Medicine®

OPEN

Association of metabolic syndrome and its components with all-cause and cardiovascular mortality in the elderly

A meta-analysis of prospective cohort studies

Sang-Yhun Ju, MD, PhD[a,*], June-Young Lee, PhD[b,*], Do-Hoon Kim, MD, PhD[c]

Abstract

There is increasing evidence regarding the relationship between metabolic syndrome and mortality. However, previous research examining metabolic syndrome and mortality in older populations has produced mixed results. In addition, there is a clear need to identify and manage individual components of metabolic syndrome to decrease cardiovascular disease (CVD) mortality. In this meta-analysis, we searched the MEDLINE databases using PubMed, Cochrane Library, and EMBASE databases. Based on 20 prospective cohort studies, metabolic syndrome was associated with a higher risk of all-cause mortality [relative risk (RR), 1.23; 95% confidence interval (CI), 1.15–1.32; $I^2 = 55.9\%$] and CVD mortality (RR, 1.24; 95% CI, 1.11–1.39; $I^2 = 58.1\%$). The risk estimates of all-cause mortality for single components of metabolic syndrome were significant for higher values of waist circumference or body mass index (RR, 0.94; 95% CI, 0.88–1.00), higher values of blood glucose (RR, 1.19; 95% CI, 1.05–1.34), and lower values of high-density lipoprotein (HDL) cholesterol (RR, 1.11; 95% CI, 1.02–1.21). In the elderly population, metabolic syndrome was associated with an increased risk of all-cause and CVD mortality. Among the individual components of metabolic syndrome, increased blood glucose and HDL cholesterol levels were significantly associated with increased mortality. However, older obese or overweight individuals may have a decreased mortality risk. Thus, the findings of the current meta-analysis raise questions about the utility of the definition of metabolic syndrome in predicting all-cause mortality and CVD mortality in the elderly population.

Abbreviations: AHA-NHLBI = American Heart Association/National Heart Lung and Blood Institute, BMI = body mass index, CI = confidence interval, CVD = cardiovascular disease, FBG = fasting blood glucose, HBP = high blood pressure, HDL = high density lipoprotein, IDF = International Diabetes Federation, NCEP = National Cholesterol Education, NOS = Newcastle-Ottawa Scale, RR = relative risk, TG = triglycerides, WC = waist circumference, WHO = World Health Organization.

Keywords: all-cause mortality, cardiovascular disease, cohort studies, meta-analysis, metabolic syndrome X

1. Introduction

Metabolic syndrome is defined as a combination of impaired glucose metabolism, dyslipidemia, abdominal obesity, and elevated blood pressure. The association of this syndrome with an increased risk of cardiovascular disease (CVD)[1] and all-cause mortality[2] in the general population is well known. However, the strength of the association between metabolic syndrome and the risk of CVD and mortality outcomes varies by population according to factors such as race/ethnicity, sex, and age.[3–5]

Metabolic syndrome should be considered an important issue in elderly individuals, as aging is a major contributor to the prevalence of the constellation of cardiovascular and metabolic risk factors that constitute the syndrome.[6,7] However, recent

Editor: Ziyuan Zhou.

J.S.Y. drafted the initial article. J.S.Y. and L.J.Y. had full access to the entire study dataset; were responsible for the study's integrity and the accuracy of the data analysis; designed the study; drafted, reviewed and revised the final article; and contributed to the conception, design, statistical analysis, and data interpretation of this study. J.S.Y. and K.D.H. contributed to data extraction by evaluating the quality of each study's methodology according to previously established criteria. K.D.H. contributed to the interpretation of the data. All authors approved the final article for submission.

S.Y.J. and J.Y.L. contributed equally to this work and are both corresponding authors.

The authors declare conflicts of interest.

Supplemental Digital Content is available for this article.

[a] Department of Family Medicine, College of Medicine, Yeouido St. Mary's Hospital, the Catholic University of Korea, [b] Department of Biostatistics, Korea University College of Medicine, [c] Department of Family Medicine, Korea University Ansan Hospital, Ansan-Si Gyeonggi, Republic of Korea.

[*] Correspondence: Sang-Yhun Ju, Department of Family Medicine, College of Medicine, Yeouido St. Mary's Hospital, the Catholic University of Korea, 10, 63-ro, Yeongdeungpo-gu, Seoul 150–713, Republic of Korea (e-mail: kolpos@daum.net); June-Young Lee, Department of Biostatistics, Korea University College of Medicine, 145, Anam-ro, Seongbuk-gul, 136–701, Republic of Korea (e-mail: jyleeuf@korea.ac.kr).

Medicine (2017) 96:45(e8491)

Received: 21 January 2017 / Received in final form: 4 September 2017 / Accepted: 6 October 2017

http://dx.doi.org/10.1097/MD.0000000000008491

observational studies that have investigated metabolic syndrome as a predictor of mortality in elderly cohorts have shown conflicting results. Several studies[8–11] have indicated that metabolic syndrome is significantly associated with mortality in the elderly, whereas others[12–16] have found no significant association.

In providing an overview of metabolic syndrome in the elderly, regardless of whether metabolic syndrome is considered a unique entity, there is a clear need to identify and manage its individual components to reduce the morbidity and mortality associated with diabetes and CVD.[17] Recently, a large retrospective cohort study[18] indicated that in elderly adults, individual components of metabolic syndrome were better predictors of all-cause and cause-specific mortality than metabolic syndrome as a whole. Moreover, there may be different or even opposing effects of individual components of metabolic syndrome on mortality, such as the reduced risk of CVD and all-cause mortality associated with obesity.[19,20] Therefore, in the current article, we provide a systematic review and meta-analysis of studies assessing the impact of metabolic syndrome on CVD and all-cause mortality among the elderly, focusing on the strength of the association of each component of metabolic syndrome.

2. Methods

We planned, conducted, and reported this systematic review according to widely accepted quality standards for reporting meta-analyses of observational studies in epidemiology. Ethical approval for this study was not necessary as it was a meta-analysis that collect and analysis data from the existing literatures.

2.1. Literature search

A medical librarian with experience in systematic reviews participated in designing the search strategy. We searched the MEDLINE databases using PubMed, Cochrane Library, and EMBASE databases via Elsevier for reports published between April 1979 and May 2017. A PubMed search for studies on aging, metabolic syndrome, cardiovascular disease, and mortality was conducted without restrictions by combining search terms that were synonymous with or related to metabolic syndrome and mortality. The keywords used in the PubMed search were converted into search tags for the Cochrane Library and EMBASE databases (Supplementary Table 1, http://links.lww.com/MD/B933). Furthermore, the reference lists of relevant articles were manually searched to identify additional studies.

