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**The metabolic syndrome adds utility to the prediction of mortality over its components: the Vietnam Experience Study**

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**Short title:** Metabolic syndrome and mortality

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## Abstract

**Background:** The metabolic syndrome increases mortality risk. However, as “non-affected” individuals may still have up to two risk factors, the utility of using three or more components to identify the syndrome, and its predictive advantage over individual components have yet to be determined.

**Methods:** Participants, male Vietnam-era veterans (n = 4265) from the USA, were followed-up from 1985/86 for 14.7 years (61,498 person-years), and all-cause and cardiovascular disease deaths collated. Cox’s proportional-hazards regression was used to assess the effect of the metabolic syndrome and its components on mortality adjusting for a wide-range of potential confounders.

**Results:** At baseline, 752 participants (17.9%) were identified as having metabolic syndrome. There were 231 (5.5%) deaths from all-causes, with 60 from cardiovascular disease. After adjustment for a range of covariates, the metabolic syndrome increased the risk of all-cause, HR 2.03, 95%CI 1.52, 2.71, and cardiovascular disease mortality, HR 1.92, 95%CI 1.10, 3.36. Risk increased dose-dependently with increasing numbers of components. The increased risk from possessing only one or two components was not statistically significant. The adjusted risk for four or more components was greater than for only three components for both all-cause, HR 2.30, 95%CI 1.45, 3.66 vs. HR 1.70, 95%CI 1.11, 2.61, and cardiovascular disease mortality, HR 3.34, 95%CI 1.19, 9.37 vs. HR 2.81, 95%CI 1.07, 7.35. The syndrome was more informative than the individual components for all-cause mortality, but could not be assessed for cardiovascular disease mortality due to multicollinearity. **Hyperglycaemia was the individual strongest parameter associated with mortality.**

**Conclusions:** The metabolic syndrome is informative in predicting mortality, with risk increasing as the number of components increase above the threshold required for diagnosis.

**Keywords:** all-cause, cardiovascular disease, metabolic syndrome, mortality, veterans

## **Introduction**

The metabolic syndrome, a constellation of symptoms encompassing central obesity, hypertension, hyperglycaemia, hypertriglyceridaemia, and low HDL-cholesterol, has been associated with increased all-cause and cardiovascular disease mortality in a number of populations.<sup>1-14</sup> Most studies have focussed on whether the presence of the metabolic syndrome increases all-cause or cardiovascular disease mortality and often do not appear to exclude existing cardiovascular disease,<sup>15</sup> a major determinant of subsequent events.<sup>16</sup> Additionally, the utility of using three or more components to identify the condition, given that a significant proportion of the non-affected population may have up to two risk factors, has yet to be determined, as has the advantage of using the metabolic syndrome over its individual components. Similarly, the question arises whether those with the condition but with more than the three components required are at greater risk than those who just meet the threshold for diagnosis. In this study we use the well-characterised Vietnam Experience Study to address these issues in a sample of male veterans.

## **Methods**

### **Participants and procedure**

Details of sampling at each stage of data collection performed in 1985/86 are shown in Figure 1.

Inclusion criteria were: entered military service for the United States of America between January 1, 1965 and December 31, 1971; served only one term of enlistment; served at least 16 weeks of active duty; earned a military specialty other than “trainee” or “duty soldier”; had a military pay grade at discharge no higher than sergeant. Information on place of service and ethnicity was extracted from the military archives. From the subsequent telephone survey, socio-economic position was measured using household income in midlife and the grade from which participants left school. Frequency of alcohol consumption was classified as number of units per week. Smoking habits and marital status were ascertained using standard questions. Participants were asked whether they had a range of physician-diagnosed diseases including hypertension, cancer, coronary heart disease (CHD), and diabetes.<sup>17,18</sup>

From a fasted blood sample, triglycerides and cholesterol fractions were assessed using a Kodak Ektachem 700 autoanalyzer.<sup>17,18</sup> Serum glucose level was determined with an adaptation of the glucose oxidase-peroxidase-chromogen-coupled system.<sup>17,18</sup> Blood pressure was measured twice in the right arm using a sphygmomanometer and an average computed. Height and weight were measured to calculate body mass index (BMI, kg/m<sup>2</sup>).

