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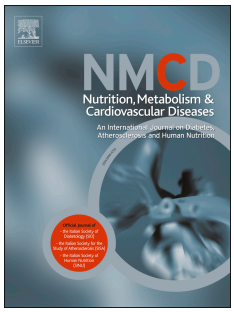

Gender Differences In The Impact Of Metabolic Syndrome Components On Mortality In Older People: A Systematic Review And Meta-Analysis

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GENDER DIFFERENCES IN THE IMPACT OF METABOLIC SYNDROME COMPONENTS ON MORTALITY IN OLDER PEOPLE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Running head: metabolic syndrome components and mortality in older people

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ABSTRACT

Background and Aims: The influence of metabolic syndrome (MetS) on mortality may be influenced by age- and gender-related changes affecting the impact of individual MetS components. We investigated gender differences in the association between MetS components and mortality in community-dwelling older adults.

Methods and Results: Prospective studies were identified through a systematic literature review up to June 2019. Random-effect meta-analyses were run to estimate the pooled relative risk(RR) and 95% confidence intervals(95%CI) of all-cause and cardiovascular (CV) mortality associated with the presence of MetS components (abdominal obesity, high triglycerides, low HDL cholesterol, high fasting glycemia, and high blood pressure) in older men and women. Meta-analyses considering all-cause (103,859 individuals, 48,830 men, 55,029 women; 10 studies) and CV mortality (94,965 individuals, 44,699 men, 50,266 women; 8 studies) did not reveal any significant association for abdominal obesity and high triglycerides in either gender. Low HDL was associated with increased all-cause (RR=1.16,95%CI:1.02-1.32) and CV mortality (RR=1.34, 95%CI:1.03-1.74) among women, while weaker results were found for men. High fasting glycemia was associated with higher all-cause mortality in older women (RR=1.35, 95%CI:1.22-1.50) more than in older men (RR=1.21, 95%CI:1.13-1.30), and CV mortality only in the former (RR=1.36, 95%CI:1.04-1.78). Elevated blood pressure was associated with increased all-cause mortality (RR=1.16, 95%CI:1.03-1.32) and showed marginal significant results for CV death only among women.

Conclusions: The impact of MetS components on mortality in older people present some gender differences, with low HDL cholesterol, hyperglycemia, and elevated blood pressure being more strongly associated to all-cause and CV mortality in women**.**

Keywords: metabolic syndrome components; all-cause mortality; cardiovascular mortality; sex; older people.

INTRODUCTION

Metabolic Syndrome (MetS) is a clinical condition characterized by a complex cluster of metabolic dysfunctions. Although MetS has been variously defined in recent decades, it has been most commonly considered as the presence of at least three components among: large waist circumference, high triglyceride levels, low HDL cholesterol, elevated blood pressure, and high fasting glycemia [1]. As estimated by the International Diabetes Federation (IDF), around one out of four individuals worldwide are affected by MetS, with possible differences according to the age, gender and ethnic origin of the population under study [2,3]. The most unifying hypothesis for MetS pathophysiology is that it involves the mechanisms of insulin resistance, mild chronic inflammation, and neuroendocrine activation, which may be triggered concurrently by an increase in visceral adiposity [3–5]. Hence, environmental and lifestyle factors leading to excess weight play an extremely important role in the development of MetS [6], although even individuals with normal weight can present with MetS [7] and are therefore equally exposed to an increased risk of accumulating additional cardiovascular (CV) and metabolic dysfunctions [8].

While MetS has been largely associated with higher all-cause and CV mortality in adult age, mixed results have emerged from studies on older populations, where MetS is even more prevalent [9,10]. In light of this discrepancy, the relationship between MetS and mortality could be more deeply explored by analyzing how the impact of each single component changes with aging. Changes in the effects of MetS components on mortality in advanced age may be due to differences in the extent of their pathological actions, but also to the inappropriateness for older populations of the threshold levels commonly used to define the syndrome [11–13]. Gender is a further issue. Although the prevalence of MetS and its components is generally higher in men than in women of adult age, after menopause such differences tend to disappear or even to reverse [11]. This is likely due to specific biological connotates linked to each sex (e.g., hormonal changes), as well as to gender-related factors (e.g. risk behaviors) leading to a steeper increase in the prevalence of MetS in women, who present more frequently with visceral obesity and low HDL cholesterol, while elevated blood pressure,

hypertriglyceridemia, and hyperglycemia seem to be the major contributors to MetS in men [11]. Sex/gender may also play a role in the impact of MetS on CV risk [14], which increases *per se* in women after menopause. Previous studies have shown that MetS is more strongly associated with CV risk in women than in men, although the difference seems to be mostly driven by an increased risk of hyperglycemia, so it is still unclear whether the impact of individual MetS components on health-related outcomes is subject to gender differences [11,15].

In light of the above considerations, we carried out a systematic review and meta-analysis of the current literature with the aim of summarizing the impact of individual MetS components on mortality in older men and women. Our hypothesis was that the individual components for MetS determined by the standard cutoffs are poorly associated with mortality in the older population, and that the relationship is subject to gender differences.