2.2. Eligibility criteria

Published articles were included in the meta-analysis if they met the following inclusion criteria: assessed elderly participants (age ≥60 ys); used a prospective cohort study design; included all-cause mortality or CVD mortality as a specified outcome; conducted a baseline assessment of metabolic syndrome; included data on adjusted relative risk (RR), generally expressed as the risk ratio in prospective cohort studies, and the corresponding 95% confidence interval (CI); were written in English and published in their entirety; and included the most recent or most informative study if cohorts were duplicated in more than 1 study.

2.3. Exclusion criteria, data extraction, and quality assessment

Review articles, editorials, commentaries, letters without new data analyses, meta-analyses, and abstracts were excluded. The exclusion criteria for this study were as follows: enrollment that depended on a particular condition or risk factor, such as diabetes mellitus or chronic kidney disease and participants who were not elderly (age <60 ys).

Two investigators (J.S.Y. and K.D.H.), coauthors of the current study, independently performed 2 subsequent rounds of screening. In the first round of screening, we excluded irrelevant studies and reviews based on the title or abstract. In the second round of screening, we reviewed the full-text articles to further exclude unrelated studies that did not meet the inclusion criteria. One investigator (J.S.Y.) performed data extraction, and the other investigator (K.D.H.) assessed the results for accuracy. Disagreements between the 2 reviewers were resolved by consensus. The following information was extracted: family name of the first author, year of publication, country of origin, age and sex of the participants, sample size, definition of metabolic syndrome used, prevalence of metabolic syndrome, deaths, follow-up duration, adjustment factors, the adjusted risk estimates and corresponding 95% CIs of all-cause, and CVD mortality for metabolic syndrome. We extracted the adjusted RRs that reflected the greatest degree of control for potential confounding factors for use in our main analysis. To determine the influence of single components of metabolic syndrome, we also collected risk estimates for each single component and compared them with the estimates for metabolic syndrome obtained in the same studies. The quality score of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) criteria for cohort studies[21] (Supplementary Table 2, http://links.lww.com/MD/B933).

2.4. Data synthesis and analysis

We synthesized the results of the included studies using a random-effects meta-analysis. The synthesized results are presented as RRs with corresponding 95% CIs. The statistical heterogeneity between studies was assessed using Q and I^2 statistics. For the Q statistic, heterogeneity was considered present if $P < .1$, and we defined low, moderate, and high heterogeneity as I^2 values of 25%, 50%, and 75%, respectively. To explore heterogeneity, we performed subgroup analyses according to prespecified study-level characteristics using a random-effects meta-analysis. Potential sources of heterogeneity included geographic location, sex, age, definition of metabolic syndrome, sample size, prevalence of metabolic syndrome, follow-up duration, and adjustment for frailty and quality score. Sensitivity analyses were performed to test the robustness of the overall analysis. We also performed a meta-analysis of the effects of single components of metabolic syndrome, that is, the effects of individual components compared against the effect calculated for metabolic syndrome as a whole using the same datasets. Publication bias was evaluated by visual inspection of Begg's funnel plot and was tested using Begg's test. $P < .1$ for Begg's test indicated publication bias. All statistical analyses were performed using Stata software, version 14.0 (Stata Corp., College Station, TX).

3. Results

3.1. Study search and selection and characteristics of eligible studies

Figure 1 shows the details of the study selection process. Briefly, we identified 178 potentially relevant articles on metabolic syndrome in relation to mortality after an initial screening of titles and abstracts. After we examined the 178 assembled articles, 158

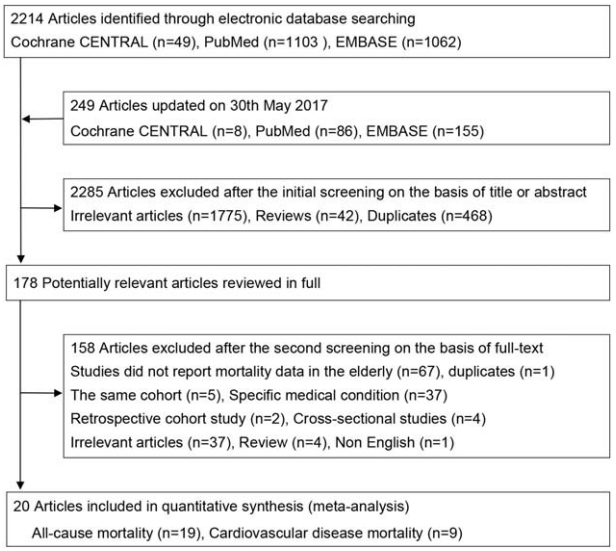

Figure 1. Flow diagram of the search strategy and study selection.

articles were excluded. Finally, we identified 20 articles[8–16,22–32] (all-cause mortality, 19 articles;[8–16,22–27,29–32] CVD mortality, 9 articles)[9,11,12,14,16,22,23,28,32] that met the inclusion criteria. The characteristics of the included studies and the quality assessment are summarized in Table 1[8–16,23–27,29–32] and Table 2.[9,11,12,14,16,22,23,28,32] All included studies were published in 2006 or later, had sample sizes ranging from 680 to 10,547 participants, and had a follow-up duration ranging from 3 to 19 years. Our studies included a total of 57,202 subjects. The prevalence of metabolic syndrome in these studies ranged from 11% in a study[29] of 3050 adults aged 65 years and older to 57% in a study[12] of 986 adults aged 75 years and older who were undergoing general health examinations. Participant ages ranged from 60 to 89 years. Two studies[24,31] included men only, and 18 studies[8–16,22,23,25–30,32] included both men and women. Many studies followed specific subsamples, which accounted for much of the variability. Seven studies[10,11,14,16,25,28,32] reported outcomes for men and women. One study[12] reported mortality outcomes for participants aged 60 to 74 and 75 to 89 years. Thirteen studies[10,12–16,22,25,26,28,30–32] were conducted in Europe, 4 studies[8,23,27,29] in the United States, and 3[11,24,30] in Asia. Eleven studies[8,13,16,22,23,25,26,28,30–32] defined metabolic

Table 1

Characteristics of included studies regarding metabolic syndrome and all-cause mortality[8–16,23–27,29–32].

