UNIVERSITY^{OF} BIRMINGHAM University of Birmingham Research at Birmingham

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

Thomas, Graham; Phillips, Anna; Carroll, Douglas; Gale, CR; Batty, GD

DOI: 10.1016/j.atherosclerosis.2009.10.045

Document Version Peer reviewed version

Citation for published version (Harvard):

Thomas, G, Phillips, A, Carroll, D, Galé, CR & Batty, GD 2010, 'The metabolic syndrome adds utility to the prediction of mortality over its components: The Vietnam Experience Study', *Atherosclerosis*, vol. 210, no. 1, pp. 256-261. https://doi.org/10.1016/j.atherosclerosis.2009.10.045

Link to publication on Research at Birmingham portal

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.

•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.

•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?) •Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

1

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

G. Neil Thomas, PhD^a, Anna C. Phillips, PhD^b, Douglas Carroll, PhD^b, Catharine R. Gale, PhD^{c,d}, G. David Batty, PhD^{c,e}

^aEpidemiology, Public Health and Biostatistics, College of Medical and Dental Sciences, University of Birmingham, UK ^bSchool of Sport & Exercise Sciences, University of Birmingham, UK ^cMRC Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, UK ^dMRC Epidemiology Resource Centre, University of Southampton, UK ^eMRC Social & Public Health Sciences Unit, University of Glasgow, UK

Short title: Metabolic syndrome and mortality

ddress correspondence to:	G Neil Thomas		
	Epidemiology, Public Health and Biostatistics		
	College of Medical and Dental Sciences		
	University of Birmingham		
	Birmingham B15 2TT, UK		
	Tel: (44) 0121 414 8696		
	Fax: (44) 0121 414 7878		
	E-mail: gneilthomas@yahoo.co.uk		

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.¹⁻¹⁴ 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,¹⁵ a major determinant of subsequent events.¹⁶ 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.^{17,18}

From a fasted blood sample, triglycerides and cholesterol fractions were assessed using a Kodak Ektachem 700 autoanalyzer.^{17,18} Serum glucose level was determined with an adaptation of the glucose oxidase-peroxidase-chromogen-coupled system.^{17,18} 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/m²).

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.^{17,18}

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.¹⁹, which made slight modifications to the Adult Treatment Panel III recommended diagnostic criteria.²⁰ According to this definition, participants were classified as having the metabolic syndrome if any three of the following were present: BMI >30 kg/m² (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;²¹) 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.^{22,23} and others (e.g.,²⁴) 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

Thomas, N., Phillips, A.C., Carroll., D., Gale, C.R., & Batty, G.D., & et al., (2010). The metabolic syndrome adds utility to the prediction of mortality over its components: the Vietnam Experience Study. Atherosclerosis, 210, 256-261. http://dx.doi.org/10.1016/j.atherosclerosis.2009.10.045 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. High 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 =

Thomas, N., Phillips, A.C., Carroll., D., Gale, C.R., & Batty, G.D., & et al., (2010). The metabolic syndrome adds utility to the prediction of mortality over its components: the Vietnam Experience Study. *Atherosclerosis*, 210, 256-261. <u>http://dx.doi.org/10.1016/j.atherosclerosis.2009.10.045</u> 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.¹⁻¹⁴ 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.²⁵ 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

Thomas, N., Phillips, A.C., Carroll., D., Gale, C.R., & Batty, G.D., & et al., (2010). The metabolic 9 syndrome adds utility to the prediction of mortality over its components: the Vietnam Experience Study. *Atherosclerosis*, 210, 256-261. <u>http://dx.doi.org/10.1016/j.atherosclerosis.2009.10.045</u> 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.² 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.² 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 in 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,¹⁻³ but not all studies.^{13,26}

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^{1,3,8,13} and all-cause mortality,^{3,8} 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.^{2,26} 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,^{3,8,13} contrasting those that did not identify an association.²⁶

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.²¹ 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.

Acknowledgements

Mortality surveillance of the cohort in the post-service VES was funded by the National Center for Environmental Health, Atlanta, US. David Batty is a Wellcome Trust Fellow (WBS U.1300.00.006.00012.01). The UK Medical Research Council and the University of Edinburgh provide core funding for the MRC Centre for Cognitive Ageing and Cognitive Epidemiology which supported the preparation of this manuscript.

References

- Thomas GN, Schooling M, McGhee SM, Ho SY, Cheung BMY, Wat NMS, Janus ED, Lam KSL, Lam TH, for the Hong Kong Cardiovascular Risk Factor Prevalence Study Steering Committee, Metabolic syndrome increases all-cause and vascular mortality: the Hong Kong Cardiovascular Risk Factor Study, Clin Endocrinol, 2007, 66: 666-71.
- Ho JS, Cannaday JJ, Barlow CE, Mitchell TL, Cooper KH, FitzGerald SJ, Relation of the number of metabolic syndrome risk factors with all-cause and cardiovascular mortality, Am J Cardiol, 2008, 102: 689-92.
- Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP, San Antonio Heart Study, National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study, Circulation, 2004, 110: 1251-7.
- 4. Katzmarzyk PT, Church TS, Janssen I, Ross R, Blair SN, Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness, Diabetes Care, 2005, 28: 391-7.
- Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L, Cardiovascular morbidity and mortality associated with the metabolic syndrome, Diabetes Care, 2001, 24: 683-9.
- Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR, Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults, Circulation, 2004, 110: 1245-50.
- Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K, DECODE Study Group, Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women, Arch Intern Med, 2004, 164: 1066-76.

