Age and Sex Differences in the Clustering of Metabolic Syndrome Factors

Association with mortality risk

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OBJECTIVE — The metabolic syndrome is a general term given to a clustering of cardiometabolic risk factors that may consist of different phenotype combinations. The purpose of this study was to determine the prevalence of the different combinations of factors that make up the metabolic syndrome as defined by the National Cholesterol Education Program and to examine their association with all-cause mortality in younger and older men and women.

RESEARCH DESIGN AND METHODS — A total of 2,784 men and 3,240 women from the Third National Health and Nutrition Examination Survey with public-access mortality data linkage (follow-up = 14.2 ± 0.2 years) were studied.

RESULTS — Metabolic syndrome was present in 26% of younger (aged ≤65 years) and 55.0% of older (aged >65 years) participants. The most prevalent metabolic syndrome combination was the clustering of high triglycerides, low HDL cholesterol, and elevated blood pressure in younger men (4.8%) and triglycerides, HDL cholesterol, and elevated waist circumference in younger women (4.2%). The presence of all five metabolic syndrome factors was the most common metabolic syndrome combination in both older men (8.0%) and women (9.2%). Variation existed in how metabolic syndrome combinations were associated with mortality. In younger adults, having all five metabolic syndrome factors was most strongly associated with mortality risk, whereas in older men, none of metabolic syndrome combinations were associated with mortality. In older women, having elevated glucose or low HDL as one of the metabolic syndrome components was most strongly associated with mortality risk.

CONCLUSIONS — Metabolic syndrome is a heterogeneous entity with age and sex variation in component clusters that may have important implications for interpreting the association between metabolic syndrome and mortality risk. Thus, metabolic syndrome used as a whole may mask important differences in assessing health and mortality risk.

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Since the introduction of the metabolic syndrome operational criteria by the National Cholesterol Education Program (NCEP) in 2001 (1), the surveillance of metabolic syndrome has garnered considerable research interest. Metabolic syndrome has been shown to be associated with increased all-cause and cardiovascular disease (CVD) mortality risk (2,3), but, of late, the clinical utility of metabolic syndrome has also been criticized (4,5). One of the criticisms is that because metabolic syndrome is operationalized as three or more of the five components, the 16 possible combinations that result may present with different pathophysiology, consequences, and treatment options, depending on which factors are present. Indeed, studies that have compared metabolic syndrome clusters for their ability to predict mortality have demonstrated variations in mortality risk among the different metabolic syndrome operational definitions (6,7) and the different metabolic syndrome clusters or components (6,8).

However, it has also been reported that the prevalence of each metabolic syndrome risk factor differs with sex (9,10), and, thus, it follows that men and women may be characterized by different metabolic syndrome combinations. To date, it is unclear whether these sex differences are consistent across the life span and whether the different combinations of metabolic syndrome are similarly related with mortality risk in younger and older men and women. Thus, the purpose of this study was to provide U.S. estimates of the prevalence of the different metabolic syndrome combinations and quantify the risk of all-cause mortality for these unique metabolic syndrome phenotypes in younger and older men and women.

RESEARCH DESIGN AND METHODS

— The Third National Health and Nutrition Examination Survey (NHANES III) is a nationally representative cross-sectional survey conducted between 1988 and 1994 in 33,994 individuals, aged ≥2 months. The sample was collected using a stratified, multistage, probability cluster design. Participants were examined at home and at a mobile examination center for various markers of health, such as demographics, socioeconomic status, medical history, dietary practices, physical activity, blood profile, blood pressure, and anthropometrics. Complete details of the study design and procedures are reported elsewhere (11,12).

A public access mortality linkage data file with follow-up through 31 December 2006 was used for these analyses (13). Mortality status was ascertained through a probabilistic match to a National Death Index record using Social Security number, name, and date of birth. Cause of death coding followed ICD-9 and ICD-10 guidelines. All study participants gave their informed written consent before participation in the examination, and the study protocol was approved by the National Center for Health Statistics.

Participants were excluded if they were missing any of the metabolic syndrome criteria (n = 27,740) or age (n = 4,877), were aged <18 years (n = 14,477), or were pregnant (n = 196). This left a final sample of 2,784 men and 3,240 women.