Author	Country	Age mean, range, ys	Sex, Participant no.	Definition of metabolic syndrome, prevalence, %	Death, no.	Follow-up, ys	Quality score	Adjustment factors
Otiniano et al[29]	USA	72, ≥65	M and F 3050	WHO 11	1128	7	8	Age, sex, live alone, education, smoking, alcohol, activities of daily living, diabetes, hypertension, and obesity
Butler et al[23]	USA	73.6, 70–79	M and F 3035	NCEP 38	434	6	7	Age, sex, race, smoking, marital status, cohort site, and diabetes
Ravaglia et al[30]	Italy	74, ≥65	M and F 981	NCEP 37.2	137	3.8	8	Age, sex, education, albumin, smoking, physical activity, and preexisting diseases
Sundström et al[31]	Sweden	70	M 1221	NCEP 24	302	9.1	8	Smoking, diabetes, hypertension, and total cholesterol
Simons et al[10]	Australia	70, ≥60	M 1233	AHA/NHLBI 31	704	16	7	Age, smoke, alcohol, hypertension, total cholesterol, diabetes, prior coronary heart disease, and peak expiratory flow
			F 1572	34	683			
Wang et al[16]	Finland	70, 65–74	M and F 1025	NCEP 42.7	443	13.5	9	Age, sex, history of myocardial infarction and stroke, smoking, alcohol, physical activity, and total cholesterol
			M 377		218			
			F 648		255			
Mozaffarian et al[8]	USA	73, ≥65	M and F 4528	NCEP 34	2116	15	9	Age, sex, race, education, smoking, physical activity, and alcohol
Wen et al[11]	Taiwan	70, ≥65	M and F 10547	AHA/NHLBI 50.1	1312	8	7	Age, smoking, total cholesterol, estimated glomerular filtration rate
			M 5761	45.6				
			F 4786	54.6				
Hildrum et al[12]	Norway	67, 60–74	M and F 1973	IDF 47	364	7.9	8	Age, sex, physical activity, smoking, total cholesterol, and depression
		82, 75–89	M and F 986	57	503			
Zambon et al[32]	Italy	74, ≥65	M and F 2910	NCEP 39	632	4.4	8	Age, sex, smoking, physical activity, major disease, body mass index, albumin, and low density lipoprotein cholesterol
			M 1174	25.6	341			
			F 1736	48.1	291			
Akbaraly et al[22]	France	73, ≥65	M and F 7118	NCEP 21.2	575	7	8	Sex, education, study center, occupation, living alone, smoking, fish consumption, fruit and vegetable consumption, body mass index, self-report history of vascular disease, cognitive deficit, self-report history of cancer, and self-report history of depression
Salminen et al[14]	Finland	73.5 ≥64	M and F 1260	Modified IDF 19	422	9	7	Age, sex, smoking, exercise, cardiovascular disease, and low density lipoprotein cholesterol
			M 533	17	198			
			F 727	21	224			
Thomas et al[15]	France	69, >65	M and F 6210	Harmonized 40	344	4.9	7	Age, sex, smoking, family history of diabetes, hypertension, cardiovascular events, ECG changes, previous stroke and myocardial infarction, physical activity, and socioeconomic level
Chiang et al[24]	Taiwan	82.5, ≥75	M 680	IDF 31.6	140	3	8	Age, total cholesterol, triglycerides, and diabetes mellitus
Forti et al[25]	Italy	73.2, ≥65	M 917	NCEP 22.4	193	6.5	7	Age, education and cohort of origin, smoking, alcohol, sedentary lifestyle, body mass index, pre-existing major diseases, use of statins, total cholesterol, serum C-reactive protein, and serum interleukin-6
		74, ≥65	F 1043	33.3	179			
Noale et al[13]	Italy	72, 65–84	M and F 2592	NCEP 49.3	297	3.2	8	Age, sex, individual metabolic syndrome criteria and predictors, education, smoking, marital status, hypertension, myocardial infarction, heart failure, angina, stroke, distal symmetrical neuropathy, arrhythmia, claudication, and disability
Mozaffary et al[9]	Iran	73, ≥65	M and F 922	WHO 9.9	193	9.9	7	Age, sex, total cholesterol, smoking, and family history of cardiovascular disease
Kane et al[27]	USA	74.7, ≥65	M and F 2152	IDF 45.5	581	10	9	Age, sex, education, race, and frailty index
Hoogendijk et al[26]	Netherlands	75.4, 65–88	M and F 1247	NCEP 37	982	19	9	Age, sex, educational level, and frailty

AHA/NHLBI = American Heart Association/National Heart, Lung, and Blood Institute, IDF = International Diabetes Foundation, NCEP = National Cholesterol Education Program, WHO = World Health Organization.

Table 2

Characteristics of included studies regarding metabolic syndrome and cardiovascular disease mortality[9,11,12,14,16,22,23,28,32].

Author	Country	Age mean, range, ys	Sex, Participant, no.	Definition of metabolic syndrome, Prevalence, %	Death, No.	Follow-up, ys	Quality score	Adjustment factors
Butler et al[23]	USA	73.6, 70–79	M and F 3055	NCEP 38	130	6	7	Age, sex, race, smoking, marital status, cohort site, and diabetes
Maggi et al[28]	Italy	71, 65–84	M 1357	NCEP 25.9	109	4	7	Age, smoking, fasting insulin, and fibrinogen
		71, 65–84	F 1724	55.2	134			
Wang et al[16]	Finland	70, 65–74	M and F 1025	NCEP 42.7	250	1.35	9	Age, sex, history of myocardial infarction and stroke, smoking, alcohol, physical activity, and total cholesterol
			M 377		126			
			F 648		124			
Wen et al[11]	Taiwan	70, ≥65	M and F 10547	AHA/NHLBI 50.1	300	8	8	Age, smoking, total cholesterol, estimated glomerular filtration rate
			M 5761	45.6				
			F 4786	54.6				
Hildrum et al[12]	Norway	77, 60–74	M and F 1973	IDF 47	219	7.9	8	Age, sex, physical activity, smoking, total cholesterol, and depression
		82, 75–89	986	57	331			
Zambon et al[32]	Italy	74, ≥65	M and F 2910	NCEP 39	230	4.4	8	Age, sex, smoking, physical activity, major disease, body mass index, albumin, and low density lipoprotein cholesterol
			M 1174	25.6	102			
			F 1736	48.1	128			
Akbaraly et al[22]	France	73, ≥65	M and F 7118	NCEP 21.2	133	7	8	Sex, education, study center, occupation, living alone, smoking, fish consumption, fruit and vegetable consumption, body mass index, self-report history of vascular disease, cognitive deficit, self-report history of cancer and self-report history of depression
Salminen et al[14]	Finland	73.5 ≥64	M and F 1260	Modified IDF 19	181	9	9	Age, sex, smoking, exercise, cardiovascular disease, and low density lipoprotein cholesterol
			M 533	17	81			
			F 727	21	100			
Mozaffary et al[9]	Iran	73, ≥65	M and F 922	WHO 40.6	82	9.9	7	Age, smoke, alcohol, hypertension, total cholesterol, diabetes, prior coronary heart disease, and peak expiratory flow

AHA/NHLBI = American Heart Association/National Heart, Lung, and Blood Institute, IDF = International Diabetes Foundation, NCEP = National Cholesterol Education Program, WHO = World Health Organization.

syndrome in accordance with the third report of the National Cholesterol Education Program (NCEP)-Adult Treatment Panel (ATP-III). Three studies[12,24,27] assessed metabolic syndrome using the International Diabetes Federation (IDF) criteria. Two studies[10,11] used criteria from the American Heart Association/National Heart Lung and Blood Institute (AHA/NHLBI). Finally, 2 studies[9,29] used the World Health Organization criteria for metabolic syndrome, and 1 study[15] used the Harmonized criteria. As one study[14] did not measure waist circumference, modified IDF criteria were used, with body mass index (BMI) ≥30 kg/m^2 serving as a proxy for central obesity. The overall quality of the studies averaged 8 points (range, 7–9 points) on a scale from 0 to 9.

