Age and Sex Differences the Clustering of Metabolic Syndrome Factors: Association with Mortality Risk

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Running Head: Metabolic Syndrome Combinations and Mortality

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Objective: The metabolic syndrome (MetS) is a general term given to a clustering of cardiometabolic risk factors that may consist of different phenotype combinations. To determine the prevalence of the different combinations of factors that make up National Cholesterol Education Program defined MetS, and to examine their association with all-cause mortality in younger and older men and women.

Methods: 2,784 men and 3,240 women from NHANES III with public-access mortality data linkage (follow-up=14.2±0.2y). Results: MetS was present in 26% of younger (<65 years) and 55.0% of older (>65 years) participants. The most prevalent MetS combination was the clustering of high triglycerides, low high-density lipoprotein cholesterol (HDL) and elevated blood pressure in younger men (4.8%), and triglycerides, HDL and elevated waist circumference in younger women (4.2%). The presence of all five MetS factors was the most common MetS combination in both older men (8.0%) and women (9.2%). Variation existed in how MetS combinations were associated with mortality. In younger adults, having all five MetS factors was most strongly associated with mortality risk, whereas in older men, none of MetS combinations were associated with mortality. In older women, having elevated glucose or low HDL as one of the MetS components was most strongly associated with mortality risk.

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

Since the introduction of the metabolic syndrome (MetS) operational criteria by the National Cholesterol Education Program (NCEP) in 2001 (1), the surveillance of MetS has garnered considerable research interest. MetS 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 MetS has also been criticized (4; 5). One of the criticisms is that because MetS 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 MetS clusters for their ability to predict mortality have demonstrated variations in mortality risk between the different MetS operational definitions (6; 7) and the different MetS clusters or components (6; 8).

However, it is also reported that the prevalence of each MetS risk factor differs with sex (9; 10), and thus it stands to follow that men and women may be characterized by different MetS combinations. To date, it is unclear whether these sex differences are consistent across the lifespan, and whether the different combinations of MetS are similarly related with mortality risk in younger and older men and women.

Thus, the purpose of this study is to provide U.S. estimates of the prevalence of the different MetS combinations, and quantify the risk of all-cause mortality for these unique MetS phenotypes in younger and older men and women.

METHODS
Participants. 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 persons, ages 2 months and older. The sample was collected using a stratified, multistage, probability cluster design. Participants were examined at home and at a mobile exam 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).

Public access Mortality Linkage data file with follow-up through December 31st, 2006 was used for these analyses (13). Mortality status was ascertained through a probabilistic match to a National Death Index (NDI) record using social Security number, name, date of birth. Cause of death coding followed the 9th and 10th revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death (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 MetS criteria (n=27,740) or age (n=4,877), were less than 18 years of age (n = 14,477), or were pregnant (n=196). This left a final sample of 2,784 men and 3,240 women.

Survey Methods. Age, sex, income, ethnicity (White, or non-White), smoking status (never, current and former), physical activity (exercise frequency ≥5 times per week), medications (lipid, blood pressure and diabetes) and physician diagnosis of hypertension or diabetes were self-reported by questionnaire. Waist circumference (WC) 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 hours prior to the morning examination or for six hours 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 five minutes. MetS was diagnosed as three or more of the following five factors as defined by the revised NCEP criteria (1):

1) Fasting triglycerides (TG) ≥1.69 mM or lipid medications
2) Systolic blood pressure (BP) ≥130 mmHg, diastolic BP ≥85 mmHg or antihypertensive medications
3) Fasting plasma glucose ≥5.6 mM or diabetic medications
4) High-density lipoprotein cholesterol (HDL-C) <1.04 mM (men), HDL-C <1.29 mM (women)
5) WC ≥ 102 cm (men), WC ≥ 88 cm (women).

Statistical analysis. All analyses were stratified by age (18 to 65 y and >65 y) and sex. Sex differences in the frequencies and prevalence of each MetS combination within each age group were determined using Chi-square. To account for the potential effects of prevalent CVD on mortality risk, participants with 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 MetS definitions, adjusting for age, sex, income, smoking status, White ethnicity and physical activity. Due to the low number of deaths associated with some of the definitions, the analyses were only conducted for MetS definitions with one, two, three, four, all five factors with each factor as a required component (i.e. 3 MetS factors with one of the factors being elevated glucose, 4 MetS factors with one of the factors being low HDL, etc.). To account for the hierarchical sampling structure of the data, all statistical analyses were performed using SAS v9.1 survey procedures or SUDDAN 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 MetS factor combination and the prevalence of having one, two, three, four or five MetS factors in younger and older adults are shown in Figure 1 and 2. In younger adults, the most common MetS component was low HDL (41%), and the least common was high glucose (M: 22%; F: 17%). In older adults, BP was the most common MetS component (M: 81%; F: 83%), whereas TG (M: 45%; F: 40%) and HDL (M: 43%; F: 42%) were the least common factors.