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Table 1—*Characteristics of participants in the NHANES III mortality follow-up*

	Younger men		Older men		Younger women		Older women	
	Value	%	Value	%	Value	%	Value	%
n	2,110		700		2,548		779	
Age (years)	38.9 ± 0.5		73.0 ± 0.3		40.3 ± 0.3		74.1 ± 0.3	
BMI (kg/m^2)	26.5 ± 0.1	17.8	27.1 ± 0.2	21.7	26.6 ± 0.2	26.1	26.8 ± 0.3	23.7
Waist circumference (cm)	94.3 ± 0.4	24.8	101.2 ± 0.7	48.5	88.1 ± 0.5	43.7	93.4 ± 0.7	65.5
Glucose (mmol/l)	5.4 ± 0.1	22.2	6.1 ± 0.1	50.9	5.2 ± 0.1	16.7	5.8 ± 0.1	41.2
Triglycerides (mmol/l)	1.8 ± 0.1	37.5	1.8 ± 0.1	44.7	1.4 ± 0.1	21.6	1.8 ± 0.1	40.5
Systolic blood pressure (mmHg)	121.9 ± 0.5	37.6	140.1 ± 1.0	80.9	115.6 ± 0.4	28.9	142.0 ± 0.8	82.7
Diastolic blood pressure (mmHg)	76.9 ± 0.4	—	75.7 ± 0.8	—	72.0 ± 0.3	—	72.7 ± 0.5	—
HDL cholesterol (mmol/l)	1.2 ± 0.1	40.6	1.2 ± 0.1	43.2	1.4 ± 0.1	41.3	1.4 ± 0.1	42.2
Follow-up (months)	175.8 ± 2.9		126.4 ± 4.1		175.7 ± 2.7		140.2 ± 3.8	
All-cause deaths*	243 (215)		533 (391)		206 (190)		494 (401)	
CVD deaths*	89 (71)		270 (174)		52 (48)		248 (196)	
Cancer deaths*	61 (56)		107 (97)		88 (84)		75 (64)	

Data are means ± SEM or % (percentage of individuals with obesity or abnormal metabolic values). *Number of deaths in parentheses is with prevalent CVD at baseline excluded.

Survey methods

Age, sex, income, ethnicity (white or nonwhite), smoking status (never, current, and former), physical activity (exercise frequency ≥5 times/week), medications (lipid, blood pressure, and diabetes), and physician diagnosis of hypertension or diabetes were self-reported by questionnaire. Waist circumference was assessed at the top of the iliac crest at the end of a normal expiration (14).

Metabolic syndrome

Blood samples were collected with a venipuncture at the mobile examination center or during the home examination. Participants were instructed to fast for 10–16 h before the morning examination or for 6 h before the afternoon or evening examination. Blood pressure was manually measured by a physician at the home examination after the participant had been quietly seated for 5 min. Metabolic syndrome was diagnosed as three or more of the following five factors as defined by the revised NCEP criteria (1): *1*) fasting triglycerides ≥1.69 mmol/l or lipid medications; *2*) systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or antihypertensive medications; *3*) fasting plasma glucose ≥5.6 mmol/l or diabetes medications; *4*) HDL cholesterol <1.04 mmol/l (men) or <1.29 mmol/l (women); and *5*) waist circumference ≥102 cm (men) or ≥88 cm (women).

Statistical analysis

All analyses were stratified by age (18–65 years and >65 years) and sex. Sex differences in the frequencies and prevalence of each metabolic syndrome combination within each age-group were determined using a χ^2 test. To account for the potential effects of prevalent CVD on mortality risk, participants with a reported history of stroke or heart attack were excluded from the mortality analyses. Cox proportional hazards regression was used to assess the relative risk of all-cause mortality across metabolic syndrome definitions, adjusting for age, sex, income, smoking status, white ethnicity, and physical activity. Because of the low number of deaths associated with some of the definitions, the analyses were only conducted for metabolic syndrome definitions with one, two, three, four, or all five factors with each factor as a required component (i.e., three metabolic syndrome factors with one of the factors being elevated glucose, four metabolic syndrome factors with one of the factors being low HDL cholesterol, and so on). To account for the hierarchical sampling structure of the data, all statistical analyses were performed using SAS (version 9.1) survey procedures or SUDAAN 10.0, weighted to be representative of the U.S. population. Statistical significance was set at $\alpha < 0.05$. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