3.2. Association of metabolic syndrome with all-cause and CVD mortality in the elderly

Of the 20 studies included in the meta-analysis, 19 and 9 assessed all-cause mortality and CVD mortality, respectively. In 2[10,25] studies that assessed all-cause mortality, men and women were analyzed separately. One[28] study that investigated CVD mortality had 2 datasets since men and women were analyzed separately. In 1[12] study that assessed all-cause and CVD mortality, adults aged 60 to 74 and 75 to 89 years were analyzed separately. Finally, the number of available datasets for all-cause mortality and CVD mortality in relation to metabolic syndrome was 22 and 11, respectively.

Figure 2 shows a forest plot for all-cause mortality and CVD mortality in relation to metabolic syndrome in adults aged 60 years and older. Metabolic syndrome was associated with an increased risk of all-cause mortality and CVD. The combined RRs (95% CI) of all-cause mortality in 19 studies with 22 datasets and of CVD mortality in 9 studies with 11 datasets were 1.23 (1.15–1.32) and 1.24 (1.11–1.39), respectively. There was appreciable statistical heterogeneity across the studies (all-cause mortality, $I^2 = 55.9\%$, $P = .001$; CVD mortality, $I^2 = 58.1\%$, $P = .008$). Supplementary Figure 1, http://links.lww.com/MD/B933 shows that there was no evidence of funnel plot asymmetry in Begg's test (all-cause mortality, $P = .800$; CVD mortality, $P = .243$).

3.3. Subgroup and sensitivity analyses

Subgroup analyses were performed based on age (≥median vs <median), sex (men vs women), geographic location (Europe, United States, or Asia), follow-up duration (≥10 ys vs <10 ys), sample size (≥1000 vs <1000), definition of metabolic syndrome (NCEP, IDF, AHA/NHLBI, or Harmonized), prevalence of metabolic syndrome (≥median vs <median), adjustment of frailty (yes vs no), and quality score (≥8 vs <8). Table 3 summarizes the subgroup analyses of metabolic syndrome and all-cause and CVD mortality in the elderly. Overall, a positive association between metabolic syndrome and increased risk of all-cause mortality was consistently observed in each subgroup, except for the Asian subgroup (RR 1.14, 95% CI 0.83–1.56, $I^2 = 75.1\%$), the sample size <1000 subgroup (RR 1.19, 95% CI 0.90–1.56, $I^2 = 72.8$), and the IDF definition of metabolic syndrome subgroup (RR 1.04, 95% CI 0.93–1.18, $I^2 = 29.1$). However, the positive association between metabolic syndrome and risk of CVD mortality was not statistically significant in the sample size <1000 subgroup (RR 1.41, 95% CI 0.82–2.43, $I^2 = 77.8\%$) or the IDF definition of metabolic syndrome subgroup (RR 1.10,

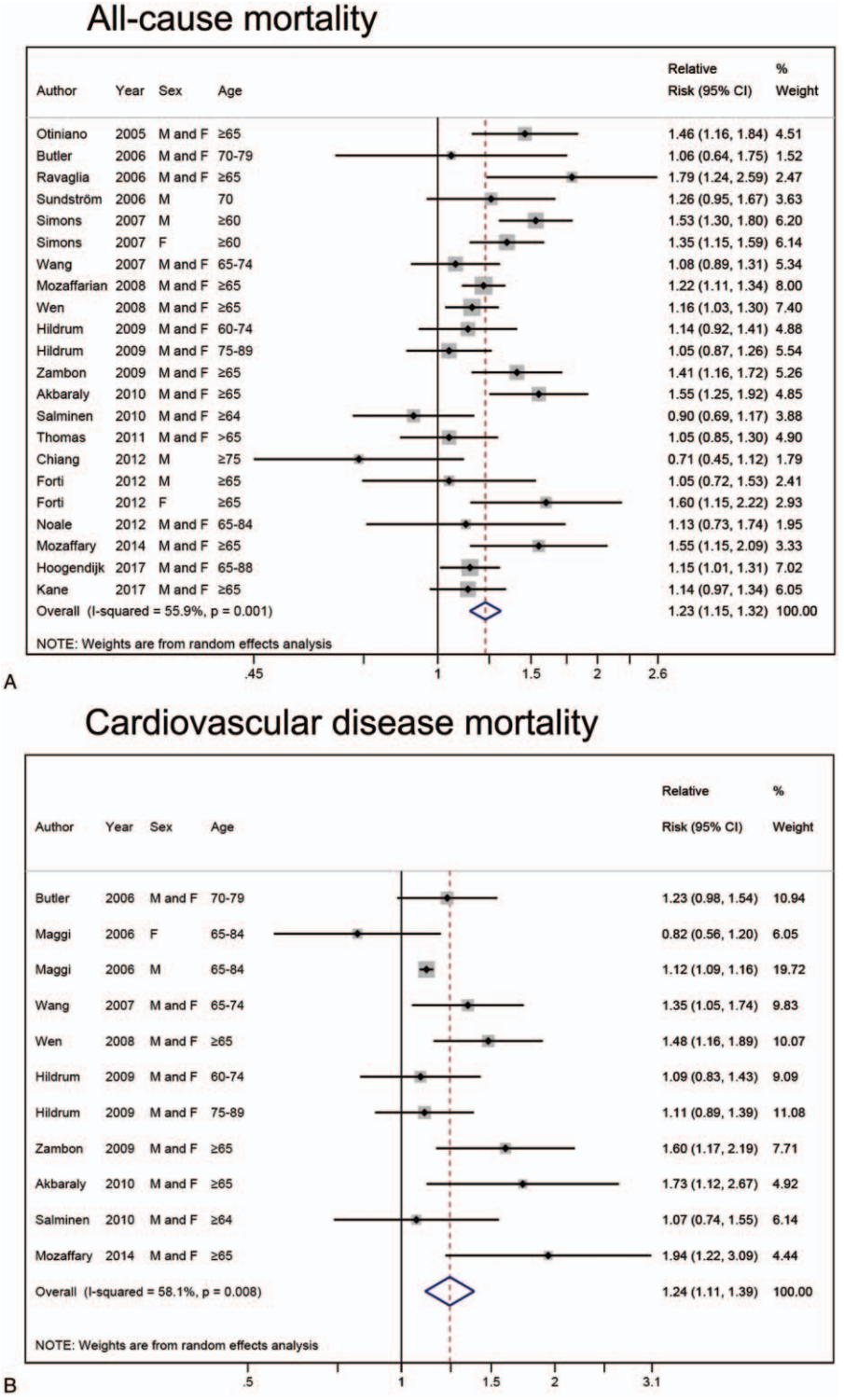

Figure 2. Forest plot of the RRs of all-cause mortality (A) and CVD mortality (B) associated with metabolic syndrome in the elderly.

