# The metabolic syndrome and cardiovascular mortality in US Air Force veterans of the Vietnam War

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## Introduction

The metabolic syndrome is a clustering of risk factors such as disturbed glucose and insulin metabolism, obesity and visceral adiposity, low HDL cholesterol, hypertension, and a systemic pro-inflammatory state. Its subsequent association with development of cardiovascular disease and type 2 diabetes makes it a major health care issue. The prevalence of the metabolic syndrome in the United States is roughly 25% for adults over 20 and up to 40% for those over 60 years old[1]. Although the estimates on the prevalence differ and various criteria have been used in classification of metabolic syndrome, few seem to disagree that it has reached epidemic proportions. Two major definitions have been proposed by World Health Organization (WHO) and the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III)[2-3]. The exact definition of the syndrome and the importance of individual components in the etiology of the syndrome are still under intense investigation[4].

The Air Force Health Study is a 25-year prospective study examining the health, mortality and reproductive outcomes in US Air Force veterans of Operation Ranch Hand who sprayed herbicides, including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) – contaminated Agent Orange, in Vietnam from 1962 to 1971. Veterans who flew or serviced C-130 transport aircraft in Southeast Asia during the same time period but did not spray herbicides served as comparisons[5-6]. In this study we examined whether the NCEP-defined metabolic syndrome in Air Force veterans who attended the 1982 baseline examination was associated with their subsequent cardiovascular and any-cause mortality and whether exposure to herbicides had any effect on this association.

## Methods

Ranch Hand and Comparison veterans who attended the baseline physical examination conducted in 1982 were included in this study. Comparison veterans were matched to Ranch Hand veterans on date of birth, race and military occupation. Participation was voluntary and informed consent was given at the examination site. Cardiovascular mortality between 1982 and December 31, 1999 was determined from the underlying cause of death on death certificates following the rules and

conventions of the International Classification of Diseases, Ninth Revision (ICD 9). Codes 390 to 459 were classified as cardiovascular (CVD) deaths. Codes 410 to 414 represented a narrower definition of coronary heart disease deaths (CHD). Diabetic status was obtained from medical records.

The NCEP guidelines defined metabolic syndrome as the presence of three or more of the following risk determinants: waist circumference over 102 cm (men); elevated triglycerides (≥150 mg/dl), low HDL cholesterol (<40 mg/dl), hypertension (≥130/≥85 mmHg), and impaired fasting glucose (≥110 mg/dl). We modified this definition by using body mass index (BMI ≥30 kg/m$^2$) as a surrogate for waist circumference greater than 102 cm because waist measurement was not performed at the baseline exam. We calculated BMI as weight (kg) divided by the square of height (m). A waist measurement was performed in 1987 and the correlation between BMI in 1987 and waist circumference in 1987 was 0.87 ($p<0.001$). Other known and probable risk factors for cardiovascular diseases were measured at the baseline examination including smoking and alcohol consumption. We defined a pack-year as smoking one pack of cigarettes per day for one year and one drink-year as the equivalent of drinking 1.5 ounces of 80-proof whiskey (or, equivalently, 5 ounces of wine or 12 ounces of beer) per day for 1 year.

A total of 2,269 veterans attended the 1982 baseline examination. Veterans with a history of any cardiovascular disease (including a wide range of conditions such as arrhythmias, hypertension, myocardial infarction, atherosclerosis, phlebitis, varicose veins etc.), cancer or diabetes at the baseline examination were excluded from the analysis (n=1,219). Another 7 veterans with missing values for one or more of the variables included in the definition of the metabolic syndrome were also excluded. After these exclusions, 1,043 veterans were available for this study. TCDD was not measured at the 1982 baseline examination, as no analytical method was yet available to measure this chemical compound in human tissue samples in parts per trillion (ppt). TCDD levels presented here refer only to the subgroup of veterans with a TCDD measurement made in 1987 or thereafter[7]. We did not exclude 180 veterans with missing TCDD (including 82 who died during the follow-up) from our analyses.