Subsequent to completion of the medical examination, attempts were made to match study participants against mortality databases over a 15 year period. Mean age at medical examination was 38.3 yr. (range: 31.1 to 49.0). The censor date for the study was taken to be at medical examination or death or 31 December 2000, whichever occurred first. The effective sample size was 4256. Ethical approval for the study was given by various bodies, including the US Centers for Disease Control.<sup>17,18</sup>

### **Definition of the metabolic syndrome**

The metabolic syndrome and its components were defined using the American Heart Association/National Heart, Lung, and Blood Institute scientific statement.<sup>19</sup>, which made slight modifications to the Adult Treatment Panel III recommended diagnostic criteria.<sup>20</sup> According to this definition, participants were classified as having the metabolic syndrome if any three of the following were present: BMI >30 kg/m<sup>2</sup> (in the absence of data on waist circumference, BMI at this threshold is regarded by the World Health Organisation as an acceptable substitute in defining the metabolic syndrome;<sup>21</sup>) fasting plasma glucose  $\geq 5.6$  mmol/l (100 mg/dl) and/or receiving medication for diabetes; triglycerides  $\geq 1.7$  mmol/l (150 mg/dl); HDL-cholesterol level <1.036 mmol/l (40 mg/dl); and blood pressure  $\geq 130/85$  mm Hg and/or use of antihypertensive medication.

### **Statistical analysis**

Data from normally distributed parameters are presented as mean  $\pm$  SD, whereas skewed data were logarithmically transformed and expressed as geometric mean with 95% confidence intervals (95% CIs).

Demographic, health behaviour, service-related, metabolic, and haemodynamic variables were compared between those with and without metabolic syndrome using chi-square and Students t-test. Multivariable Cox's proportional-hazards regression was used to assess the effect of the metabolic syndrome and its components on all-cause and cardiovascular disease mortality. Potential confounders included were: age (years), ethnicity (white, black, other (Hispanics, Asians, Pacific Islanders, Native American or, Alaskan), alcohol consumption (units per week), smoking (never, ex-, current), total cholesterol (mmol/l), education (grades:  $\leq 11$ , 12,  $\geq 12$ ), marital status (single, married, other), place of service (Vietnam, other overseas, USA), income during midlife (US\$ $\leq 20,000$ , 20,001-40,000,  $>40,000$  per year). The parameters were added in a hierarchical manner as described in tables 2 and 3. These covariates were chosen *a priori* as they have all been associated with health outcomes in this dataset.<sup>22,23</sup> and others (e.g.,<sup>24</sup>) SPSS (version 15.0 for windows, Chicago, IL, USA) was used in the analyses.

## Results

Of the 4,256 men with complete data, 56 were excluded due to a history of existing cardiovascular disease, leaving 4,200 who were included in these analyses. The participants were followed-up for a mean duration of 14.7 years, resulting in 61,498 person-years of data. There were a total of 231 (5.5%) deaths from any cause, with 60 resulting from cardiovascular disease ((ICD-9: 390–434,436–448, ICD-10: I00–I78); 67% of which were associated with ischaemic heart disease (ICD-9: 410–414,429.2, ICD-10: I20–I25)). At baseline, 752 participants (17.9%) had metabolic syndrome. As expected those with the metabolic syndrome had increased levels of the components of the syndrome (Table 1). The prevalence of lifestyle factors, smoking and alcohol consumption, were similar between the groups. Those with the metabolic syndrome generally had lower levels of education.

In Cox proportional hazards regression, having the metabolic syndrome was associated with a doubling of risk of both all-cause and cardiovascular disease mortality (Table 2). After adjustment for potential confounders (age, alcohol consumption, smoking, total cholesterol, education, ethnicity, marital

status, place of service, income during midlife), the risk effect sizes were generally undiminished.

Compared to those without any components of the metabolic syndrome those with the condition had **three times** the risk of cardiovascular mortality.