METHODS

This work has been done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Appendix 1 for the checklist).

Literature search

A systematic review of the literature was performed through the PubMed, Web of Science, and CINHAL electronic databases from inception to June 5, 2019. The reference lists of articles selected, previous systematic reviews of the topic, [16] and relevant websites (e.g., Google Scholar, EBSCO Open Dissertation) were also manually screened to identify potentially eligible studies, including doctoral and masters theses. No geographical or language restrictions were applied. We designed a search strategy for each electronic database, which included, in accordance with PICOS criteria, the following research themes: metabolic syndrome components (exposures), all-cause or CV mortality (outcomes), older people (study population) (Appendix 2). The comparison groups were people presenting with *vs* without the various metabolic syndrome components. In our study design, we applied a specific filter to narrow our search to longitudinal studies.

Study selection

The studies were selected on the basis of the following inclusion criteria:

- Population: community-based studies in which at least 60% of participants were aged 65 years or over were included.
- Exposure and comparison: studies that compared individuals who presented with and did not present with the individual MetS components (i.e., abdominal obesity, hypertriglyceridemia, low HDL-C, high fasting glucose, and high blood pressure) were included.
- Outcome: studies that examined all-cause mortality or CV mortality reporting either the number of deaths during the follow-up or the estimates for the risk of death were included.

Since we aimed to evaluate gender differences in the associations between each MetS component and mortality, we excluded studies that did not report results for each component, and that did not present separate analyses for men and women. Studies carried out in hospitals or nursing homes were also excluded, as were studies that involved only individuals affected by particular diseases (e.g., diabetes, chronic pulmonary diseases, etc.).

To identify eligible studies, a first selection by title and abstract was carried out independently by two researchers (MD and AB), who included longitudinal studies that involved community-dwelling older people and investigated the association between MetS and mortality. In a second step, two independent reviewers (MD and CT) reviewed the full texts of these studies, and selected papers based on the inclusion and exclusion criteria described above. Any disagreements during the study selection process were discussed between researchers until reaching consensus, and, if necessary, a third independent reviewer (GS) was involved.

Quality assessment

The quality of the selected studies was assessed independently by two researchers (MD and CT) using the Newcastle-Ottawa scale (NOS) for cohort studies [17]. Scores on the NOS scale range from 0 to 9, the higher scores indicating better quality. In the present work, a study with a score ≥7 was considered high quality (for details on the NOS criteria, see Supplementary Table S1) [18].

Data extraction

Two independent researchers (MD and CT) extracted data from the full texts of each of the studies on a structured Excel form. We extracted the following data from each study: the first author's last name, publication year, study cohort and country, MetS definition and criteria with possible modifications, outcome, risk estimate, and adjustments for covariates. Where available, we extracted additional information stratified by sex on: sample size, follow-up interval, age, and prevalence of MetS. For each MetS component, we extracted data on the number of all-cause and CV deaths over the study period, and, if available, the relative risk (RR) or the hazard ratio (HR), with 95% confidence interval (95%CI) [19]. In case of availability of only raw data, we computed a crude RR. Where multiple options were available in the same study, we prioritized the most adjusted risk estimate and the longest follow-up interval. Where several studies used the same study cohort, we included the most recent or the one with the most complete data relevant to the aims of our work. Where MetS components were defined according to different criteria, we used data conforming to the most common definition in the main analysis, while other cutoffs were considered in sensitivity analyses. Finally, the authors of the studies were contacted by email when additional information or clarifications were needed or to request unpublished data.

Statistical analysis

The associations between the pooled RRs with 95% CIs of all-cause and CV mortality and the presence of each MetS component in older men and women were estimated from a random-effects meta-analysis. Random-effects models were chosen because of the expected heterogeneity in the observational studies included in our work. The presence of statistical heterogeneity among studies was tested by using the Chi-squared test (setting statistical significance at a p-value <0.10), and its extent was evaluated with the I-squared (I^2) statistic [20]. In accordance with previous studies, we used I^2 values of <25% to define low heterogeneity, 25-75% for moderate heterogeneity, and >75% for high heterogeneity. The presence of publication bias was evaluated for each analysis using the Egger regression test, and was graphically illustrated using funnel plots [21].

As subgroup analyses, we performed random-effects meta-analyses to compare results by MetS criteria (only for abdominal obesity and high fasting glycemia components), study location, MetS prevalence, length of the follow-up, and adjustment for confounders. Where different studies defined the same MetS component

according to different criteria, we took the most frequently used criterion for our main analysis (i.e., the National Cholesterol Education Program [NCEP] Adult Treatment Panel III [ATP III] criteria), and the other criteria for our sensitivity analysis. Finally, we performed a leave-one-out sensitivity analysis to evaluate the impact of each study on the size of the overall effect [22]. Analyses were performed using the *epitools* (to compute crude RR) and *metaphor* [23] packages in R (R Foundation for Statistical Computing, Vienna, Austria) [24].