Statistical analyses were performed using cumulative mortality data to December 31, 1999. Associations of relevant variables with coronary, cardiovascular, and any-cause mortality were assessed with univariate Cox proportional hazards models. Associations between the modified NCEP definition of the metabolic syndrome and CHD, CVD, and any-cause mortality in the entire cohort and two exposure categories (Ranch Hand, Comparison) were analyzed with Cox proportional hazards regression models. An age-adjusted and two multivariate models were used. In multivariate model 1 we adjusted for age at baseline, smoking (pack-years), family history of CVD, and triglycerides, and in multivariate model 2 for age at baseline, smoking (pack-years), alcohol consumption (drink-years), family history of CVD, triglycerides, white blood cell (WBC) count, and military occupation.

**Results**

The median follow-up was 17 years (range 0.8-18 years). There were 162 deaths during follow up. Of these, there were 56 CVD deaths, of which 37 were due to CHD. In univariate Cox proportional models, higher systolic and diastolic blood pressure, BMI, smoking, and alcohol intake were statistically significantly associated with a higher mortality from CHD and CVD. Blood glucose levels and 2-hour postprandial glucose levels were also associated with a higher cardiovascular mortality, as were higher triglycerides and total cholesterol, but not lower HDL levels (Table 1).

In age-adjusted Cox models the metabolic syndrome was associated with almost three times higher mortality from CVD and two times higher mortality from CHD in the entire cohort of veterans (Table 2). After adjustment for additional risk factors (smoking, triglycerides, and family history of CVD), the relative risk of CVD death was attenuated but remained statistically significant for all cardiovascular diseases. Further adjustment for alcohol consumption, WBC, and occupation had little effect on the relative risks. Most of the observed increases were due to increased CVD mortality and to a lesser extent in CHD mortality in Comparison veterans (n=574). Ranch Hand veterans (n=469) who were occupationally exposed to TCDD-contaminated herbicides did not show any consistent association between metabolic syndrome and mortality from cardiovascular or any-cause deaths.

**Discussion**

This was a study of Vietnam veterans reporting the association of the metabolic syndrome, using a recently proposed definition, with coronary heart disease, cardiovascular disease, and any-cause mortality. The increased mortality found in this study was independent of other potentially confounding factors such as smoking, alcohol consumption and serum cholesterol levels. Although we could not fully explore association with TCDD levels, most of the increased mortality reported here was in the group of Comparison veterans, who had background TCDD levels. The median level for Ranch Hand veterans (26 ppt) was about six times higher than for Comparison veterans (4 ppt).

The prevalence of metabolic syndrome at baseline was 16.2 %, in a group of healthy and relatively young men (mean age 42.7 years at baseline) and was slightly higher than in an European study that also found increased cardiovascular mortality in white middle age men[8], but still much lower than current US estimates. The Third National Health and Nutrition Examination Survey reported a prevalence of roughly 30% for men 40 to 59 years of age[1]. Our data suggest that prevalence of metabolic syndrome 20-years ago was not as high as is estimated now.

The strengths of this study included long follow-up, reliable assessment of causes of death, detailed assessment of metabolic and cardiovascular risk factors and exclusion of diabetes, cancer and cardiovascular disease at baseline, as well as adjustment for the majority of known and suspected risk factors including smoking and family history of CVD. We were limited by the lack of exposure assessment for chemicals other than TCDD, and possible confounding by unknown or unmeasured risk factors could not be excluded. Using BMI instead of a waist measurement could have resulted, in spite of high correlation, in misclassification of metabolic syndrome in some

veterans. The study included only males and the number of non-white veterans was too small (6%) to make meaningful inferences. Number of CVD deaths was also too small to examine interactions with TCDD or to further stratify by other factors.

Veterans participating in the Air Force Health Study, mostly middle age white men, with the metabolic syndrome as defined by the modified NCEP criteria have experienced an increased cardiovascular mortality even when initially without diabetes and cardiovascular disease. Serum TCDD levels had limited, if any effect on CVD mortality and the most consistent increases in mortality were observed in the group of Comparison veterans who were not occupationally exposed to herbicides. Early identification and treatment of the metabolic syndrome in surviving veterans may improve their cardiovascular outcomes in the current epidemic of overweight and sedentary lifestyles.