RESULTS

— Characteristics of participants are shown in Table 1. The prevalence of each metabolic syndrome factor combination and the prevalence of having one, two, three, four, or five metabolic syndrome factors in younger and older adults are shown in Figs. 1 and 2. In younger adults, the most common metabolic syndrome component was low HDL (41%), and the least common was high glucose (22% in men and 17% in women). In older adults, blood pressure was the most common metabolic syndrome component (81% in men and 83% in women), whereas triglycerides (45% in men and 40% in women) and HDL (43% in men and 42% in women) were the least common factors.

Only 26% of younger participants had metabolic syndrome (26.6% in men and 25.1% in women), whereas 55.0% of participants aged >65 years had metabolic syndrome (55.5% in men and 54.7% in women). The most prevalent metabolic syndrome combination was the clustering of triglycerides, HDL, and blood pressure in younger men (4.8%) and of triglycerides, HDL, and waist circumference in younger women (4.2%), whereas the least common metabolic syndrome combination was HDL, waist circumference, and glucose in younger men (0.3%) and blood pressure, triglycerides, and glucose in younger women (0.1%). Overall, the presence of all five metabolic syndrome factors was the most common metabolic syndrome combination in both older men and women (8.0% in men and 9.2% in women), whereas the least common was triglycerides, HDL, and glucose in older men (0.5%) and HDL, waist circumference, and glucose in older women (0.2%).

During the 14.0 ± 0.2 year follow-up there were 1,476 (16.8%) deaths (659

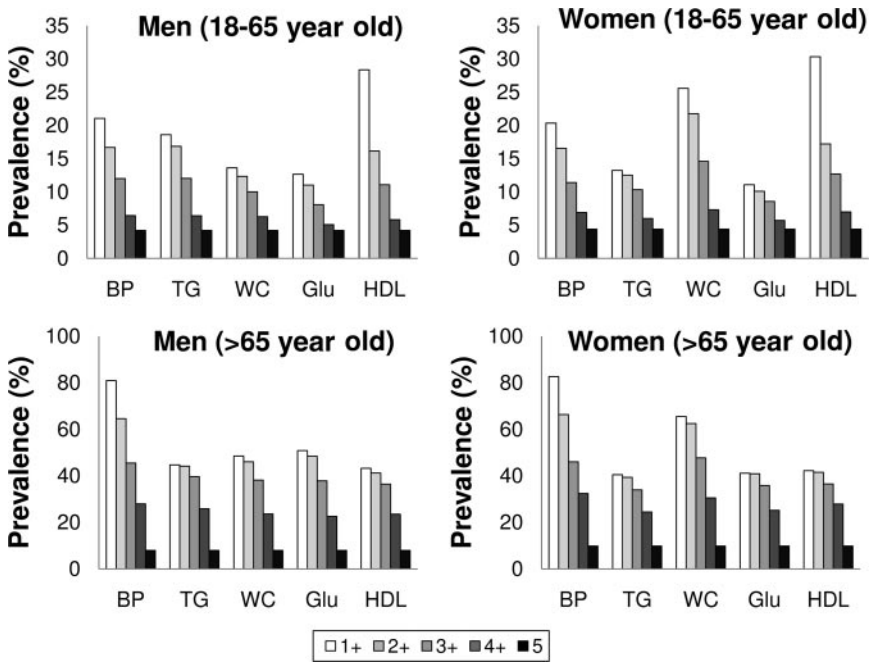

Figure 1—*Prevalence of metabolic syndrome components in younger and older men and women. BP, blood pressure; Glu, glucose; TG, triglycerides; WC, waist circumference.*