95% CI 0.94–1.28, $I^2 = 0$). When we included 2 studies[26,27] that adjusted for frailty, the association between metabolic syndrome and all-cause mortality was reduced but remained statistically significant (RR 1.15, 95% CI 1.03–1.27, $I^2 = 0.0\%$). Sensitivity analyses showed that no single study had an effect on the positive association between metabolic syndrome and risk of all-cause mortality or CVD mortality (Supplementary Figure 2, http://links.lww.com/MD/B933).

3.4. Association of components of metabolic syndrome with all-cause and CVD mortality

The 4 definitions of metabolic syndrome applied and the cut-off points for studies regarding the components of metabolic syndrome and all-cause and CVD mortality using the NCEP–ATP III,[8,16,32] AHA/NHLBI,[11] modified IDF,[14] and Harmonized criteria[15] are shown in Supplementary Table 3,

Table 3

Subgroup meta-analyses regarding metabolic syndrome and all-cause and cardiovascular disease mortality in the elderly.

		All-cause mortality				Cardiovascular disease mortality			
Group	Subgroup	Datasets	RR (95% CI)	I^2 (%)	*P* for heterogeneity	Datasets	RR (95% CI)	I^2 (%)	*P* for heterogeneity
Age, ys	≥ Median*	12	1.20 (1.01–1.33)	61.7	.003	7	1.18 (1.04–1.34)	50.4	.060
	< Median*	10	1.26 (1.15–1.38)	50.1	.035	4	1.37 (1.13–1.67)	42.8	.155
Sex	Men	8	1.20 (1.05–1.38)	54.9	.030	5	1.29 (1.09–1.53)	44.8	.124
	Women	6	1.22 (1.02–1.44)	63.1	.019	5	1.20 (0.91–1.60)	47.2	.054
Geographic location	Europe	15	1.24 (1.13–1.36)	60.5	.018	8	1.18 (1.05–1.33)	48.3	.060
	United States	4	1.22 (1.12–1.33)	8.3	.351	1	1.23 (0.98–1.54)	–	–
	Asia	3	1.14 (0.83–1.56)	75.1	.018	2	1.57 (1.26–2.67)	1.6	.313
Follow-up duration, ys	≥ 10	6	1.24 (1.13–1.36)	58.4	.035	0	–	–	–
	< 10	16	1.23 (1.11–1.35)	57.8	.002	11	1.24 (1.11–1.39)	58.1	.008
Sample size	≥ 1000	17	1.24 (1.16–1.32)	50.6	.009	9	1.23 (1.09–1.39)	57.2	.017
	< 1000	5	1.19 (0.90–1.56)	72.8	.005	2	1.41 (0.82–2.43)	77.8	.034
Definition of metabolic syndrome	WHO	2	1.49 (1.24–1.79)	0.0	.756	1	1.94 (1.22–3.09)	–	–
	NCEP	11	1.27 (1.16–1.39)	39.5	.085	6	1.24 (1.06–1.45)	64.2	.016
	IDF	4	1.04 (0.93–1.18)	29.1	.228	3	1.10 (0.94–1.28)	0.0	.985
	AHA/NHLBI	3	1.33 (1.12–1.57)	74.6	.020	1	1.48 (1.16–1.89)	–	–
	Harmonized	1	1.05 (0.85–1.30)	–	–	0	–	–	–
Prevalence of metabolic syndrome	≥ Median†	11	1.16 (1.09–1.22)	0.9	.433	6	1.23 (1.03–1.49)	59.7	.030
	< Median†	11	1.30 (1.16–1.47)	66.0	.001	5	1.26 (1.07–1.48)	58.1	.008
Adjustment of frailty	Yes	2	1.15 (1.03–1.27)	0.0	.935	–	–	–	–
	No	20	1.24 (1.15–1.34)	58.5	.001	–	–	–	–
Quality score	≥ 8	13	1.22 (1.12–1.32)	51.4	.010	6	1.27 (1.11–1.45)	30.7	0.205
	< 8	9	1.24 (1.09–1.41)	64.5	.004	5	1.24 (1.01–1.51)	67.8	0.014

AHA-NHLBI = American Heart Association/National Heart Lung and Blood Institute, CI = confidence interval, IDF = International Diabetes Federation, NCEP = National Cholesterol Education, RR = relative risk, WHO = World Health Organization.

* Median, 73 and 72.5 years old for all-cause mortality and cardiovascular disease mortality, respectively.

† Median, 35.5% and 40.6% for all-cause mortality and cardiovascular disease mortality, respectively.

http://links.lww.com/MD/B933. Supplementary Table 4, http://links.lww.com/MD/B933 summarizes the influence of single components of metabolic syndrome on all-cause mortality (Supplementary Table 4a, http://links.lww.com/MD/B933) and CVD mortality (Supplementary Table 4b, http://links.lww.com/MD/B933), indicating the diagnostic criteria used for these components and the estimates of risk. Figure 3 shows the risk estimates of all-cause[8,11,14,15,32] and CVD mortality[11,14,16,32]