RESULTS

Of the 4503 records identified from the literature search, 167 were eligible at the title-abstract selection, and 12 studies were ultimately included in our meta-analysis (a flow-chart of the study selection process is given in Supplementary Figure S1). Six studies evaluated both all-cause and CV mortality, four only all-cause mortality, and two only CV mortality. The main features of the selected works are shown in Table 1. The mean or median age of participants in most of the studies was over 70 years, and the median length of the follow-up interval was 9 years (range 4-16 years). Regarding location, six studies were conducted in Europe [25–30], three in Asia [31–33], two in the USA [9,34], and one in Australia [35]. The majority of the studies (n=5) used NCEP ATP III criteria to define MetS [25–27,30,34], two used the revised NCEP ATP III (R-NCEP) [9,33], two the International Diabetes Federation (IDF) definition [28,29], two the American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) criteria [32,35], and one the HC2009 criteria [31]. Two studies presented data referring to more than one MetS definition [25,29]. Based on these criteria, we found that the median prevalence of MetS was 29.5% in men, and 48.3% in women. Figures 1-5 illustrate the sex-specific results of the meta-analyses of each MetS component and all-cause mortality (103,859 individuals [48,830 men, 55,029 women]), and CV mortality (94,965 individuals [44,699 men, and 50,266 women]). The pooled estimates obtained after stratifying studies by adjustment for potential confounders are presented in Table 2. The results for each MetS criterion in older men and women are described in the following paragraphs.

Abdominal obesity. Overall, the presence of abdominal obesity was not significantly associated with either all-cause or CV mortality, in both men and women (Figure 1). The between-studies heterogeneity was moderate in the analysis of all-cause mortality in men (Q-test: P = 0.02, I^2 = 60.7%), and low for CV

mortality (Q-test: $P = 0.18$, $I^2 = 11.4\%$), but was not estimable for women. The Egger regression test showed there to be no publication bias ($P > 0.05$ for all analyses; Supplementary Figures S2-S3). No significant differences were observed between studies presenting unadjusted vs. adjusted results (Table 2). Our subgroup analyses (Supplementary Table S2) showed a significant inverse association between high waist circumference and all-cause mortality when the component was defined based on ethnic-specific criteria (*P* for heterogeneity = 0.02). The leave-one-out analysis (Supplementary Table S3-S4) revealed that the Simons study potentially attenuated the indirect association between abdominal obesity and all-cause mortality in men [35], while no relevant differences were observed when excluding studies whose risk estimates were adjusted for BMI [25,30].

High triglyceride levels. A marginal significant association between high triglyceride levels and reduced all-cause mortality was observed in older women, while no significant results were found considering CV mortality for both genders, and all-cause mortality for older men (Figure 2). The between-studies heterogeneity was low (Q-test: $P = 0.34$, $I^2 = 2.5\%$) for men for CV mortality, but moderate for the other analyses. No publication bias emerged at the Egger regression test ($P > 0.05$ for all analyses; Supplementary Figure S2). The non-significant association between hypertriglyceridemia and mortality did not substantially change at our subgroup analyses (Table 2, Supplementary Table S5), while the leave-one-out analyses suggested that the Simons [35] and Wen [32] studies potentially attenuated the indirect association between high triglycerides and all-cause death in women (Supplementary Table S3-S4).

Low HDL cholesterol. Low levels of HDL-C increased both all-cause (RR = 1.16, 95% CI: 1.02-1.32) and CV mortality (RR = 1.34, 95% CI: 1.03-1.74) among women, while similar but weaker results were found for men, with marginal significant estimates for CV mortality (Figure 3). The between-studies heterogeneity was moderate for all analyses, and there was no evidence of publication bias (Supplementary Figures S2-S3). Our subgroup analyses (Supplementary Table S6) showed that in the studies with longer follow-up there were stronger associations between low HDL-C and all-cause mortality in both genders (*P* for heterogeneity <0.05), and CV mortality among women (*P* for heterogeneity <0.001). Similarly, as shown in Table 2, the association between low HDL-C and increased all-cause and CV mortality seemed to be accentuated when considering studies with adjusted results in both genders, especially in men (*P* for heterogeneity <0.05). The

leave-one-out analyses (Supplementary Table S3-S4) revealed that the Kuk [9] Salminen [28] and Zambon [30] studies potentially attenuated the pooled results on the association between HDL-C and CV mortality in men. A similar effect was observed in the female gender for the studies of Kuk [9], Sun [31] and Wang [29], while the work of Yen [33] tended to strengthen the direct association between HDL-C and CV mortality.

