/m^2) state without demonstrable obesity-related metabolic abnormalities such as dyslipidemia or impaired glucose tolerance.

blood pressure ≥130/85 mm Hg (or use of blood pressure–lowering agents), triglycerides ≥150 mg/dl (or use of lipid-lowering therapies), high-density lipoprotein cholesterol <40 mg/dl in men (or <50 mg/dl in women), and a homeostasis model of insulin resistance ≥2.5. A comprehensive questionnaire pertaining to past medical history and measures of physical activity, alcohol consumption, and smoking habits was also collected. All patients had BMI measured; however, less than one-third of the population had waist circumference measured. This metabolically-healthy population was then stratified according to BMI into 1 of 4 categories: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5 to 22.9 kg/m^2), overweight (BMI 23.0 to 24.9 kg/m^2), and obese (BMI ≥25 kg/m^2). CAC scores were analyzed across these BMI strata.

Puri R. J Am Coll Cardiol 2014;63:2687-2688

MHO and CVD

Q 1: MHO does increase the risk of CVD?

↓

Absolutely, YES

Q 2: Do we need to treat a subset of obese people labelled as MH differently?

↓

Absolutely, NO

MHO and CVD

The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness

Francisco B. Ortega[1,2,3]*, Duck-chul Lee[4], Peter T. Katzmarzyk[5], Jonatan R. Ruiz[1,3], Xuemei Sui[4], Timothy S. Church[5], and Steven N. Blair[4,6]

Aims Current knowledge on the prognosis of metabolically healthy but obese phenotype is limited due to the exclusive use of the body mass index to define obesity and the lack of information on cardiorespiratory fitness. We aimed to test the following hypotheses: (i) metabolically healthy but obese individuals have a higher fitness level than their metabolically abnormal and obese peers; (ii) after accounting for fitness, metabolically healthy but obese phenotype is a benign condition, in terms of cardiovascular disease and mortality.

Methods and results Fitness was assessed by a maximal exercise test on a treadmill and body fat per cent (BF%) by hydrostatic weighing or skinfolds (obesity = BF% ≥25 or ≥30%, men or women, respectively) in 43 265 adults (24.3% women). Metabolically healthy was considered if meeting 0 or 1 of the criteria for metabolic syndrome. Metabolically healthy but obese participants (46% of the obese subsample) had a better fitness than metabolically abnormal obese participants ($P < 0.001$). When adjusting for fitness and other confounders, metabolically healthy but obese individuals had lower risk (30–50%, estimated by hazard ratios) of all-cause mortality, non-fatal and fatal cardiovascular disease, and cancer mortality than their metabolically unhealthy obese peers; while no significant differences were observed between metabolically healthy but obese and metabolically healthy normal-fat participants.

Conclusions (i) Higher fitness should be considered a characteristic of metabolically healthy but obese phenotype. (ii) Once fitness is accounted for, the metabolically healthy but obese phenotype is a benign condition, with a better prognosis for mortality and morbidity than metabolically abnormal obese individuals.

Eur Heart J 2013;34:389-397

MHO and CVD

Table 4 Hazard ratios of cardiovascular disease mortality and incidence in metabolically healthy but obese individuals compared with metabolically abnormal obese and metabolically healthy normal-weight individuals, using both body mass index and body fat percentage to define obesity

	BMI-based obesity			BF%-based obesity		
	Cases (total)	HR (95% CI)[a]	Fitness-adjusted HR (95% CI)[b]	Cases (total)	HR (95% CI)[a]	Fitness-adjusted HR (95% CI)[b]
CVD mortality						
Metabolically abnormal obese[c]	81 (3911)	1.77 (1.05–2.99)	1.48 (0.87–2.52)	153 (6900)	1.76 (1.31–2.37)	1.44 (1.06–1.95)
Metabolically healthy but obese	17 (1738)	1 (Ref.)	1 (Ref.)	64 (5959)	1 (Ref.)	1 (Ref.)
Metabolically healthy normal-weight/fat[d]	98 (16 002)	0.41 (0.24–0.70)	0.73 (0.42–1.28)	144 (21 023)	0.74 (0.54–1.00)	1.13 (0.82–1.56)
Non-fatal CVD events[e]						
Metabolically abnormal obese[c]	107 (1300)	1.44 (0.96–2.17)	1.39 (0.92–2.10)	231 (2598)	1.61 (1.29–2.01)	1.51 (1.20–1.89)
Metabolically healthy but obese	30 (544)	1 (Ref.)	1 (Ref.)	123 (2340)	1 (Ref.)	1 (Ref.)
Metabolically healthy normal-weight/fat[d]	261 (7001)	0.58 (0.39–0.86)	0.78 (0.52–1.18)	353 (9263)	0.78 (0.63–0.96)	0.95 (0.76–1.20)

Ortega FB et al. Eur Heart J 2013;34:389-397

Summary

At the population level, it is clear that obesity is an established risk factor for all-cause mortality and CV events.

However, the concept of MHO phenotype emphasizes the remarkable heterogeneity of obesity.

Current data suggest that the MHO does not seem to be a benign phenotype, although there is still some debates.

There needs to be a consensus on how best to define the MHO and additional long-term follow-up data including fitness or physical activity as a relevant covariate.

Thank you for your attention!