Only 26% of younger participants had MetS (M: 26.6%; F: 25.1%), whereas 55.0% of participants over the age of 65 years had MetS (M: 55.5%; F: 54.7%). The most prevalent MetS combination was the clustering of TG, HDL and BP in younger men (4.8%), and TG, HDL and WC in younger women (4.2%), whereas the least common MetS combination was HDL, WC and glucose in younger men (0.3%) and BP, TG, glucose in younger women (0.1%). Overall, the presence of all five MetS factors was the most common MetS combination in both older men and women (M: 8.0% and F: 9.2%), whereas the least common was TG, HDL and glucose in older men (0.5%) and HDL, WC and glucose in older women (0.2%).

During the 14.0±0.2 year follow-up there were 1,476 (16.8%) deaths (659 CVD, 331 cancer, 133 respiratory and 49 due to diabetes). In the crude unadjusted model, MetS was associated with higher mortality risk in younger adults (M: HR, 95%CI =2.53, 1.66-3.85; F: HR, 95%CI =4.22, 2.36-7.55) and older women (HR=1.44, 1.08-1.92). By contrast, MetS was not associated with all-cause mortality risk in older men (HR=0.78, 0.56-1.09). MetS remained significantly associated with all-cause mortality risk in younger adults (M: HR, 95%CI =1.68, 1.13-2.50; F: HR, 95%CI =2.61, 1.39-4.91), but not older women (HR=1.29, 0.97-1.72) after adjusting for relevant covariates. In general, age, smoking status and income were the only significant covariates (P <0.05).

The association between the various MetS factor combinations and mortality risk varied, and the patterns differed by age and sex (Figure 3). In younger men and women, having all five MetS factors was most strongly associated with mortality risk, with no clear association between the number of MetS factors and mortality risk (ie. more MetS factors did not equal greater mortality risk). In older men, the various MetS combinations were not associated with elevated mortality risk, whereas in older women, regardless of the absolute number of MetS components, having elevated glucose or low HDL were most strongly associated with mortality. None of the most prevalent MetS definitions within each age- and sex- specific strata (ie. Younger men: BP, TG and HDL; Younger women: TG, HDL, waist; Older adults: all 5 criteria) were significantly associated with all-cause mortality (P >0.10).

DISCUSSION

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

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

As expected, the prevalence of all MetS 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 MetS factor combinations were largely abolished in older adults. In the adults over 65 years of age, 27 of 31 combinations of MetS factors were equally prevalent in men and women. This may be because of the large number of people developing metabolic risk factors by the time they are over 65 years of age (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).

MetS 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 MetS phenotypes has been recently described (7; 20), and taken together with our results suggest that important variation in mortality risk by prevalent clusters of components may be masked when using MetS as a whole. Indeed, these results are in accordance with a study by Guize et al. (6) who report that different combinations of MetS factors are differently associated with risk of all-cause mortality, wherein the combination of waist, TG and glucose was most strongly associated with all-cause mortality. However, this study combined men and women, and used participants with no MetS factors as the referent group. 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 BP, TG, 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 making treatment decisions on the basis of MetS combinations. Indeed, differences in how the various MetS combinations relate to mortality risk may be in part due to the differences in how these MetS combinations relate to incident CHD, CVD and T2D 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 MetS combinations relate to mortality risk; however, the association between the various MetS combinations and mortality risk does not appear to be related to their prevalence. For example, although HDL was one of the most common MetS 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 to previous observations (22), the association between MetS and mortality risk does not appear to be related to the number of MetS
factors one displays. Although having all five MetS factors was most strongly associated with mortality risk in younger men and women, there was no clear association between the number of MetS factors and mortality risk. For example, in younger women, having elevated waist or elevated waist with at least 3 other MetS factors were associated with a similar hazards ratio for mortality. (HR = 2.01 vs. 1.88, respectively). Similarly, in older women, regardless of the absolute number of MetS components, having elevated glucose or low HDL were associated with a similar mortality risk. Clearly, more research is needed to determine whether certain specific combinations of MetS 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, due to the low prevalence and low number of deaths for some MetS definitions, we were unable to examine the association between each of the specific MetS combinations and mortality risk, or specific causes of deaths (ie. CVD and cancer). This is likely also reflective of the clustering nature of the MetS factors, as they are risk factors for each other. Further, there are reported ethnic differences in the prevalence of MetS factors (10). Whether this also influences the association with mortality risk requires further examination in diverse samples.

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

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

ACKNOWLEDGEMENTS
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REFERENCES
Table 1: Characteristics of Participants in the NHANES III Mortality Follow-Up.