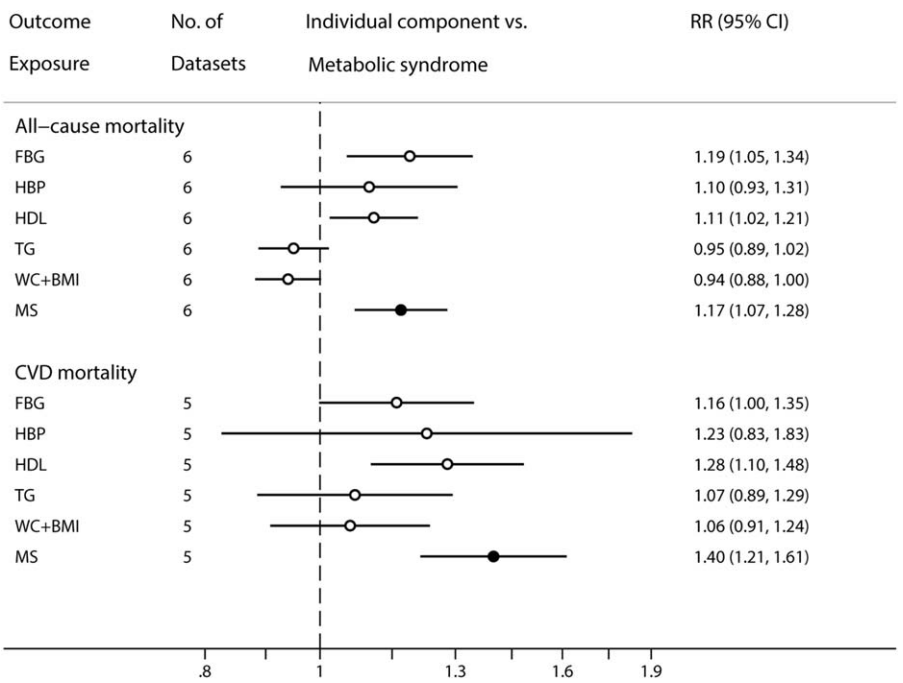

Figure 3. Results of the meta-analysis of each component of metabolic syndrome, full metabolic syndrome, all-cause mortality and CVD mortality. BMI = body mass index, CVD = cardiovascular disease, FBG = fasting blood glucose, HBP = high blood pressure, HDL = high-density lipoprotein, MS = metabolic syndrome, TG = triglycerides, WC = waist circumference.

for each component of metabolic syndrome and for full metabolic syndrome. The overall risk estimate of all-cause mortality for full metabolic syndrome in six datasets was 1.17 (1.07–1.28). The risk estimates of all-cause mortality for higher values of triglycerides and obesity (waist circumference or BMI), compared with lower values, were 0.95 (0.89–1.02) and 0.94 (0.88–1.00), respectively. These estimates were significantly lower than those associated with the full syndrome in the same datasets (all $P < .001$). The overall risk estimates of all-cause mortality for higher values of blood glucose and blood pressure (compared with lower values) and lower values of HDL cholesterol (compared with higher values) were 1.19 (1.05–1.34), 1.10 (0.93–1.31), and 1.11 (1.02–1.21), respectively. These estimates were similar to those recorded for the full syndrome in the same datasets ($P = .826$, $P = .532$, and $P = .405$, respectively). The overall risk estimate of CVD mortality for full metabolic syndrome in 5 datasets was 1.40 (1.22–1.62). The risk estimates of CVD mortality for higher values of triglycerides and obesity (waist circumference or BMI) compared with lower values were 1.07 (0.89–1.29) and 1.06 (0.91–1.24), respectively. These estimates were significantly lower than those associated with the full syndrome in the same datasets ($P = 0.026$ and $P = 0.033$, respectively). The overall risk estimates of CVD mortality for higher values of blood glucose and blood pressure (compared with lower values) and lower values of HDL cholesterol (compared with higher values) were 1.16 (1.00–1.35), 1.23 (0.83–1.81), and 1.28 (1.10–1.48), respectively. These estimates did not differ from those recorded for the full syndrome in the same datasets ($P = .074$, $P = .547$, and $P = .392$, respectively).

4. Discussion

The findings of this meta-analysis indicate that metabolic syndrome is associated with an increased risk of CVD mortality and all-cause mortality in elderly populations. Summarizing the results, we observed a 24% increased risk of CVD mortality and 23% increased risk of all-cause mortality among elderly adults with metabolic syndrome compared to those without metabolic syndrome. The pooled RR values of CVD mortality and all-cause mortality were similar. However, the 95% CI of all-cause mortality was narrower, likely because of the larger sample size. The association of metabolic syndrome with CVD and all-cause mortality was slightly affected by geographic location, sample size, definition of metabolic syndrome, and adjustment for frailty in the subgroup meta-analyses.

A meta-analysis conducted by Wu et al[2] examined the association between metabolic syndrome and all-cause mortality among adults aged ≥20 years in 21 studies. They found that in the general adult population, adults with metabolic syndrome had an increased risk of all-cause mortality compared with those without (RR 1.46, 95% CI 1.35–1.57). As aging is a major contributor to the growing prevalence of metabolic syndrome, it is reasonable to assume that older persons are more frequently affected by the constellation of cardiovascular and metabolic risk factors that constitute metabolic syndrome. Metabolic syndrome predicts cardiovascular mortality, including in older persons.[7,33] However, the pooled RR of our study was much lower than that reported in the meta-analysis of Wu et al, which found an opposite trend in the elderly population (mean age 72.9 ys, >60 ys) than in the overall adult population (mean age 57.5 ys, ≥20 ys). This discrepancy may because of aging-related factors, such as frailty, malnutrition, and immunocompromised states.[34] Under these conditions, the chance that older people will acquire infectious diseases is greater, thus increasing the risk of mortality because of the impairments in homeostasis and functional reserve needed to cope with these stressors.[35] The relationship between metabolic syndrome and mortality in older adults may be explained by other health outcomes, such as frailty and chronic disease. A study[27] showed that metabolic syndrome was positively correlated with frailty index in younger adults (<65 ys) but not in older people (≥65 ys). Furthermore, the frailty index was a better predictor of mortality risk than metabolic syndrome at all ages. Another study[26] showed that physical frailty and chronic disease together constituted a large part of the association between metabolic syndrome and 19-year all-cause mortality in older adults. In our subgroup analyses conducted with adjustment for frailty, the association between metabolic syndrome and mortality was reduced (RR 1.15, 95% CI 1.03–1.27) but remained statistically significant. The results of the RR analyses were not significantly heterogeneous ($I^2 = 0.0\%$, $P = .935$). Nevertheless, a small number[26,27] of studies was used in the analyses. Thus, these results should be interpreted cautiously.

It can be assumed that the association between metabolic syndrome and mortality is influenced by individual components of metabolic syndrome. Therefore, we evaluated the influence of each component of metabolic syndrome using the data available from 6 studies.[8,11,14–16,32] These results indicated that the increased risk of all-cause mortality and CVD mortality caused by metabolic syndrome was not greater than the summed risk of individual metabolic syndrome components, namely, increased fasting glucose, elevated blood pressure, and decreased HDL. Two exceptions were increased triglycerides and obesity (WC and BMI), which were inversely associated with all-cause mortality. Among the metabolic syndrome components, high glucose and low HDL cholesterol significantly predicted the risk of CVD and all-cause mortality. Low HDL cholesterol has already been established as an independent risk factor for mortality in the geriatric population.[36–38] Finally, among metabolic syndrome components, elevated glucose level has consistently predicted higher mortality in older adults.[8,11,16,32]

