

Accepted Manuscript

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PII: S0002-9149(17)30955-4

DOI: <http://dx.doi.org/doi: 10.1016/j.amjcard.2017.05.054>

Reference: AJC 22672

To appear in: *The American Journal of Cardiology*

Received date: 5-4-2017

Accepted date: 31-5-2017

Please cite this article as: Sae Young Jae, Abraham Babu, Eun Sun Yoon, Sudhir Kurl, Jari A. Laukkanen, Yoon-Ho Choi, Barry A. Franklin, Impact of Cardiorespiratory Fitness and Risk of Systemic Hypertension in Non-Obese Versus Obese Men Who are Metabolically Healthy or Unhealthy, *The American Journal of Cardiology* (2017), <http://dx.doi.org/doi: 10.1016/j.amjcard.2017.05.054>.

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Impact of Cardiorespiratory Fitness and Risk of Systemic Hypertension in Non-Obese versus
Obese Men who are Metabolically Healthy or Unhealthy

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Running head: *Body Phenotype, Fitness and Systemic Hypertension*

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Abstract

Few data are available regarding the influence of body phenotype on systemic hypertension (SH) and whether cardiorespiratory fitness (CRF) attenuates this relation. We tested the hypothesis that obesity phenotypes and CRF would predict incident hypertension, evaluating 3800 Korean men who participated in 2 health examinations between 1998 and 2009. All participants were normotensive at baseline and divided into 4 groups based on body mass index (BMI) using the Asia-Pacific descriptors for obesity and metabolic health status and the ATP-III criteria. Metabolically healthy obese (MHO) phenotype was defined as BMI ≥ 25 kg/m² with < 2 metabolic abnormalities. CRF was directly measured by peak oxygen uptake (VO_{2peak}) and participants were divided into unfit and fit categories based on age-specific VO_{2peak} percentiles. Incident SH was defined as resting systolic or diastolic blood pressure $\geq 140/90$ mmHg and/or diagnosed by a physician at the second examination. Compared with the metabolically healthy non-obese (MHNO) phenotype, MHO and metabolically unhealthy non-obese (MUNO) phenotypes were at increased risk for SH (relative risk (RR) = 1.47, 95% confidence interval (CI): 1.07-2.02 and 1.62, 1.21-2.16) after adjusting for potential confounders. Fit men had a 21% decreased relative risk of incident SH compared with unfit men in a multivariable adjusted model. Joint analysis showed that MHO or MUNO unfit men had 1.91 and 2.27 greater risk of incident SH, respectively. However, MHO fit men had no significant RR of incident SH (RR 1.37 95% CI, 0.93-2.03), whereas MUNO fit men remained at increased risk (RR 1.48 95% CI, 1.04-2.11) as compared with their MHNO fit counterparts. In conclusion, MHO and MUNO men were at increased risk of SH, but these risks were attenuated by fitness in the former cohort. These findings may partially explain the association between the MHO phenotype and more favorable cardiovascular outcomes.

Key words: *metabolically healthy obesity, hypertension, cardiorespiratory fitness.*

Metabolically healthy obese (MHO) individuals comprise a cohort of the obese population who do not have metabolic abnormalities and are at relatively low risk for cardiovascular disease (CVD).¹ Metabolically unhealthy non-obese (MUNO) individuals, who are of normal weight but with abnormal metabolic profiles, appear to be at greater risk for CVD.²⁻⁴ Some studies have suggested that MHO and/or MUNO are at increased risk of incident systemic hypertension (SH),⁵⁻⁸ but potential confounding variables were not adequately accounted for in these reports. Cardiorespiratory fitness (CRF), an important confounding variable in body phenotype cohorts,^{9,10} is inversely associated with obesity and metabolic risk factors.¹¹ Although high fitness may favorably modify the prognosis of MHO and MUNO individuals,^{10,12,13} the inclusion of CRF along with metabolic parameters and body habitus may help to clarify the relative contribution of fitness to long term health outcomes.¹⁴ Because fitness reduces the risk of SH independent of obesity and metabolic abnormalities,^{15,16} the impact of CRF on the association between body phenotype and risk of SH needs clarification. We tested the hypothesis that body phenotype is associated with the risk of incident SH, but that CRF modifies these associations.