Of the five individual components, hyperglycaemia, obesity, and low HDL-cholesterol levels were all associated with increased all-cause mortality. As in the analyses of metabolic syndrome, adjustment for potential confounding factors had a minimal effect on the risk estimates. However, when the components were mutually adjusted, only hyperglycaemia and obesity remained independent determinants of all-cause mortality, increasing risk by **58%** and **57%**, respectively. Of the individual components, hyperglycaemia was most strongly associated with cardiovascular disease mortality with a 126% excess risk, and 109% when adjusted for the other metabolic syndrome components. However, for the remaining individual components the relatively small number of deaths from cardiovascular disease meant that despite excess risks of **about** 60% or more none reached significance in the fully adjusted model. The adjustment for total blood cholesterol attenuated the risk effect estimates, particularly for triglycerides. Mutual adjustment reduced the strength of the associations for the metabolic syndrome components. **H**igh blood pressure, as defined by using blood pressure  $\geq 130/85$  mm Hg and/or use of antihypertensive medication, showed no evidence of an association with cardiovascular mortality. In part this may be due to the close relationship between ethnic background and hypertension. The black participants had significantly more hypertension (64.0%) when compared to the whites (48.7%) or those of other origin (53.0%,  $p < 0.001$ ).

A total of 2308 (55.0%) had one or two components of the metabolic syndrome. For cardiovascular mortality, there was a clear dose-dependent increase in the hazard ratios with an increasing number of components (Table 2, Figure 2), with the presence of a single component non-significantly increasing risk by 71% 95%CI -29, 309%. Only the presence of three (or more) components was associated with significantly increased risk of death,  $p = 0.036$ . The risk associated with four or more components was significantly greater than that associated with only three components for both all-cause,

HR 2.30, 95%CI 1.45, 3.66, vs. HR 1.70, 95%CI 1.11, 2.61, and cardiovascular disease mortality, HR 3.34, 95%CI 1.19, 9.37, vs. HR 2.81, 95%CI 1.07, 7.35). The overall p for trend in this analysis (p = 0.083) did not quite reach significance. However, if those with existing cardiovascular disease were included in the analysis the trend was statistically significant (p = 0.035). When the grouping was none; one or two; and three or more components there was a clear significant dose-dependent effect for both all-cause and cardiovascular disease mortality (Table 2). For all-cause mortality, risk only appeared to increase in those with three or more components (Table 2, Figure 2). To assess whether the composite variable, metabolic syndrome, provided additional predictive information over the individual components, metabolic syndrome was also added to the analyses. For all-cause mortality, only the metabolic syndrome variable remained significant, increasing risk by 81%, 95%CI 6, 11%, p = 0.031. However, in parallel analyses for cardiovascular disease mortality, **the model appeared to be invalid as multicollinearity was identified, and the associations are thus not shown**. Accordingly, this model may not afford an appropriate test in this instance, **and thus the associations are not shown**.

A number of other parameters that have been shown in earlier studies to contribute to mortality were also identified as significant predictors of mortality in the current study. For instance current smoking increased mortality by 65%, 95%CI 16, 136%, p = 0.005. Using alcohol consumption as a continuous variable, there was a significant increase in all-cause mortality of 0.7%, 95%CI 0.2, 1.1% per unit of alcohol per week, p=0.005. However, this was largely the result of those consuming 21 units per week or more where the risk increased by 51%, 95%CI 3, 112%, p = 0.035 when compared to those not consuming alcohol. Being divorced/separated/widowed, HR 2.00, 95%CI 1.35, 2.97, p = 0.001, significantly increased the risk of all-cause mortality relative to those that had remained single. Having black ancestry or being Hispanic, Asian, a Pacific Islander, Native American or Alaskan increased the risk of all-cause mortality by 80%, 95%CI 25, 160, p = 0.001, and 77%, 95%CI 12, 179%, p = 0.014, respectively. Likewise, the indicators of higher socioeconomic status were associated with a reduction in risk. For instance, those earning more than US\$40,000 had a 57% reduction in risk, 95%CI 28, 74%, p =

0.001 compared to those earning less than US\$20,000. There was also a significant trend for increasing education to be associated with reduced mortality,  $p = 0.020$ , although the individual categories failed to reach significance, eg those with the highest education level had 28% 95%CI -10, 54% reduction in risk,  $p = 0.129$ . Total cholesterol was a clear determinant of cardiovascular disease mortality increasing the risk 48% per mmol/l, 95%CI 23, 78%,  $p < 0.001$  in the mutually adjusted analyses.