Notably, obesity had a borderline significant inverse association with all-cause mortality. We found a 6% decreased risk of all-cause mortality among obese elderly adults with an increased waist circumference and BMI ≥30 kg/m^2. Several hypotheses have been proposed to explain the obesity paradox observed in our study. First, selective survival bias is a concern in observational studies. Specifically, individuals who are more susceptible to the adverse health effects of obesity caused by environmental or genetic factors may die when they are younger, resulting in a more resilient overweight older population. Second, in older people, although fat proportion increases with age, higher BMI may also be the result of higher muscle mass, which may result in functional benefits and better survival.[39,40] Finally, obesity may also provide an energy reserve during periods of poor intake in stress or illness.[41] Therefore, the more fat an elderly individual has, the better his or her survival in old age may be, and thus, overweight or obese people may have higher life expectancies than others. For example, in a study that obtained body composition data from community-living older men, the waist circumference associated with the lowest mortality risk was in the overweight range.[42] A recent meta-analysis[19] of an elderly population (median age ≥80 ys) demonstrated that compared with normal-weight individuals (BMI 18.5–24.9 kg/m^2), all-cause mortality decreased by 12% for those who were overweight (BMI 25–29.9 kg/m^2) and 26% for those who were obese (BMI ≥30 kg/m^2). However, all-cause mortality increased by 39% for underweight individuals (BMI

$<18.5\,kg/m^2$). Consistent with a prior meta-analysis of the elderly general population,[43] our meta-analysis showed that obesity reduced all-cause mortality risk among the elderly. However, the studies included in this meta-analysis were limited in terms of the associations between each component of metabolic syndrome and all-cause mortality. Therefore, the results of this analysis should be interpreted with caution.

In several studies, high blood pressure was postulated to be an independent risk factor for CVD mortality and all-cause mortality.[15,44–46] A meta-analysis suggested that prehypertension may be an independent risk factor for CVD mortality in the adult population,[47] showing that prehypertension (systolic blood pressure of 120–139 mmHg or diastolic blood pressure of 80–89 mmHg) was associated with increased CVD but not all-cause mortality. Notably, in our analyses, elevated blood pressure (≥130/85 mmHg or treated hypertension) was not associated with CVD mortality or all-cause mortality. Several mechanisms may explain this nonsignificant effect of elevated blood pressure on mortality in elderly persons. A considerable proportion of elderly individuals with functional disability suffer from widespread vascular alterations, ranging from atherosclerosis and arterial stiffness to microcalcification.[48] Elevated blood pressure may be a compensatory mechanism that preserves the perfusion of vital organs, such as the heart and brain, thereby ultimately preventing morbidity, and mortality among some older adults.[49] It is also possible that poorly functioning older persons may be more vulnerable to the adverse effects of antihypertensive medications.[50] Our findings are consistent with prior studies that have found that the association between blood pressure and mortality diminishes with age because the prevalence of frailty increases with age.[50,51]

Potential limitations of this study should be noted. Residual or unmeasured confounding factors may have influenced the results despite the calculation of risk estimates that reflected the greatest degree of control for potential confounders. Only studies published in English were considered. We were limited to data reported in published articles and did not have access to individual patient-level data. There was some heterogeneity in the different definitions of metabolic syndrome used. Because of the potential heterogeneity between studies, we synthesized the results of the included studies using a random-effects meta-analysis, which incorporates both within- and between-study variability. In addition, to explore heterogeneity, we performed subgroup analyses according to prespecified study-level characteristics using random-effects meta-analyses.

In summary, metabolic syndrome is associated with moderately increased CVD mortality and all-cause mortality in older populations. Of the individual components of metabolic syndrome, both elevated blood glucose and HDL cholesterol were associated with significantly increased mortality, equaling the association of full metabolic syndrome. Regardless of the presence of metabolic syndrome, elderly individuals with high blood glucose and low HDL cholesterol should receive greater attention because of their higher risk of mortality. In contrast, obese or overweight elderly individuals may be likely to have lower all-cause mortality. Thus, the findings of the current meta-analysis raise questions about the utility of the current definition of metabolic syndrome in predicting all-cause mortality and CVD mortality in the elderly population.

Acknowledgments

The authors would like to thank Na-Jin Kim for conducting the database searches and Soon-Jin Ji from the Medical Library, College of Medicine, Catholic University of Korea, for reviewing and editing this article.

References

[1] Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol 2010;56:1113–32.
[2] Wu SH, Liu Z, Ho SC. Metabolic syndrome and all-cause mortality: a meta-analysis of prospective cohort studies. Eur J Epidemiol 2010;25:375–84.
[3] Devers MC, Campbell S, Simmons D. Influence of age on the prevalence and components of the metabolic syndrome and the association with cardiovascular disease. BMJ Open Diabetes Res Care 2016;4:e000195.
[4] Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care 2005;28:1769–78.
[5] Rochlani Y, Pothineni NV, Mehta JL. Metabolic syndrome: does it differ between women and men? Cardiovasc Drugs Ther 2015;29:329–38.
[6] Aguilar M, Bhuket T, Torres S, et al. Prevalence of the metabolic syndrome in the United States, 2003-2012. JAMA 2015;313:1973–4.
[7] Dominguez LJ, Barbagallo M. The biology of the metabolic syndrome and aging. Curr Opin Clin Nutr Metab Care 2016;19:5–11.
[8] Mozaffarian D, Kamineni A, Prineas RJ, et al. Metabolic syndrome and mortality in older adults: the Cardiovascular Health Study. Arch Intern Med 2008;168:969–78.
[9] Mozaffary A, Bozorgmanesh M, Sheikholeslami F, et al. Added value of different metabolic syndrome definitions for predicting cardiovascular disease and mortality events among elderly population: Tehran Lipid and Glucose Study. Eur J Clin Nutr 2014;68:853–8.
[10] Simons LA, Simons J, Friedlander Y, et al. Does a diagnosis of the metabolic syndrome provide additional prediction of cardiovascular disease and total mortality in the elderly? The Dubbo Study. Med J Aust 2007;186:400–3.
[11] Wen CJ, Lee YS, Lin WY, et al. The metabolic syndrome increases cardiovascular mortality in Taiwanese elderly. Eur J Clin Invest 2008;38:469–75.
[12] Hildrum B, Mykletun A, Dahl AA, et al. Metabolic syndrome and risk of mortality in middle-aged versus elderly individuals: the Nord-Trondelag Health Study (HUNT). Diabetologia 2009;52:583–90.
[13] Noale M, Maggi S, Zanoni S, et al. The metabolic syndrome, incidence of diabetes and mortality among the elderly: the Italian Longitudinal Study of Ageing. Diabetes Metab 2012;38:135–41.
[14] Salminen M, Kuoppamaki M, Vahlberg T, et al. The metabolic syndrome defined by modified International Diabetes Federation criteria and mortality: a 9-year follow-up of the aged in Finland. Diabetes Metab 2010;36(6 Pt 1):437–42.
[15] Thomas F, Pannier B, Benetos A, et al. The impact of the metabolic syndrome—but not of hypertension—on all-cause mortality disappears in the elderly. J Hypertens 2011;29:663–8.
[16] Wang J, Ruotsalainen S, Moilanen L, et al. The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns. Eur Heart J 2007;28:857–64.
[17] Denys K, Cankurtaran M, Janssens W, et al. Metabolic syndrome in the elderly: an overview of the evidence. Acta Clin Belg 2009;64:23–34.
[18] Yen YF, Hu HY, Lin IF, et al. Associations of metabolic syndrome and its components with mortality in the elderly: a cohort study of 73,547 Taiwanese adults. Medicine (Baltimore) 2015;94:e956.
[19] Veronese N, Cereda E, Solmi M, et al. Inverse relationship between body mass index and mortality in older nursing home residents: a meta-analysis of 19,538 elderly subjects. Obes Rev 2015;16:1001–15.
[20] Wu CY, Chou YC, Huang N, et al. Association of body mass index with all-cause and cardiovascular disease mortality in the elderly. PLoS One 2014;9:e102589.
[21] Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. University of Ottawa, Department of Epidemiology and Community Medicine, Ottawa, Canada:2009.
[22] Akbaraly TN, Kivimaki M, Ancelin ML, et al. Metabolic syndrome, its components, and mortality in the elderly. J Clin Endocrinol Metab 2010;95:E327–32.
[23] Butler J, Rodondi N, Zhu Y, et al. Metabolic syndrome and the risk of cardiovascular disease in older adults. J Am Coll Cardiol 2006;47:1595–602.
[24] Chiang PH, Liu CL, Lin MH, et al. Survival benefits of metabolic syndrome among older men aged 75 years and over in Taiwan. J Nutr Health Aging 2012;16:520–4.