High fasting glycemia. Our pooled results showed that high fasting glycemia was associated with increased all-cause mortality in older men (RR = 1.21, 95% CI: 1.13-1.30), and more markedly in older women (RR = 1.35, 95% CI: 1.22-1.50) (Figure 4). The findings were similar for CV mortality only among women (RR = 1.36, 95% CI: 1.04-1.78). Between-studies heterogeneity was moderate for all analyses, except CV mortality in men (non-estimable). Possible publication bias emerged only among studies on high fasting glycemia and CV mortality in women (P = 0.03, Supplementary Figure S2). Our subgroup analyses (Supplementary Table S7) revealed a stronger association between a high fasting glycemia level ≥6.1 mM and CV mortality in women (P for heterogeneity = 0.05). Moreover, in studies conducted in Asia or Australia there was an increased risk of all-cause mortality among women (P for heterogeneity = 0.09), and among men in studies with longer follow-up intervals (P for heterogeneity = 0.05). No substantial differences were observed, instead, when comparing studies that presented unadjusted vs. adjusted results (Table 2). At the leave-one-out analysis, the Salminen [28], Wen [32] and Yen [33] studies seemed to attenuate the association between high fasting glycemia and CV mortality among women. No substantial differences where seen after excluding the study of Maggi [26], whose results were adjusted for fasting insulin levels (Supplementary Table S3-S4).

Elevated blood pressure. The presence of high blood pressure was associated with increased all-cause mortality (RR = 1.16, 95% CI: 1.03-1.32), and showed a marginal significant relationship with CV mortality (RR = 1.39, 95% CI: 1.00-1.94) in women, but not in men (Figure 5). Between-studies heterogeneity was moderate in the analyses on women, but high in those on males. No publication bias emerged from the Egger regression test (P >0.05 for all analyses; Supplementary Figure S2). No significant differences emerged when comparing studies by confounders' adjustment, although the direct association between elevated blood pressure and all-cause and CV mortality seemed to be more marked in adjusted models for men (Table 2). In the other subgroup analyses (Supplementary Table S8), European study populations seemed to weaken the

association between high blood pressure and all-cause mortality in men (*P* for heterogeneity = 0.05), and CV mortality in both men (*P* for heterogeneity = 0.003) and women (*P* for heterogeneity = 0.02). Instead, studies with longer follow-up reported stronger associations between high blood pressure and all-cause mortality among women (*P* for heterogeneity <0.001). The leave-one-out analysis showed that the Wang [29] study potentially attenuated the results on CV mortality among women (Supplementary Table S3-S4).

DISCUSSION

Our systematic review and meta-analysis suggest that the impact of MetS components on all-cause and CV mortality changes with advancing age and presents some differences between men and women.

Abdominal obesity. Abdominal obesity has been suggested as playing an important role in MetS and has been largely associated with a higher risk of mortality in young and adult individuals. However, the results regarding its impact on mortality in advanced age have been mixed [31,33,36–38]. Interestingly, the pooled results of our meta-analysis did not show any significant association between abdominal obesity and all-cause or CV mortality. Among the studies we assessed, only Simons et al., who used BMI instead of waist circumference, reported a direct association between obesity and all-cause mortality in older men [35], while Kuk and colleagues even found the opposite [9]. These findings raise several issues. First of all, in older populations waist circumference is not always indicative of visceral obesity due to possible age-related reductions in stature and changes in body composition [39], which could lead to misclassification bias and may skew the association between abdominal obesity and mortality. On the other hand, the use of BMI as a proxy for abdominal obesity in older age could also be problematic because it does not provide information on body composition, and older adults with reduced muscle mass and high adiposity could still have a normal BMI [40]. Secondly, our results may be influenced by selective survival, since the individuals who are more vulnerable to the adverse effects of obesity on health could have died at a younger age, while the survivors may represent the most resilient overweight/obese older population [16]. Previous studies have shown that mortality increases only with a marked excess of weight, while overweight or grade 1 obesity carried a similar or even lower risk of all-cause death compared with normal weight [36–38,41]. Although the survival advantage linked to modest excess weight is still unclear, it has been suggested that it is less

likely to be associated with the presence of chronic diseases, but, instead, may increase the resilience of older individuals [16,34].

High triglyceride levels. Our pooled results did not show any strong significant association between high triglycerides levels and all-cause or CV mortality in older men and women. However, mixed results emerged when we evaluated individual studies. In some cases, hypertriglyceridemia even seemed to be associated with a lower risk of CV [31] or all-cause mortality in only one gender (male [9,31] or female [28,31,34]), and in another case in both men and women [33]. Conversely, only Forti et al. found that hypertriglyceridemia increased all-cause mortality in older men [25], confirming previous findings [42]. Similarly to what we found for abdominal obesity, the lack of strong associations between hypertriglyceridemia and mortality in older people could be due to selective survival, since individuals with higher CV risk associated with elevated triglycerides could have died earlier, while the more resilient adults reached older age. Moreover, higher triglycerides in the elderly could reflect better nutritional status, and low levels could be sign of illness or frailty [25].

Low HDL cholesterol. As well known, HDL cholesterol has antioxidant and anti-inflammatory actions that may prevent the onset or slow the progression of atherosclerosis and related diseases [43,44]. In agreement with some studies [45], but conflicting with others [34], our meta-analysis confirms a low HDL-C level as a significant risk factor of mortality in older people [46]. This effect was more marked for women, and when we considered the CV mortality in studies with shorter follow-up intervals. As suggested by previous works, the observed gender differences could be due to the changes in sex hormones occurring after menopause, which alter lipid metabolism and increase the prognostic value of lipid alterations in women more than in men [47–49]. In addition, as mentioned for other MetS component, an aspect to consider is selective survival, since men with worse CV prognosis linked to unhealthy lipid profiles could have died at an earlier age.