CVD, 331 cancer, 133 respiratory causes, and 49 diabetes). In the crude unadjusted model, metabolic syndrome was associated with higher mortality risk in younger adults (men: hazard ratio [HR] 2.53 [95% CI 1.66–3.85]; women 4.22 [2.36–7.55]) and older women (1.44 [1.08–1.92]). In contrast, metabolic syndrome was not associated with mortality risk in older men (0.78 [0.56–1.09]). Metabolic syndrome remained significantly associated with all-cause mortality risk in younger adults (men: 1.68 [1.13–2.50]; women: 2.61 [1.39–4.91]) but not in older women (1.29 [0.97–1.72]) after adjustment for relevant covariates. In general, age, smoking status and income were the only significant covariates ($P < 0.05$).

The association between the various metabolic syndrome factor combinations and mortality risk varied, and the patterns differed by age and sex (Fig. 3). In younger men and women, having all five metabolic syndrome factors was most strongly associated with mortality risk, with no clear association between the number of metabolic syndrome factors and mortality risk (i.e., more metabolic syndrome factors did not equal greater mortality risk). In older men, the various metabolic syndrome combinations were not associated with elevated mortality risk, whereas in older women, regardless of the absolute number of metabolic syndrome components, having elevated glucose or low HDL was most strongly associated with mortality. None of the most prevalent metabolic syndrome definitions within each age- and sex-specific strata (i.e., younger men: blood pressure, triglycerides, and HDL; younger women: triglycerides, HDL, waist circumference; and older adults: all five criteria) were significantly asso-