## Discussion

The present analyses of data from middle-aged male veterans indicate that the metabolic syndrome doubles the risk of both all-cause and cardiovascular disease mortality. As such, our results are consistent with the vast bulk of previous studies.<sup>1-14</sup> The main outcomes were not attenuated following adjustment for a wide-range of potential confounders. The metabolic syndrome proved to be a stronger predictor of all-cause mortality than its individual components, a result for which there is precedent.<sup>25</sup> The predictive value of the metabolic syndrome was similar whether the other components were included in the hazard model or not, suggesting that in our analysis multicollinearity was not a major issue. This contrasted with the analysis of determinants of cardiovascular mortality. Examination of the model containing the metabolic syndrome and its components, suggested that the hyperglycaemic component was the most informative, and that the metabolic syndrome was non-significantly associated with reduced risk, a result that is almost certainly artefactual. It is therefore important in studies assessing the utility of the syndrome in predicting risk relative to its components to consider the issue of multicollinearity.

The extent of the risk faced by those without the metabolic syndrome but carrying component risk factors remains unclear. In the current study, as the number of metabolic syndrome components increased there was a clear dose-dependent increase in risk of all-cause and cardiovascular mortality, including for those with the metabolic syndrome where having 4 or 5 components was associated with greater risk than having only 3 components. The increase in risk was particularly evident for cardiovascular mortality, whereby the presence of even one component increased risk by 71%, although

confidence intervals around this estimate were wide. Given that 55% of the current population had one or two components this could constitute a large potentially undertreated group if treatment were only initiated if based solely on the presence of the metabolic syndrome. A larger study with about 1500 deaths also found incremental risk commencing from one risk factor for cardiovascular disease mortality and two components for all-cause mortality consistent with our findings.<sup>2</sup> These data show a continuum of risk, as seen with the individual components, rather than there being a threshold effect occurring at the level used to define the metabolic syndrome.

Hypertension showed no evidence of a relationship with either all-cause or cardiovascular disease mortality.<sup>2</sup> In part this may be due to the close relationship between ethnic background and hypertension. The black participants had significantly more hypertension when compared to the whites or those of other origin (15 and 11% more, respectively). Therefore in the analyses, adjusting for ethnicity may have removed some of the variance that would have otherwise been attributed to the hypertension risk factor. However, even in the crude analyses the increased hazard ratios did not reach significance, suggesting other parameters may be masking the association. Hypertension has been shown to be associated with cardiovascular disease mortality in some,<sup>1-3</sup> but not all studies.<sup>13,26</sup>

The relationship between hyperglycaemia and mortality is more heterogeneous. Although many studies do not report the associations of the individual components, some reported similar observations to those in the current study with hyperglycaemia being strongly associated with cardiovascular disease<sup>1,3,8,13</sup> and all-cause mortality,<sup>3,8</sup> with a similar strength of relationship to that exhibited by the metabolic syndrome in these studies. However, in other studies hyperglycaemia was not an independent predictor of mortality.<sup>2,26</sup> Although some of the variation is likely the result of differing definitions and population structures, duration may also be an issue with those studies finding a stronger effect of glucose, including the current study, tending to have follow-up periods of more than a decade,<sup>3,8,13</sup> contrasting those that did not identify an association.<sup>26</sup>

One limitation of the current study is the lack of availability of waist circumference measures. However, a number of studies have replaced the central obesity criterion for the metabolic syndrome with the BMI threshold for obesity; this is also regarded by the WHO as an acceptable substitute in defining the metabolic syndrome.<sup>21</sup> Another limitation is that in some of the subgroup analyses, the numbers of deaths are small which results in larger confidence intervals. This means that hazard ratios of a similar magnitude to others that are statistically significant do not reach conventional levels of significance. However, this is not an issue with the primary study outcomes, and was large enough to allow for the assessment of the level of risk of increasing numbers of components of the syndrome. The study was very well characterised which enabled the adjustment of a wide range of potential confounders.