High fasting glycaemia. Our results highlight gender differences in the role of hyperglycemia as a risk factor of mortality. In particular, high fasting glycemia was associated with increased all-cause mortality by 21% in older men, and by 35% in older women, while the risk of CV death was significantly higher (+36%) only in women. The greater predictive values of elevated glycemia and high blood pressure compared with MetS itself in advanced age was already reported in the Cardiovascular Health Study (CHS) [34]. This

finding may be related to the substantial role of insulin resistance in promoting chronic inflammation and atherosclerosis, which overall increase CV risk [50–53]. In the older population of the CHS, the association with mortality was tested with the most commonly used cutoff levels of fasting glycaemia – 5.6 and 6.1 mM – and, in line with previous works [34], we found that higher thresholds could be better predictors of mortality in advanced age. This issue needs to be further corroborated in the future, as well as the potential differential impact on mortality of prediabetes vs. overt diabetes. As far as gender differences on the association of elevated fasting glycaemia with mortality are concerned, we observed stronger results in older women, especially regarding CV mortality. These findings corroborate previous meta-analyses, which showed that the relative risk of CV diseases and stroke associated with hyperglycemia was higher in women than in men [52,54–57]. Although the higher CV risk profile of diabetic women could play a role in explaining these disparities, the results were unchanged after adjustment for other CV risk factors, suggesting that other mechanisms may be involved [56,57]. Among these, variations in sex hormones, a longer period in the pre-diabetes stage, and delayed diagnosis and treatment of CV could contribute to the observed gender differences, but this needs further clarification [54,56–58].

Elevated blood pressure. The pooled results of our meta-analysis suggest that high blood pressure may be associated with an increased risk of all-cause and CV mortality only in older women. Similar results were found in the CHS, with women showing a higher mortality risk linked to this MetS component than men, after adjusting for sociodemographic, lifestyle, and other cardio-metabolic factors. However, mixed findings have emerged from other studies, although only a few of them focused extensively on older people. Despite similar increases in systolic blood pressure were associated with greater CVD risk in women than in men [59–62], no differences emerged for CV mortality [62] or other outcomes, such as ischemic heart diseases or stroke [63]. Our results support a stronger impact of elevated blood pressure on mortality among older women, and this could be due both to sex-specific (e.g., hormonal changes after menopause) and gender-specific (e.g., risk behaviors, disparities in the management of the disease) aspects, which will deserve future investigations [64]. A further issue to be considered when interpreting our results is the possible selective survival of those men less vulnerable to the adverse effects of hypertension in young and adult age, when women's CV risk is lower due to the action of estrogens. Finally, it should be considered that older people are susceptible not only to high but also to low blood pressure. Studies suggest that the relationship between

blood pressure and mortality in advanced age seems to be J-shaped with a nadir around 100 mmHg [28,59], confirming that in older people low blood pressure could be a marker of frailty and health deterioration. This may have influenced our results since the additional risk of death due to low blood pressure seems to be more marked in older men than in women, and could therefore have offset the mortality risk due to elevated blood pressure [59].

Potential limitations of our work include the relatively small number of studies, and the heterogeneity among them, especially due to ethnic-related factors, use of different MetS criteria and residual confounding on the studied associations. Moreover, as reported when discussing the single MetS criteria, potential misclassification and selective survival biases need to be taken into account in the interpretation of our findings. In particular, both the duration of exposure to the cardio-metabolic components of MetS, and the interference of therapeutic actions (that could have changed over time) on the presence of such conditions are substantial factors that may have influenced the observed associations. On the other hand, the use of random-effect meta-analysis and the sensitivity and subgroup analyses performed support our main findings, and the gender-specific focus on the association between single MetS criteria and mortality might represent a source of novelty of our work.

CONCLUSIONS

Our systematic review and meta-analysis suggest that the influence of individual MetS components on all-cause and CV mortality differs in older people compared with young or middle-age adults, and presents some gender-specific features. While low HDL cholesterol, hyperglycemia, and hypertension also seem to predict mortality in the elderly, especially among women, the associations of both abdominal obesity and high triglyceride levels with mortality seem to weaken in advanced age. These findings support the need to use a personalized approach when evaluating metabolic health of older people in the clinical practice. Such approach should prefer the assessment of single MetS components rather than the overall syndrome and should account for age- and gender-related aspects that could modify the impact of single MetS components on individuals' prognosis.