METHODS

A total of 5616 men participated in 2 general health examinations between 1998 and 2009 at the Samsung Medical Center, Seoul, South Korea. Among them, participants with a diagnosis of SH (i.e., resting systolic and/or diastolic blood pressure (SBP/DBP) ≥ 140 or ≥ 90 mmHg), type 2 diabetes mellitus (i.e., fasting glucose >126 mg/dl), history of CVD, and the use of antihypertensive or oral hypoglycemic medications were excluded. After applying these exclusion criteria, 3800 men (mean age 48 ± 6 years, range 20-76 years) remained for analyses. Written informed consent was obtained from all participants before the health

screening program, and the study was approved by the medical center institutional review board.

All participants underwent progressive cardiopulmonary exercise testing (CPX) to determine peak oxygen uptake (VO_{2peak}) (Jaeger Oxycon Delta, Eric Jaeger, Hoechberg, Germany) using methods previously described.¹⁷ The metabolic profile was partially obtained from blood samples collected after a 12 h overnight fasting state.¹⁷ Blood pressure was measured during seated rest using an automated blood pressure monitor after 5 min of quiet rest (Dinamap PRO 100, Milwaukee, WI). Incident SH was defined as SBP/DBP \geq 140/90 mmHg and/or diagnosed SH by a physician at the second examination. Body composition (relative body fatness in %) was measured using bioelectrical impedance and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Smoking habits and alcohol intake were evaluated via self-reported questionnaires.

All participants were divided into 4 groups based their BMI by the Asia-Pacific criteria for obesity and metabolically unhealthy categorization using the ATP-III criteria (i.e., blood pressure $>$ 130/85 mmHg, high density lipoprotein cholesterol (HDL-C) $<$ 40 mg/dl, triglyceride (TG) $>$ 150 mg/dl, and glucose $>$ 100 mg/dl). Definitions of metabolically healthy or unhealthy in non-obese and obese cohorts were as follows: metabolically healthy non-obese (MHNO) - BMI $<$ 25 kg/m^2 with \leq 1 metabolic abnormality, MUNO - BMI $<$ 25 kg/m^2 with \geq 2 metabolic abnormalities, MHO - BMI \geq 25 kg/m^2 with \leq 1 metabolic abnormality, and metabolically unhealthy obese (MUO) - BMI \geq 25 kg/m^2 with \geq 2 metabolic abnormalities. VO_{2peak} was divided into tertiles and classified into unfit (lowest tertile) and fit (middle and upper tertiles) categories based on age-specific VO_{2peak} percentiles as previously described.¹⁸ We further divided our study population into 8 groups based on cross-classification of metabolic health, body habitus phenotypes and CRF.

Data are presented as mean \pm SD or median interquartile range for continuous variables and proportions for categorical variables. For group comparisons by body habitus phenotypes, variables were assessed using an ANOVA with Scheffe's post hoc and χ^2 tests for continuous and categorical variables, respectively. To determine the associations between body habitus phenotypes and fitness status with incident SH, relative risks (RRs) and 95% CI (95% CIs) from the Cox proportional hazards regression models were calculated after adjusting for age, % body fat, low density lipoprotein cholesterol, white blood cell, uric acid, smoking, alcohol consumption and fitness (when body habitus phenotype was considered) or body habitus phenotype (when fitness was considered). The joint effects of body habitus and fitness on the risk of SH was examined using combined groups. Participants were divided into groups based on metabolic health and body habitus phenotypes (MHNO, MUNO, MHO, and MUO) and CRF (fit and unfit). MHNO-fit was used as the reference group. Statistical significance was set at $p < 0.05$, and analyses were conducted using the SPSS 22.0 (SPSS, Armonk, NY).