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<thead>
<tr>
<th></th>
<th>Younger Men</th>
<th>Older Men</th>
<th>Younger Women</th>
<th>Older Women</th>
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<tbody>
<tr>
<td>N</td>
<td>2,110</td>
<td>700</td>
<td>2,548</td>
<td>779</td>
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<tr>
<td>Age (yr)</td>
<td>Mean ± SE</td>
<td>%</td>
<td>Mean ± SE</td>
<td>%</td>
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<tr>
<td>BMI (kg m⁻²)</td>
<td>26.5 ± 0.1</td>
<td>17.8</td>
<td>27.1 ± 0.2</td>
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<td>Waist (cm)</td>
<td>94.3 ± 0.4</td>
<td>24.8</td>
<td>101.2 ± 0.7</td>
<td>48.5</td>
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<td>Glucose (mM)</td>
<td>5.4 ± 0.1</td>
<td>22.2</td>
<td>6.1 ± 0.1</td>
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<td>Triglycerides (mM)</td>
<td>1.8 ± 0.1</td>
<td>37.5</td>
<td>1.8 ± 0.1</td>
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<td>SBP (mmHg)</td>
<td>121.9 ± 0.5</td>
<td>37.6</td>
<td>140.1 ± 1.0</td>
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<td>DBP (mmHg)</td>
<td>76.9 ± 0.4</td>
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<td>HDL-C (mM)</td>
<td>1.2 ± 0.1</td>
<td>40.6</td>
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<td>Follow-up (months)</td>
<td>175.8 ± 2.9</td>
<td>126.4 ± 4.1</td>
<td>175.7 ± 2.7</td>
<td>140.2 ± 3.8</td>
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<td>All-Cause Deaths (♯)</td>
<td>243 (215)</td>
<td>533 (391)</td>
<td>206 (190)</td>
<td>494 (401)</td>
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<tr>
<td>CVD Deaths (♯)</td>
<td>89 (71)</td>
<td>270 (174)</td>
<td>52 (48)</td>
<td>248 (196)</td>
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<tr>
<td>Cancer Deaths (♯)</td>
<td>61 (56)</td>
<td>107 (97)</td>
<td>88 (84)</td>
<td>75 (64)</td>
</tr>
</tbody>
</table>

% - Percentage of individuals with obesity or abnormal metabolic values
The number of deaths in brackets is with prevalent CVD at baseline excluded.

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic Blood Pressure; HDL-C: High Density Lipoprotein Cholesterol

Figure Legends

Figure 1 – Prevalence of Metabolic Syndrome Components in Younger and Older Men and Women

BP: Blood pressure; TG: Triglycerides; WC: Waist Circumference; Glu: Glucose; HDL: High Density Lipoprotein

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; TG: Triglycerides; WC: Waist Circumference; Glu: Glucose; HDL: High Density Lipoprotein;

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=5736).
BP: Blood pressure; TG: Triglycerides; WC: Waist Circumference; Glu: Glucose; HDL: High Density Lipoprotein;
Figure 1

Men (18-65 y old)

Women (18-65 y old)

Men (>65 y old)

Women (>65 y old)

Legend:

- 1+
- 2+
- 3+
- 4+
- 5
<table>
<thead>
<tr>
<th>Age 18 to 65 years</th>
<th>Age &gt;65 years</th>
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</table>

**More Prevalent in Men (P < 0.05)**

- BP, TG, HDL
- TG, HDL, BP
- TG, HDL, WC
- TG, HDL, Glu
- BP, TG, HDL, WC
- BP, TG, HDL, Glu
- BP, HDL, WC
- BP, HDL, Glu
- TC, HDL, WC
- TC, HDL, Glu
- Fasting Glucose

**Equally Prevalent (P > 0.10)**

- BP, TG, HDL, Glu
- BP, WC, Glu
- BP, TG, HDL, WC
- BP, TG, HDL, Glu
- BP, HDL, WC
- BP, HDL, Glu
- TC, HDL, WC
- TC, HDL, Glu
- Fasting Glucose

**More Prevalent in Women (P < 0.05)**

- BP, TG, HDL
- TG, HDL, BP
- TG, HDL, WC
- TG, HDL, Glu
- BP, TG, HDL, WC
- BP, TG, HDL, Glu
- BP, HDL, WC
- BP, HDL, Glu
- TC, HDL, WC
- TC, HDL, Glu
- Fasting Glucose

**Most Prevalent**

- BP, Glu
- BP, WC
- BP, TG, HDL, Glu
- BP, TG, HDL, WC
- BP, TG, HDL

**Least Prevalent**

- TG, WC, Glu
- HDL, Glu
- HDL, WC

**Prevalence**

- M: 6.3% M: 8.2% M: 8.3% F: 7.9% F: 5.7%
- M: 2.6% M: 1.1% F: 7.9% F: 5.7%
- M: 2.1% F: 4.7% M: 1.3% F: 3.4%
- M: 3.6% M: 2.8% F: 3.0% F: 2.2%
- M: 2.0% M: 2.1% F: 1.5% F: 2.0%
- M: 2.0% M: 2.1% F: 1.5% F: 2.0%
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Figure 3

Metabolic Syndrome Combinations and Mortality

Men (18-65y old)

Women (18-65y old)

Men (>65y old)

Women (>65y old)