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Table 1. Characteristics of the 12 studies included in the systematic review and meta-analysis

Author, year	Cohort (Country)	Sample size	Age	Follow-up (years)	MetS criteria	MetS prevalence	Outcomes [n deaths]	Adjustment factors
Kuk, 2010 [9]	NHANES III (US)	700 (M) 779 (F)	73.0±0.3 (M) 74.1±0.3 (F)	10.5 (M) 11.7 (F)	R-NCEP	55.5 (M) 54.7 (F)	All-cause mortality [n=1027] CV mortality [n=518]	None
Forti, 2012 [25]	CSBA and PS studies (Italy)	917 (M) 1043(F)	73.2±5.9 (M) 74.0±6.4 (F)	6.5	NCEP	22.4 (M) 33.3 (F)	All-cause mortality [n=372]	Age, education, cohort, smoking status, alcohol intake, sedentary lifestyle, BMI, pre-existing major diseases, use of statins, total cholesterol, serum CRP and IL-7
Maggi, 2006 [26]	ILSA (Italy)	1169 (M) 1493 (F)	71.6±4.9 (M) 72.2±6.1 (F)	4	NCEP	25.9 (M) 55.2 (F)	CV mortality[a] [n=203]	Age, smoking status, fasting insulin levels, fibrinogen
Ohrvik, 2009 [27]	Population-based study (Sweden)	197 (M) 203 (F)	75	9 (M) 10.3 (F)	NCEP	24.2 (M) 36.9 (F)	All-cause mortality [n=228]	None
Salminen, 2010 [28]	Population-based study (Finland)	533 (M) 727 (F)	≥64	9	IDF (BMI≥30 was used instead of WC)	17.0 (M) 21 (F)	All-cause mortality [n=422] CV mortality[b] [n=181]	Age, current smoking, frequency of exercise, CVD, LDL cholesterol, other MetS components
Wang, 2007 [29]	Population-based study (Finland)	377 (M) 648 (F)	65-75	13.5	IDF		CV mortality[a] [n=250]	Age, history of MI or stroke, current smoking, alcohol consumption, physical activity, total cholesterol
Zambon, 2009 [30]	Pro.V.A. study (Italy)	1174 (M) 1736 (F)	≥65	4.4	NCEP	25.6 (M) 48.1 (F)	All-cause mortality [n=632] CV mortality[a] [n=230]	Age, smoking, physical activity, BMI, LDL cholesterol, MetS. For all-cause mortality, model adjusted also for major diseases and albumin.
Sun, 2012 [31]	Population-based study (China)	994 (M) 541 (F)	61.1±5.6 (M) 59.6±4.4 (F)	15.1	HC2009	28.0 (M) 48.4 (F)	All-cause mortality [n=414] CV mortality[c] [n=153]	Age, marital status, education, occupation, current smoking, current drinking, LDL-C.
Wen, 2008 [32]	Population-based study (Taiwan)	5761 (M) 4786 (F)	70.2±4.4 (M) 70±4.5 (F)	8	AHA/NHLBI	45.6 (M) 54.4 (F)	All-cause mortality [n=1312] CV mortality[a] [n=300]	Age, smoking, total cholesterol, eGFR
Yen, 2015 [33]	Population-based study (Taiwan)	33991 (M) 39556 (F)	≥65	4	R-NCEP	40.5 (M) 59.5 (F)	All-cause mortality [n=2944] CV mortality[d] [n=704]	Age, marital status, education, smoking, alcohol consumption, regular exercise, renal function status, hyperuricemia, hypoalbuminemia, anemia, platelet count, liver function
Mozaffarian, 2008 [34]	Cardiovascular Health Study (US)	1665 (M) 2593 (F)	73.0±5.1 (M) 73.0±5.2 (F)	15	NCEP	31.0 (M) 38.0 (F)	All-cause mortality [n=2116]	Age, race, education, smoking status, smoking history, physical activity, alcohol use, and each of the other MetS criteria
Simons, 2007 [35]	Dubbo study (Australia)	1233 (M) 1572 (F)	68.6±6.7 (M) 69.6±7.3 (F)	16	AHA/NHLBI (BMI≥29.3 instead of WC)	31.0 (M) 34.0 (F)	All-cause mortality [n=1387]	Age, smoking habits, alcohol consumption, total cholesterol, prior CHD, PEF (all criteria are included in the model)

Notes. CV mortality refers to: [a] ICD-9 codes 390-459; [b] ICD-10 codes I10-I15, I20-I25, I50, I60-I66, I69, I71, I74; [c] ICD-9 codes 390-398.9, 401.0-429.9, 430.0-438.9; [d] ICD-9 codes 390-459, ICD-10 codes I00-I99. *Abbreviations*: AHA/NHLBI, American Heart Association/the National Heart, Lung, and Blood Institute; BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; F, female; HC2009, Harmonized Criteria of 2009; ICD, International Classification of Diseases; IDF, International Diabetes Federation; IL-7, Interleukin 7; LDL-C, low density-lipoprotein cholesterol; MetS, metabolic syndrome; M, male; MI, myocardial infarction; NCEP, National Cholesterol Education Program; R-NCEP, Revised National Cholesterol Education Program; PEF, peak expiratory flow; WC, waist circumference.