- Ford ES, The metabolic syndrome and mortality from cardiovascular disease and all-causes: findings from the National Health and Nutrition Examination Survey II Mortality Study, Atherosclerosis, 2004, 173: 309-14.
- Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT, The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men, JAMA, 2002, 288: 2709-16.
- Onat A, Ceyhan K, Basar O, Erer B, Toprak S, Sansoy V, Metabolic syndrome: major impact on coronary risk in a population with low cholesterol levels-a prospective and cross-sectional evaluation, Atherosclerosis, 2002, 165: 285-92.
- 11. Sundstrom J, Riserus U, Byberg L, Zethelius B, Lithell H, Lind L, Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study, BMJ, 2006, 332: 878-82.
- Simons LA, Simons J, Friedlander Y, McCallum J, Does a diagnosis of the metabolic syndrome provide additional prediction of cardiovascular disease and total mortality in the elderly? The Dubbo Study, Med J Aust, 2007, 186: 400-3.
- 13. Eberly LE, Prineas R, Cohen JD, Vazquez G, Zhi X, Neaton JD, Kuller LH, Multiple Risk Factor Intervention Trial Research Group, Metabolic syndrome: risk factor distribution and 18-year mortality in the multiple risk factor intervention trial, Diabetes Care, 2006, 29: 123-30.
- 14. Ford ES, Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence, Diabetes Care, 2005, 28: 1769-78.
- Ardern CI, Janssen I, Metabolic syndrome and its association with morbidity and mortality, Appl Physiol Nutr Metab, 2007, 32: 33-45.
- 16. Kannel WB, Hazards, risks, and threats of heart disease from the early stages to symptomatic coronary heart disease and cardiac failure, Cardiovasc Drugs Ther, 1997, 11 (Suppl 1): 199-212.

- The Centers for Disease Control Vietnam Experience Study, Health status of Vietnam veterans. I.
 Psychosocial characteristics, JAMA, 1988, 259: 2701-7.
- The Centers for Disease Control Vietnam Experience Study, Health status of Vietnam veterans. II. Physical Health, JAMA, 1988, 259: 2708-14.
- Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith Jr SC, Spertus JA, Costa F, American Heart Association, National Heart L, and Blood Institute, Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement, Circulation, 2005, 112: 2735-52.
- 20. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults, Executive summary of the third report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), JAMA, 2001, 285: 2486-97.
- 21. Alberti KG, Zimmet PZ, for the WHO Consultation Group, Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation, Diabet Med, 1998, 15: 539-53.
- Batty GD, Gale CR, Mortensen LH, Langenberg C, Shipley MJ, Deary IJ, Pre-morbid intelligence, the metabolic syndrome and mortality: the Vietnam Experience Study, Diabetologia, 2008, 51: 436-43.
- 23. Batty GD, Shipley MJ, Mortensen LH, Boyle SH, Barefoot J, Gronbaek M, Gale CR, Deary IJ, IQ in late adolescence/early adulthood, risk factors in middle age and later all-cause mortality in men: the Vietnam Experience Study, J Epidemiol Community Health, 2008, 62: 522-31.
- 24. Smith GD, Neaton JD, Wentworth D, Stamler R, Stamler J, Mortality differences between black and white men in the USA: contribution of income and other risk factors among men screened for the MRFIT. MRFIT Research Group. Multiple Risk Factor Intervention Trial, Lancet, 1998, 351: 934-9.

- 25. Sundström J, Risérus U, Byberg L, Zethelius B, Lithell H, Lind L, Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study, BMJ, 2006, 332: 878-82.
- 26. Sattar N, McConnachie A, Shaper AG, Blauw GJ, Buckley BM, de Craen AJ, Ford I, Forouhi NG, Freeman DJ, Jukema JW, Lennon L, Macfarlane PW, Murphy MB, Packard CJ, Stott DJ, R G Westendorp, Whincup PH, Shepherd J, Wannamethee SG, Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies, Lancet, 2008, 371: 1927-35.

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

participants.

Parameters	arameters 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 ²)	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)	5.69 (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	

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

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

		All-cause mortality			Cardiovascular disease mortality			
Adjustments	Deaths/	Crude	Age,	Age, SES,	Deaths/	Crude	Age	Age, SES,
	Ν			demographics/	Ν			demographics/
				lifestyle				lifestyle
Metabolic syndrom	e							
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 syndrom	ie							
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).

Components	All-cause mortalit	У		Cardiovascular disease mortality			
Adjustments	Crude	Age	Age, SES,	Crude	Age	Age, SES,	
			demographics			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)	
Mutually-adjusted							
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)	

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

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).

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