In summary, as the number of metabolic syndrome components increased so did the risk of mortality and even in those defined as having the syndrome those with four components or more were at increased risk of dying relative to those with only three components. The metabolic syndrome was a better predictor of all-cause mortality than its components suggesting additional utility of the parameters in identifying those at greater risk. These important factors have been rarely reported in studies assessing the impact of the syndrome on mortality. Overall, the metabolic syndrome at least doubled the likelihood of all-cause and cardiovascular disease mortality after removal of the effects of potential confounding factors and is clearly a useful measure of identifying those at elevated risk of dying in this population.

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**Table 1 Baseline anthropometric, blood pressure and plasma biochemical characteristics in the participants.**

Parameters	Metabolic syndrome (n=4200)		p value
	Without (n=3448)	With (n=752)	
Age (years)	38.3±2.5	38.7±2.5	<0.001
Systolic blood pressure (mm Hg)	121±11	131±12	<0.001
Diastolic blood pressure (mm Hg)	83±9	91±9	<0.001
Body mass index (kg/m <sup>2</sup> )	25.0±3.0	30.0±4.2	<0.001
Body weight (kg)	79.6±11.3	95.4±15.3	<0.001
Total cholesterol (mmol/l)	5.4±1.1	5.8±1.1	<0.001
HDL-cholesterol (mmol/l)	1.21±0.32	0.90±0.20	<0.001
Triglyceride (mmol/l)	0.91 (0.89, 0.92)	2.05 (1.97, 2.14)	<0.001
Fasting glucose (FPG, mmol/l)	5.1±0.7	5.8±1.6	<0.001
Tobacco consumption (units/wk)	6.69 (6.38, 7.00)	6.75 (6.03, 7.57)	0.868
Alcohol consumption (%)			
Former / Current	28.2 / 46.2	29.2 / 45.7	0.850
Black ethnicity / other* (%)	12.1 / 5.9	9.6 / 8.5	0.005
Education: 12 / ≥13grade (%)	36.6 / 52.1	37.3 / 47.1	0.001
Marital status (%)			
Divorced, separated, widowed / Married	19.2 / 72.3	12.8 / 79.2	0.003
Income: 20,001-40,000 / ≥40,001 (%)	50.2 / 22.0	49.2 / 20.6	0.349
Service in Vietnam / Other overseas (%)	54.7 / 25.8	57.4 / 25.2	0.292
Mortality: all-cause/CHD (%)	4.7 / 1.0	9.2 / 2.7	<0.001 / <0.001

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Normal data, Mean±SD; Skewed data, Geometric mean (geometric 95 % confidence intervals of the mean); categorical data, percentages; \*Comprises Hispanics, Asians, Pacific Islanders, American Indians, and Alaskan Natives

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**Table 2: Adjusted hazard ratios (CIs) for all-cause and cardiovascular disease mortality associated with the metabolic syndrome (MES)**

Adjustments	Deaths/ N	All-cause mortality			Cardiovascular disease mortality			
		Crude	Age,	Age, SES, demographics/ lifestyle	Deaths/ N	Crude	Age	Age, SES, demographics/ lifestyle
Metabolic syndrome								
No components	51/1140	1 (ref)	1 (ref)	1	7/1140	1	1	1
1-2 components	111/2308	1.11 (0.80, 1.54)	1.10 (0.79, 1.53)	0.95 (0.68, 1.33)	34/2308	2.48* (1.10, 5.58)	2.40* (1.06, 5.40)	1.87 (0.82, 4.26)
≥3 components	69/752	2.12* (1.48, 3.03)	2.08* (1.45, 2.98)	1.96* (1.35, 2.85)	19/752	4.58* (1.95, 10.8)	4.29* (1.82, 10.1)	3.14* (1.30, 7.60)
p for trend		<0.001	<0.001	<0.001		<0.001	0.003	0.03
Metabolic syndrome								
0-2 components		1	1	1		1	1	1
≥3 components		1.97* (1.50, 2.61)	1.95* (1.48, 2.58)	2.03* (1.52, 2.71)		2.30* (1.36, 3.89)	2.20* (1.30, 3.72)	1.92* (1.10, 3.36)