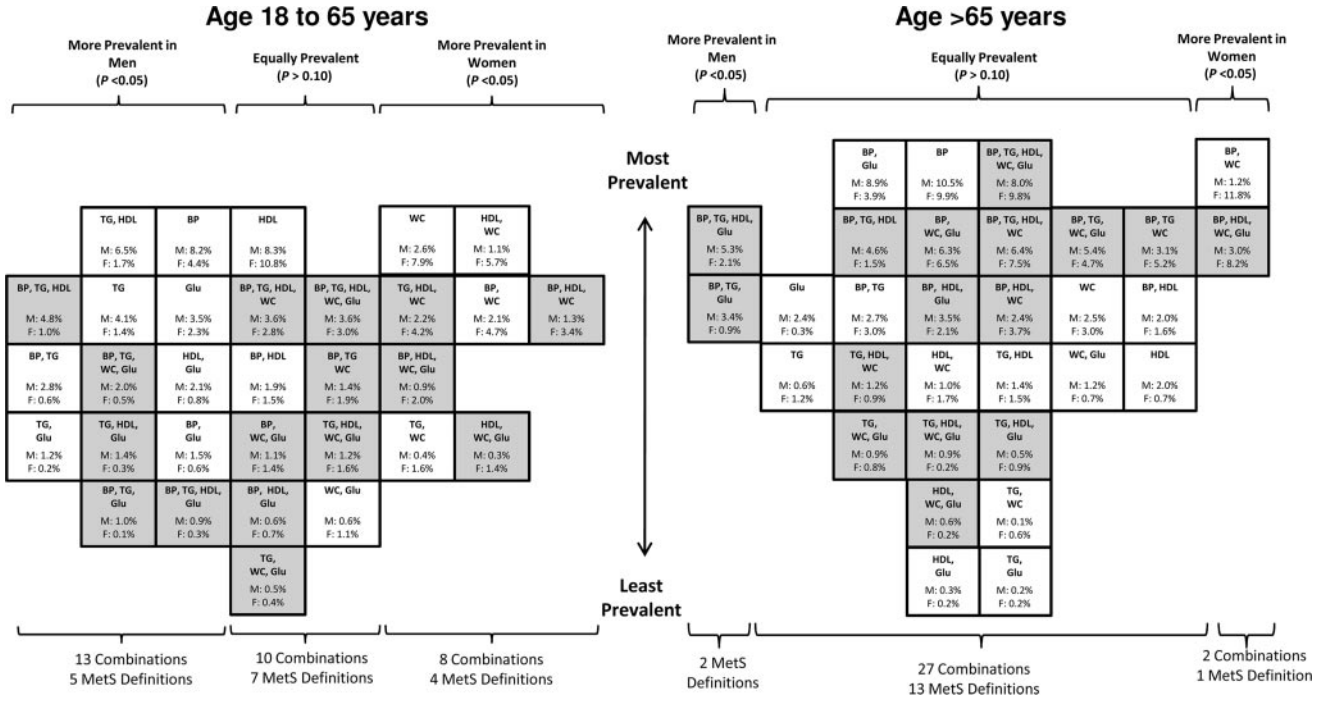

Figure 2—*Prevalence of each metabolic syndrome combination in younger and older men and women. Shaded cells represent 16 metabolic syndrome classifications with three or more components present. BP, blood pressure; Glu; glucose; MetS, metabolic syndrome; TG; triglycerides; WC, waist circumference.*

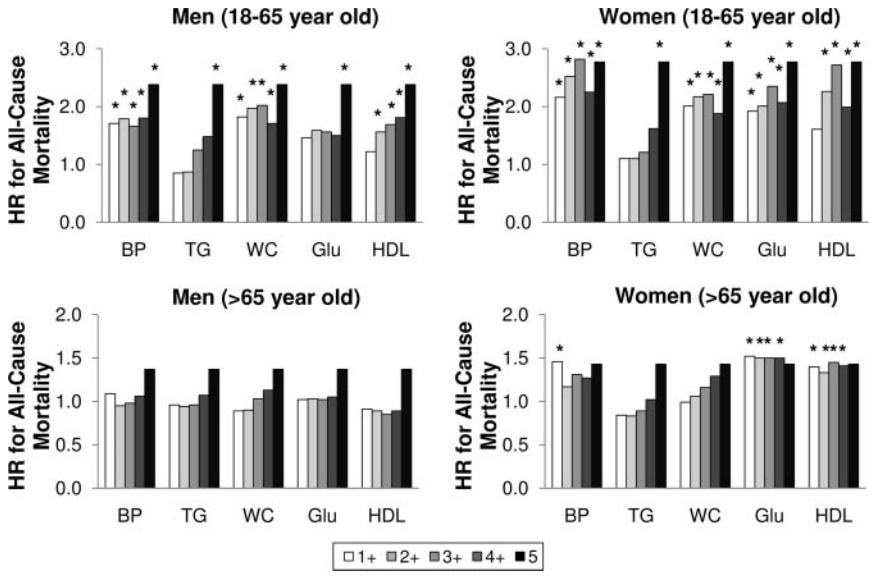

Figure 3—*Variation in the relative risk of all-cause mortality in younger and older men and women according to metabolic syndrome components.* *P < *0.05, adjusted for age, income category, smoking status, white ethnicity, and physical activity level. Analyses were conducted excluding individuals with prevalent CVD at baseline* (n = *5,736). BP, blood pressure; Glu, glucose; TG, triglycerides; WC, waist circumference.*

ciated with all-cause mortality ($P > 0.10$).

CONCLUSIONS — Results of this analysis provide evidence that there are age and sex differences in the way metabolic syndrome is expressed and in the way that the different metabolic syndrome combinations are associated with mortality risk. This observation suggests that metabolic syndrome is a heterogeneous entity and, when used as a dichotomous outcome, may mask the differential associations with health risk.

The clinical definitions for metabolic syndrome are evolving (15,16), and it is clear that the presentation of metabolic syndrome is different between the sexes and changes with age. As reported previously, abdominal obesity is the most common metabolic syndrome factor in women (9). In fact, all combinations that were more common in women than men contained waist circumference, whereas the metabolic syndrome combinations in men were more heterogeneous in their make-up. This finding may suggest a greater relative importance of abdominal obesity in the development of metabolic risk in women than men. We have reported previously in this cohort that anthropometric measures of obesity are more strongly associated with mortality risk in women than in men (17).