Table 2. Pooled Relative Risk of mortality according to the presence of MetS criteria considering studies stratified by adjustment for potential confounders

MetS component	All-cause mortality					Cardiovascular mortality				
	N studies	Men RR (95%CI)	*P*-value	Women RR (95%CI)	*P*-value	N studies	Men RR (95%CI)	*P*-value	Women RR (95%CI)	*P*-value
Abdominal obesity										
Unadjusted models	2	0.83 (0.64-1.08)	0.26	0.91 (0.76-1.10)	0.57	1	0.83 (0.61-1.13)	0.29	0.96 (0.69-1.34)	0.70
Adjusted models	8	0.98 (0.87-1.10)		0.97 (0.90-1.04)		7	1.00 (0.86-1.17)		0.89 (0.76-1.05)	
High triglyceride levels										
Unadjusted models	2	0.83 (0.66-1.16)	0.45	0.91 (0.67-1.23)	0.90	1	0.86 (0.62-1.19)	0.66	0.78 (0.41-1.49)	0.71
Adjusted models	8	0.98 (0.84-1.13)		0.89 (0.78-1.02)		7	0.93 (0.79-1.11)		0.89 (0.67-1.18)	
Low HDL cholesterol										
Unadjusted models	2	0.93 (0.80-1.08)	0.04	1.08 (0.77-1.52)	0.66	1	0.94 (0.73-1.22)	0.02	1.08 (0.53-2.21)	0.53
Adjusted models	8	1.11 (1.04-1.19)		1.18 (1.01-1.37)		7	1.33 (1.16-1.54)		1.39 (1.03-1.88)	
High fasting glycemia										
Unadjusted models	2	1.17 (0.97-1.41)	0.70	1.39 (1.04-1.86)	0.83	1	1.05 (0.82-1.34)	0.78	1.30 (0.58-2.93)	0.87
Adjusted models	8	1.22 (1.12-1.32)		1.34 (1.18-1.53)		7	1.01 (0.88-1.15)		1.40 (1.00-1.96)	
Elevated blood pressure										
Unadjusted models	2	0.89 (0.57-1.37)	0.27	1.34 (0.93-1.95)	0.41	1	1.09 (0.39-3.03)	0.74	1.82 (0.71-4.69)	0.55
Adjusted models	8	1.16 (0.96-1.40)		1.14 (0.99-1.31)		7	1.32 (0.87-2.00)		1.33 (0.90-1.96)	

Abbreviations: RR, relative risk; 95%CI, 95% confidence interval.

FIGURE LEGENDS

Figure 1. Association between the presence of abdominal obesity and all-cause and cardiovascular mortality in older men and women

Abbreviations: CI, confidence interval.

Figure 2. Association between the presence of high triglyceride levels and all-cause and cardiovascular mortality in older men and women

Abbreviations: CI, confidence interval.

Figure 3. Association between the presence of low HDL cholesterol and all-cause and cardiovascular mortality in older men and women

Abbreviations: CI, confidence interval.

Figure 4. Association between the presence of high fasting glycemia and all-cause and cardiovascular mortality in older men and women

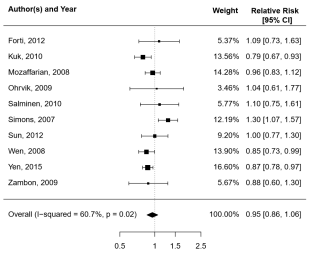
Abbreviations: CI, confidence interval.

Figure 5. Association between the presence of elevated blood pressure and all-cause and cardiovascular mortality in older men and women

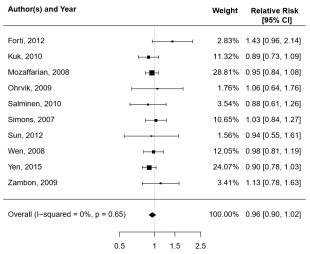
Abbreviations: CI, confidence interval.