RESULTS

Table 1 shows the characteristics of participants by metabolic health (i.e., healthy or unhealthy), with the prevalence of non-obese and obese phenotypes. We found that 21.1% and 17.8% among the participants were classified as MHO and MUNO, respectively. Individuals with MHO or MUNO had greater relative BMI, waist circumference, body fatness, SBP/DBP, total cholesterol, triglyceride, glucose, white blood cell and uric acid, but lower high density lipoprotein cholesterol and CRF than men who were categorized as MHNO. Compared with the MUO individuals, the MHO individuals had lower relative SBP/DBP, triglyceride, glucose and uric acid, but greater high density lipoprotein cholesterol.

During an average follow-up of 5 years, 371 (9.8%) men developed SH. Compared with MHNO individuals, MHO and MUNO individuals demonstrated a 1.47-fold and 1.62-fold increased risk for SH, respectively, after adjusting for potential confounders. In addition, fit men had a 21% reduced risk of incident SH compared with unfit men in our multivariable adjusted model (Table 2).

Combined analysis showed that unfit MHO or MUNO men had greater risk of incident SH as compared with their fit MHNO counterparts (reference group) after adjusting for potential confounders (RR: 1.91, 95% CI, 1.25-2.92 or RR: 2.27, 95% CI, 1.51-3.40, respectively) (Figure 1). However, fit MHO men had no significantly greater risk for incident SH (RR 1.37, 95% CI, 0.93-2.03) than did fit men who comprised the MHNO cohort. Fit MUNO men had a lower risk of incident SH than their unfit peers, but the risk remained higher (RR 1.48, 95% CI, 1.04-2.11) than their MHNO fit counterparts (Figure 1).

DISCUSSION

Two main findings from the present study are that MHO and MUNO men were at increased risk of SH as compared with the MHNO group. However, these risks were attenuated by moderate-to-high levels of CRF in MHO, but not in MUNO men, compared to their fit MHNO counterparts.

Obese individuals have a higher risk of incident SH than normal-weight individuals, but not all obese individuals become hypertensive,¹⁹ which highlights the heterogeneity of obesity relative to the development of SH.²⁰ The risk of SH in obese individuals depends on the individual's body habitus with and without metabolic abnormalities. The present findings are compatible with those previously reported in that MHO was associated with an increased risk of incident SH⁵⁻⁸ as compared with MHNO individuals.

However, the risk for incident SH in MHO men was significantly reduced by increasing fitness levels in the present study. Ortega et al¹² reported that CRF, defined as the total duration of symptom-limited treadmill exercise testing, favorably modified the associations between MHO phenotypes and all-cause mortality, non-fatal and fatal CVD, and cancer mortality. We found that unfit MHO men had a greater risk for incident SH as compared with fit MHNO men, but fit MHO men had no significant increased risk of incident SH than their fit MHNO counterparts. These data suggest that fitness may partially explain the association between MHO phenotype and the risk of SH. Similarly, we previously demonstrated that MHO men had a higher prevalence of subclinical carotid atherosclerosis as compared with MHNO men; however, these findings were also attenuated by increasing levels of fitness.¹³ Our results are consistent with these findings, and further extend the role of CRF in determining the impact of MHO on cardiovascular outcomes,¹⁰ with specific reference to incident SH as an early risk factor for CVD. These results may help to clarify the fact that MHO men with higher fitness levels have better cardiovascular outcomes than unfit MHO men. Accordingly, studies on the relation between MHO and cardiometabolic outcomes should consider the individual's fitness as an important confounding variable. To our knowledge, this is the first study to clarify the role of CRF in the association between MHO and incident SH. However, further studies needed to confirm these results and other cardiovascular outcomes.

Our results showed that MUNO individuals are at a greater risk for incident SH. Even non-obese individuals with increased cardiometabolic risk factors appear to be at greater risk for incident SH, as compared with MHNO individuals. The present findings are consistent with previous studies that reported increased risk of incident SH in MUNO as compared with MHNO.^{7,8} In contrast, other studies have reported that MUNO adults,⁵ children and

adolescents⁶ had no increased risk of incident SH. We believe that age and follow-up duration differences may, at least in part, be responsible for the conflicting data in the literature, and suggest the need to further clarify the associations between MUNO and incident SH after considering previously unaccounted for potential confounders.