[25] Forti P, Pirazzoli GL, Maltoni B, et al. Metabolic syndrome and all-cause mortality in older men and women. Eur J Clin Invest 2012;42:1000–9.
[26] Hoogendijk EO, Huisman M, van Ballegooijen AJ. The role of frailty in explaining the association between the metabolic syndrome and mortality in older adults. Exp Gerontol 2017;91:5–8.
[27] Kane AE, Gregson E, Theou O, et al. The association between frailty, the metabolic syndrome, and mortality over the lifespan. GeroScience 2017;39:221–9.
[28] Maggi S, Noale M, Gallina P, et al. Metabolic syndrome, diabetes, and cardiovascular disease in an elderly Caucasian cohort: the Italian Longitudinal Study on Aging. J Gerontol A Biol Sci Med Sci 2006;61:505–10.
[29] Otiniano ME, Du XL, Maldonado MR, et al. Effect of metabolic syndrome on heart attack and mortality in Mexican-American elderly persons: findings of 7-year follow-up from the Hispanic established population for the epidemiological study of the elderly. J Gerontol A Biol Sci Med Sci 2005;60:466–70.
[30] Ravaglia G, Forti P, Maioli F, et al. Metabolic Syndrome: prevalence and prediction of mortality in elderly individuals. Diabetes Care 2006; 29:2471–6.
[31] Sundstrom J, Riserus U, Byberg L, et al. Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. BMJ 2006;332:878–82.
[32] Zambon S, Zanoni S, Romanato G, et al. Metabolic syndrome and all-cause and cardiovascular mortality in an Italian elderly population: the Progetto Veneto Anziani (Pro.V.A.) Study. Diabetes Care 2009;32:153–9.
[33] Dominguez LJ, Barbagallo M. The cardiometabolic syndrome and sarcopenic obesity in older persons. J Cardiometab Syndr 2007;2:183–9.
[34] Wysokinski A, Sobow T, Kloszewska I, et al. Mechanisms of the anorexia of aging-a review. Age (Dordr) 2015;37:9821.
[35] Rizzuto D, Fratiglioni L. Lifestyle factors related to mortality and survival: a mini-review. Gerontology 2014;60:327–35.
[36] Corti MC, Guralnik JM, Salive ME, et al. HDL cholesterol predicts coronary heart disease mortality in older persons. JAMA 1995;274:539–44.
[37] de Freitas EV, Brandao AA, Pozzan R, et al. Importance of high-density lipoprotein-cholesterol (HDL-C) levels to the incidence of cardiovascular disease (CVD) in the elderly. Arch Gerontol Geriatr 2011;52:217–22.
[38] Rahilly-Tierney C, Sesso HD, Michael Gaziano J, et al. High-density lipoprotein and mortality before age 90 in male physicians. Circ Cardiovasc Qual Outcomes 2012;5:381–6.
[39] Lee JS, Auyeung TW, Chau PP, et al. Obesity can benefit survival-a 9-year prospective study in 1614 Chinese nursing home residents. J Am Med Dir Assoc 2014;15:342–8.
[40] Reis JP, Macera CA, Araneta MR, et al. Comparison of overall obesity and body fat distribution in predicting risk of mortality. Obesity (Silver Spring) 2009;17:1232–9.
[41] Oreopoulos A, Kalantar-Zadeh K, Sharma AM, et al. The obesity paradox in the elderly: potential mechanisms and clinical implications. Clin Geriatr Med 2009;25:643–59.
[42] Lee JS, Auyeung TW, Kwok T, et al. Survival benefit of abdominal adiposity: a 6-year follow-up study with dual X-ray absorptiometry in 3,978 older adults. Age (Dordr) 2012;34:597–608.
[43] Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet 2006;368:666–78.
[44] Pannier B, Thomas F, Bean K, et al. The metabolic syndrome: similar deleterious impact on all-cause mortality in hypertensive and normotensive subjects. J Hypertens 2008;26:1223–8.
[45] Shin CY, Yun KE, Park HS. Blood pressure has a greater impact on cardiovascular mortality than other components of metabolic syndrome in Koreans. Atherosclerosis 2009;205:614–9.
[46] Sung KC, Rhee EJ, Ryu S, et al. Increased cardiovascular mortality in subjects with metabolic syndrome is largely attributable to diabetes and hypertension in 159,971 Korean adults. J Clin Endocrinol Metab 2015;100:2606–12.
[47] Huang Y, Su L, Cai X, et al. Association of all-cause and cardiovascular mortality with prehypertension: a meta-analysis. Am Heart J 2014;167: 160–8. e161.
[48] Franklin SS. Elderly hypertensives: how are they different? J Clin Hypertens (Greenwich) 2012;14:779–86.
[49] Lionakis N, Mendrinos D, Sanidas E, et al. Hypertension in the elderly. World J Cardiol 2012;4:135–47.
[50] Muller M, Smulders YM, de Leeuw PW, et al. Treatment of hypertension in the oldest old: a critical role for frailty? Hypertension 2014;63:433–41.
[51] Odden MC, Peralta CA, Haan MN, et al. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. Arch Intern Med 2012;172:1162–8.