ALL-CAUSE MORTALITY

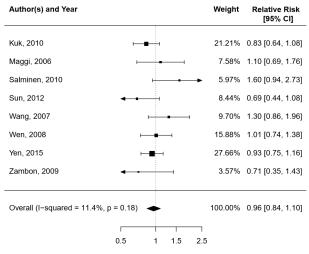
MEN

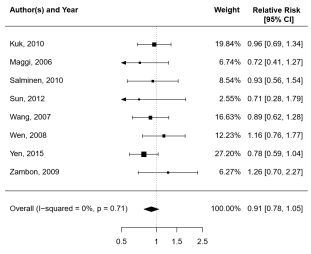


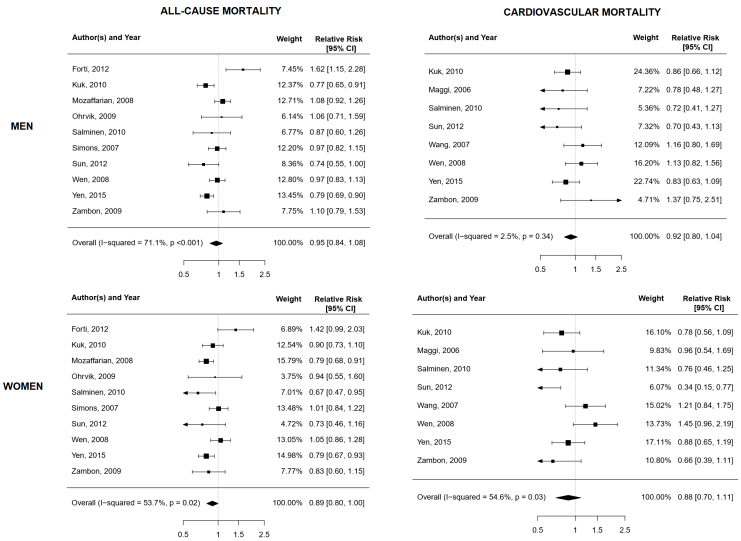
WOMEN



CARDIOVASCULAR MORTALITY

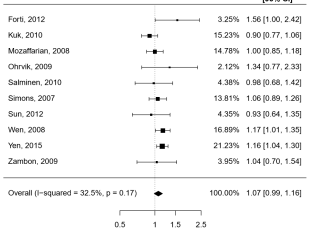






ALL-CAUSE MORTALITY

MEN



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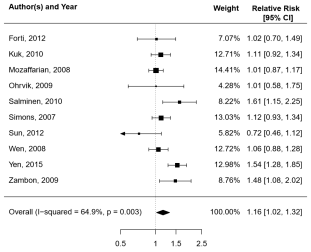
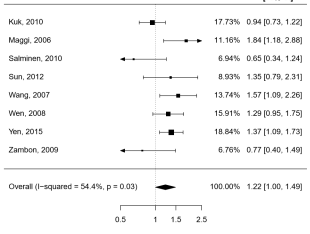
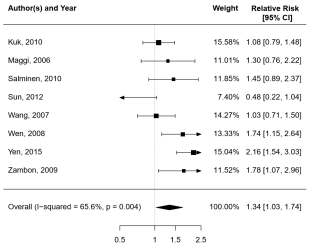


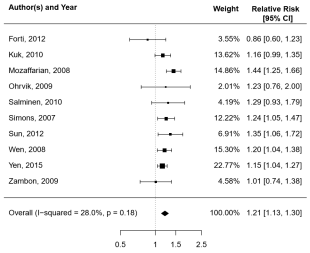
CARDIOVASCULAR MORTALITY



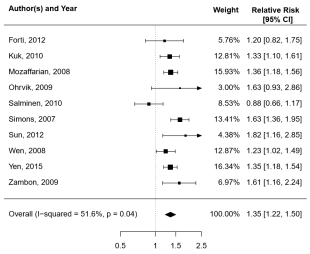


ALL-CAUSE MORTALITY

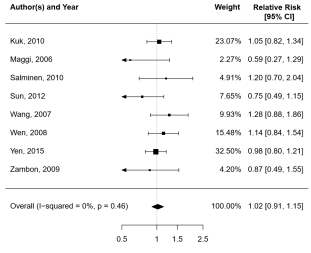
MEN

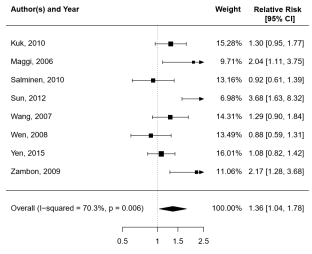


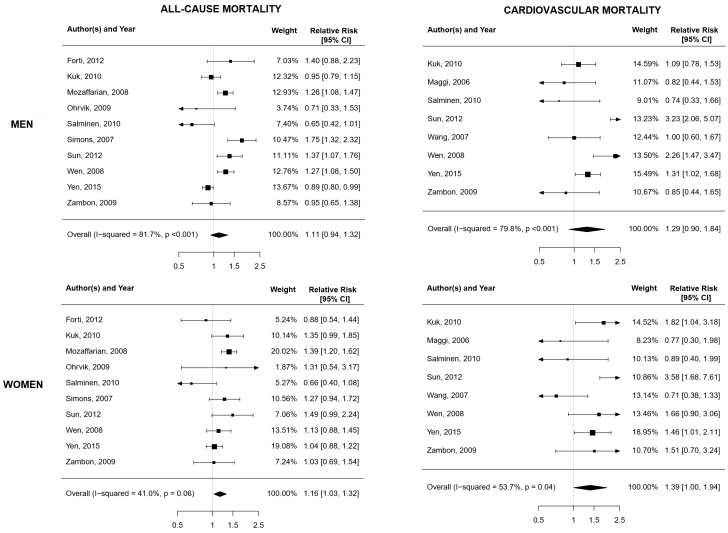
WOMEN



CARDIOVASCULAR MORTALITY







HIGHLIGHTS

- Single metabolic syndrome components influence mortality differently by age and gender

- Low HDL cholesterol and hyperglycemia predict mortality more strongly for the female gender

- Hypertension increase mortality in older women, but not in older men

- Abdominal obesity and high triglyceride scarcely influence mortality in advanced age