In the present study, fit MUNO men demonstrated an attenuated the risk of incident SH (1.5 times) as compared with unfit MUNO men (2.3 times), and the risk persisted when compared with their fit MHNO counterparts. Although the protective effect of fitness was observed in MUNO men, it did not completely eliminate the increased risk in this phenotype. These findings suggest that fitness may be less effective in MUNO individuals in attenuating incident SH. Clearly, additional studies are needed to further clarify these results with other cardiometabolic outcomes.

We acknowledge several limitations to our study. Because our participants included only men, we were unable to determine whether this association extends to women. Although we adjusted for potential confounders, it is possible that residual variables that we did not measure may have influenced these associations. In addition, we defined fitness using dichotomized fit and unfit categories based on age- and gender-specific values of VO_{2peak} . Although this approach may be somewhat subjective, both estimated and directly measured exercise capacity has been shown to strongly predict mortality and health outcomes. Finally, we defined the MHO phenotype by $BMI \geq 25 \text{ kg/m}^2$ using the Asia-Pacific descriptors for obesity and metabolic health status via ATP-III criteria. However, varied criteria have been put forth to characterize this phenotype.

In summary, our results demonstrate that compared with MHNO, MHO and MUNO men were at increased risk for incident SH, but that the likelihood of future SH was reduced

by higher levels of fitness in MHO individuals. High fitness may partially explain why some MHO individuals are largely protected against the risk of cardiovascular and other chronic diseases.

Disclosures

The authors report no relations that could be construed as a conflict of interest.

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References

1. Phillips CM. Metabolically healthy obesity: definitions, determinants and clinical implications. *Rev Endocr Metab Disord* 2013;14:219–227.
2. Romero-Corral A, Somers VK, Sierra-Johnson J, Korenfeld Y, Boarin S, Korinek J, Jensen MD, Parati G, Lopez-Jimenez F. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *Eur Heart J* 2010;31:737–746.
3. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. *Diabetes* 1998;47:699–713.
4. Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The concept of normal weight obesity. *Prog Cardiovasc Dis* 2014;56:426–433.
5. Lee SK, Kim SH, Cho GY, Baik I, Lim HE, Park CG, Lee JB, Kim YH, Lim SY, Kim H, Shin C. Obesity phenotype and incident hypertension: a prospective community-based cohort study. *J Hypertens* 2013;31:145–151.
6. Ding WQ, Yan YK, Zhang MX, Cheng H, Zhao XY, Hou DQ, Mi J. Hypertension outcomes in metabolically unhealthy normal-weight and metabolically healthy obese children and adolescents. *J Hum Hypertens* 2015;29:548–554.
7. Kang YM, Jung CH, Jang JE, Hwang JY, Kim EH, Park JY, Kim HK, Lee WJ. The association of incident hypertension with metabolic health and obesity status: definition of metabolic health does not matter. *Clin Endocrinol (Oxf)* 2016;85:207–215.
8. Ryoo JH, Park SK, Oh CM, Choi YJ, Chung JY, Ham WT, Jung T. Evaluating the risk of hypertension according to the metabolic health status stratified by degree of obesity. *J Am Soc Hypertens* 2017;11:20–27.

9. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *J Am Coll Cardiol* 2014;63:1345–1354.
10. Ortega FB, Cadenas-Sánchez C, Sui X, Blair SN, Lavie CJ. Role of fitness in the metabolically healthy but obese phenotype: a review and update. *Prog Cardiovasc Dis* 2015;58:76–86.
11. Harber MP, Kaminsky LA, Arena R, Blair SN, Franklin BA, Myers J, Ross R. Impact of cardiorespiratory fitness on all-cause and disease-specific mortality: Advances since 2009. *Prog Cardiovasc Dis* 2017 Mar 9. pii: S0033-0620(17)30043-9. doi: 10.1016/j.pcad.2017.03.001. [Epub ahead of print]
12. Ortega FB, Lee DC, Katzmarzyk PT, Ruiz JR, Sui X, Church TS, Blair SN. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. *Eur Heart J* 2013;34:389–397.
13. Jae SY, Franklin B, Choi YH, Fernhall B. Metabolically healthy obesity and carotid intima-media thickness: effects of cardiorespiratory fitness. *Mayo Clin Proc* 2015;90:1217–1224.
14. Babu AS, Veluswamy SK, Myers J, Lavie CJ. Metabolically healthy obese versus cardiorespiratory fit obese: is it time to bring them together? *J Am Coll Cardiol* 2014;64:1183–1184.
15. Juraschek SP, Blaha MJ, Whelton SP, Blumenthal R, Jones SR, Keteyian SJ, Schairer J, Brawner CA, Al-Mallah MH. Physical fitness and hypertension in a population at risk for cardiovascular disease: the Henry Ford Exercise Testing (FIT) Project. *J Am Heart Assoc* 2014;3:e001268. doi: 10.1161/JAHA.114.001268.
16. Crump C, Sundquist J, Winkleby MA, Sundquist K. Interactive effects of physical fitness and body mass index on the risk of hypertension. *JAMA Intern Med* 2016;176:210–216.

17. Jae SY, Kurl S, Laukkanen JA, Lee CD, Choi YH, Fernhall B, Franklin BA. Relation of C-reactive protein, fibrinogen, and cardiorespiratory fitness to risk of systemic hypertension in men. *Am J Cardiol* 2015;115:1714–1719.
18. McAuley PA, Artero EG, Sui X, Lavie CJ, Almeida MJ, Blair SN. Fitness, fatness, and survival in adults with prediabetes. *Diabetes Care* 2014;37:529–536.
10. Kotsis V, Nilsson P, Grassi G, Mancia G, Redon J, Luft F, Schmieder R, Engeli S, Stabouli S, Antza C, Pall D, Schlaich M, Jordan J; WG on Obesity, Diabetes, the High Risk Patient, European Society of Hypertension. New developments in the pathogenesis of obesity-induced hypertension. *J Hypertens* 2015;33:1499–1508.
20. Davy KP, Hall JE. Obesity and hypertension: two epidemics or one? *Am J Physiol Regul Integr Comp Physiol* 2004;286:R803–813.

FIGURE LEGEND

Figure 1. The combined effect of the obesity phenotypes and cardiorespiratory fitness on the incidence of systemic hypertension (Relative Risks and 95% CIs) after adjustment for age, % body fat, low density lipoprotein cholesterol, white blood cell, uric acid, smoking and alcohol consumption.

Table 1. Baseline characteristics of participants by metabolic health and body habitus phenotypes (n = 3800).

Variables	MHNO (n=1726)	MUNO (n=677)	MHO (n=803)	MUO (n=594)	p-value
Age (years)	47.7±6.5	48.3±6.1	47.8±6.2	47.5±6.2	0.146
Body mass index (kg/m ²)	22.8±1.7	23.3±1.3 ^a	26.7±1.5 ^{a,b}	26.8±1.4 ^{a,b}	<0.001
Waist girth (cm)	82.5±5.5	84.5±4.2 ^a	91.2±5.1 ^{a,b}	91.6±4.4 ^{a,b}	<0.001
Body fat (%)	19.7±3.9	21.1±3.5 ^a	24.8±3.6 ^{a,b}	24.8±3.5 ^{a,b}	<0.001
Current smokers	24.8%	21.1%	30.0%	29.1%	0.102
Alcohol intake (3d/wk)	5.2%	4.4%	6.1%	5.2%	0.390
Systolic blood pressure (mmHg)	114±11	122±12 ^a	116±10 ^{a,b}	121±12 ^{a,c}	<0.001
Diastolic blood pressure (mmHg)	73±8	79±8 ^a	74±8 ^{a,b}	78±9 ^{a,c}	<0.001
Total cholesterol (mg/dl)	197±33	205±34 ^a	204±33 ^a	207±34 ^a	<0.000
High density lipoprotein cholesterol (mg/dl)	53±11	46±11 ^a	50±10 ^{a,b}	42±9 ^{a,b,c}	<0.001
Low density lipoprotein cholesterol (mg/dl)	124±30	126±32	131±30 ^{a,b}	129±32 ^a	<0.001
Triglyceride (mg/dl)	116±52	195±93 ^a	133±64 ^{a,b}	210±98 ^{a,b,c}	<0.001
Glucose (mg/dl)	92±9	100±10 ^a	94±9 ^{a,b}	101±10 ^{a,c}	<0.001
White blood cell (×10 ⁹ cells/l)	5.8±1.6	6.2±1.6 ^a	6.1±1.5 ^a	6.3±1.5 ^a	<0.001
Uric acid (mg/dl)	5.6±1.1	5.9±1.1 ^a	5.9±1.1 ^a	6.2±1.3 ^{a,b,c}	<0.001
Peak oxygen consumption (ml/kg/min)	35.9±5.1	34.9±5.1 ^a	34.0±4.8 ^{a,b}	33.5±4.5 ^{a,b}	<0.001