p value \*<0.05. Adjusted for age, demographics/lifestyle (ethnicity, alcohol consumption, smoking, total cholesterol), and socioeconomic status (SES; education, marital status, place of service, income during midlife).

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**Table 3: Adjusted hazard ratios for all-cause and cardiovascular disease mortality associated with the metabolic syndrome components**

Components	All-cause mortality			Cardiovascular disease mortality		
	Crude	Age	Age, SES, demographics	Crude	Age	Age, SES, demographics
Hypertension	1.21 (0.94, 1.56)	1.20 (0.93, 1.09)	1.13 (0.87, 1.48)	1.29 (0.78, 2.13)	1.26 (0.76, 2.07)	1.06 (0.63, 1.77)
High fasting glucose	1.91* (1.43, 2.54)	1.88* (1.41, 2.50)	1.76* (1.30, 2.37)	2.89* (1.73, 4.82)	2.72* (1.63, 4.57)	2.26* (1.31, 3.91)
High triglycerides	1.41 (1.01, 1.89)	1.38 (1.03, 1.86)	1.34 (0.94, 1.80)	2.49* (1.49, 4.15)	2.37* (1.42, 3.96)	1.66 (0.95, 2.90)
Low HDL-cholesterol	1.31* (1.01, 1.69)	1.31* (1.01, 1.69)	1.35* (1.04, 1.77)	1.53 (0.93, 2.51)	1.52 (0.93, 2.50)	1.61 (0.95, 2.73)
Obesity	1.79* (1.31, 2.45)	1.77* (1.29, 2.43)	1.86* (1.34, 2.57)	1.78 (0.97, 3.07)	1.72 (0.93, 3.17)	1.65 (0.86, 3.14)
<b>Mutually-adjusted</b>						
Hypertension	1.00 (0.76, 1.31)	1.00 (0.76, 1.31)	0.95 (0.72, 1.24)	0.95 (0.56, 1.62)	0.95 (0.56, 1.61)	0.91 (0.53, 1.55)
High fasting glucose	1.72* (1.27, 2.32)	1.70* (1.26, 2.30)	1.58* (1.16, 2.14)	2.47* (1.43, 4.24)	2.34* (1.37, 4.07)	2.09* (1.20, 3.64)
High triglycerides	1.11 (0.80, 1.54)	1.09 (0.79, 1.52)	1.10 (0.79, 1.53)	1.94* (1.09, 3.47)	1.87* (1.04, 3.34)	1.41 (0.78, 2.55)
Low HDL-cholesterol	1.16 (0.88, 1.53)	1.16 (0.88, 1.54)	1.14 (0.86, 1.52)	1.14 (0.66, 1.97)	1.16 (0.67, 1.99)	1.28 (0.73, 2.24)
Obesity	1.48* (1.05, 2.08)	1.47* (1.05, 2.08)	1.57* (1.11, 2.22)	1.16 (0.60, 2.25)	1.15 (0.59, 2.23)	1.28 (0.65, 2.50)

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p value  $* < 0.05$ . Adjusted for age, demographics/lifestyle (ethnicity, alcohol consumption, smoking, total cholesterol), and socioeconomic status (SES; education, marital status, place of service, income during midlife).

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**Figure 1: Sampling in the Vietnam Experience Study**

**Figure 2: Increasing hazard ratios for all-cause (p for trend<0.001) and  
cardiovascular disease (p for trend=0.083) mortality with increasing components of  
the metabolic syndrome**

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