As expected, all metabolic syndrome risk factors were more prevalent in the older than younger adults; however, it was interesting to note that the sex differences in the prevalence of the various metabolic syndrome factor combinations were largely abolished in older adults. In the adults aged >65 years of age, 27 of 31 combinations of metabolic syndrome factors were equally prevalent in men and women possibly because of the large number of people developing metabolic risk factors by the time they are aged >65 years (i.e., prevalence approaching 100%). However, upon closer inspection, even in the older population, less than half had an abnormal value for most of the variables. Perhaps the diminished sex differences in the metabolic risk profile may be in part due to the diminished sex differences in total and visceral adiposity with age (18) and the cardiometabolic effects of menopause (19).

Metabolic syndrome is operationalized by NCEP for ease of use to be three or more of the five components. However, from these results, it is clear that the consequences of the 16 possible combinations may vary according to which factors are present. Variation in the risk of CVD morbidity and mortality associated with the different metabolic syndrome phenotypes has been described (7,20) and taken together with our results suggests that important variations in mortality risk by prevalent clusters of components may be masked when metabolic syndrome is used as a whole. Indeed, these results are in accordance with a study by Guize et al. (6) who reported that different combinations of metabolic syndrome factors are differently associated with risk of all-cause mortality, wherein the combination of waist, triglyceride, and glucose was most strongly associated with all-cause mortality. However, this study combined men and women and used participants with no metabolic syndrome factors as the referent group. In the other study to date, Hong et al. (8) also collapsed their sample across men and women and did not examine differences with aging, beyond the inclusion of age and sex as covariates. In that study, clear differences in mortality risk were demonstrated, along with a clustering of blood pressure, triglycerides, HDL, and glucose that was most strongly associated with all-cause mortality risk. Demographic, covariate, and analytical differences between these studies and the current analysis make it difficult to compare but provide some of the first evidence that variation in mortality risk may be an important consideration when one is making treatment decisions on the basis of metabolic syndrome combinations. Indeed, differences in how the various metabolic syndrome combinations relate to mortality risk may be in part due to the differences in how these metabolic syndrome combinations relate to incident coronary heart disease, CVD, and type 2 diabetes morbidity wherein the effects are even more pronounced (8,21).

Our results suggest that there are important sex and age differences in the way the different metabolic syndrome combinations relate to mortality risk; however, the association between the various metabolic syndrome combinations and mortality risk does not appear to be related to their prevalence. For example, although HDL was one of the most common metabolic syndrome components in younger women and among the least common in older women, it was one of the stronger correlates of mortality risk in both age strata. Furthermore, in contrast with previous observations (22), the association between metabolic syndrome and mortality risk does not appear to be related to the number of metabolic syndrome factors one displays. Although having all five metabolic syndrome factors was most strongly associated with mortality risk in younger men and women, there was no clear association between the number of metabolic syndrome factors and mortality risk. For example, in younger women, hav-

ing elevated waist circumference alone or in combination with at least three other metabolic syndrome factors was associated with a similar HR for mortality (2.01 vs. 1.88, respectively). Similarly, in older women, regardless of the absolute number of metabolic syndrome components, having elevated glucose or low HDL was associated with a similar mortality risk. Clearly, more research is needed to determine whether certain specific combinations of metabolic syndrome factors are more predictive of mortality risk.

The strengths and limitations of this study warrant mention. First, this study was conducted in a large cohort that was nationally representative of the U.S. population. Despite the large initial sample size and long follow-up, because of the low prevalence and low number of deaths for some metabolic syndrome definitions, we were unable to examine the association between each of the specific metabolic syndrome combinations and mortality risk or specific causes of deaths (i.e., CVD and cancer). This limitation is probably also reflective of the clustering nature of the metabolic syndrome factors, as they are risk factors for each other. Further, there are reported ethnic differences in the prevalence of metabolic syndrome factors (10). Whether these differences also influence the association with mortality risk requires further examination in diverse samples.

In summary, we suggest that there are age and sex differences in the way metabolic syndrome is expressed and in the way that the different metabolic syndrome combinations are associated with mortality risk. This suggestion reinforces the notion that metabolic syndrome is a heterogeneous condition that may have differential associations with health risk in men and women of different ages.

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J.L.K. conducted the data analysis and wrote the manuscript. C.I.A. contributed to discussion and reviewed/edited the manuscript.

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