MHNO: metabolically healthy non-obese, MUNO: metabolically unhealthy non-obese, MHO: metabolically healthy obese,

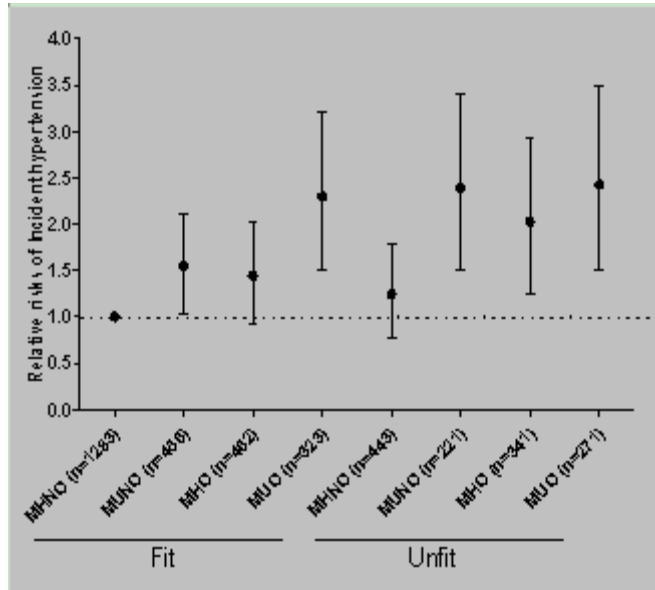
MUO: metabolically unhealthy obese. ^ap <0.05 vs. MHNO, ^bp <0.05 vs. MUNO, ^cp <0.05 vs. MHO

Table 2. Relative risk (95% CI) of incident hypertension across metabolic health status and body mass index (n = 3800).

Variables	n	No. (Incidence)	Age adjusted RR (95% CI)	Multivariable adjusted RR (95% CI)
Obesity phenotypes				
Metabolically healthy non-obese	1726	116 (6.7%)	1 (ref)	1 (ref)
Metabolically unhealthy non-obese	677	83 (12.3%)	1.67 (1.26-2.21)	1.62 (1.21-2.16)
Metabolically healthy obese	803	83 (10.3%)	1.67 (1.26-2.21)	1.47 (1.07-2.02)
Metabolically unhealthy obese	594	89 (15.0%)	2.38 (1.81-3.14)	2.04 (1.48-2.80)
p-value		<0.001	<0.001	<0.001
Cardiorespiratory fitness				
Unfit	1276	141 (11.1%)	1 (ref)	1 (ref)
Fit	2524	230 (9.1%)	0.68 (0.55-0.84)	0.79 (0.64-0.98)
p-value		0.057	<0.001	0.036

Adjusted for age, % body fat, low density lipoprotein cholesterol, white blood cell, uric acid, smoking and alcohol consumption and fitness when obesity phenotypes exposure or obesity phenotypes when cardiorespiratory fitness exposure.

Figure 1.



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