**References**

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**Table 1.** Baseline characteristics of US Air Force Vietnam veterans without initial CVD, cancer, and diabetes who died of CHD, CVD, and any cause during follow-up.

| Characteristic | Entire Cohort (n=1043) | CHD Deaths (n=37) | CVD Deaths (n=56) | Any-Cause Deaths (n=162) |
|---|---|---|---|---|
| Age, mean (SD) yrs | 42.8 (7.9) | 52.7 (9.2)[1] | 51.8 (8.3)[1] | 49.8 (8.1)[1] |
| TCDD, median (10-90%), ppt[3] | 5.3 (2.4-36.2) | 9 (2.8-47.2) | 8.7 (2.4-47.2) | 5.5 (2.1-26.7) |
| Smoking, median, pack-years | 11 (0-24) | 26 (17-43)[2] | 28 (18-43)[1] | 30 (13-44)[1] |
| Alcohol consumption, median, drink-years | 25 (3-29) | 23 (1.8-57) | 20 (2.9-52) | 22 (3.2-50)[1] |
| BMI, mean (SD) | 26.0 (3.6) | 27.5 (3.5)[2] | 26.9 (3.6) | 26.1 (4) |
| PBF, mean (SD) | 19.5 (4.5) | 21.4 (4.5)[2] | 20.6 (4.6) | 19.6 (5.1) |
| Fasting glucose, mean (SD), mg/dl | 97.7 (31) | 105.6 (38.4)[2] | 108.3 (41.1)[1] | 107.5 (44.2)[1] |
| 2 hour postprandial glucose | 97.8 (41) | 131.4 (62.4)[1] | 141 (85.7)[1] | 126.9 (88.6)[1] |
| Family history of diabetes No. (%) | 173 (16.6) | 5 (13.5) | 8 (14.3) | 22 (13.6) |
| HDL cholesterol, mean (SD) mg/dl | 47.1 (12.5) | 43.4 (11.1) | 44.8 (14.2) | 46 (13.1) |
| Triglycerides, mean (interquartile range) mg/dl | 145 (70-170) | 163 (121-281)[1] | 163 (113-286)[1] | 128 (88-205)[1] |
| Total cholesterol, mean (SD) mg/dl | 215 (42) | 242 (51)[1] | 245 (50)[1] | 227 (44)[1] |
| Family history of CHD No. (%) | 300 (28.8) | 11 (29.7) | 16 (28.6) | 39 (24.1) |
| Family history of CVD No. (%) | 524 (50.2) | 16 (43.2) | 24 (42.3) | 61 (37.7)[1] |
| Systolic BP, mean (SD), mm Hg | 131.1 (13.9) | 145.6 (21.2)[1] | 144.8 (19.5)[1] | 138.3 (18.6)[1] |
| Diastolic BP, mean (SD), mm Hg | 78.5 (9.6) | 86.1 (11.9)[1] | 86.7 (11.4)[1] | 82.3 (11.9)[1] |
| Blood pressure medication No. (%) | 25 (2.4) | 0 (0) | 3 (5.4) | 8 (4.9)[2] |
| Hypertension No. (%) | 314 (30.1) | 25 (67.6)[1] | 36 (64.3)[1] | 84 (51.9)[1] |
| Erythrocyte sedimentation rate | 3.4 (5.0) | 7.7 (10.1)[1] | 7.2 (9.1)[1] | 6.3 (9.2)[1] |
| White blood cell, mean (SD) x $10^3/\mu L$ | 7.5 (2.1) | 8.6 (1.9)[1] | 8.5 (1.9)[1] | 8.4 (2.4)[1] |
| Platelet count, mean (SD) x $10^3/\mu L$ | 270 (59) | 272 (56) | 272 (63) | 278 (67) |

1. $p<0.001$ in univariate Cox proportional hazards model with CHD, CVD, or any cause mortality as the outcome variable.
2. $p<0.05$ in univariate Cox proportional hazards model with CHD, CVD, or any cause mortality as the outcome variable.
3. ppt – parts per trillion in serum lipid.

**Table 2.** Relative risk of death from CHD, CVD, and any cause in US Air Force Vietnam veterans during 17 years of follow-up.

| | Modified NCEP Definition of Metabolic Syndrome with BMI ≥ 30 | | | | | |
|---|---|---|---|---|---|---|
| | CHD mortality | | CVD mortality | | All-cause mortality | |
| | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| Entire Cohort (n=1043)[1] | (n=37) | | (n=56) | | (n=162) | |
| Age-adjusted model | 2.13 | 1.08-4.13 | 2.80 | 1.64-4.78 | 1.80 | 1.24-2.53 |
| Multivariate model 1[2] | 1.23 | 0.54-2.79 | 2.00 | 1.03-3.84 | 1.51 | 1.00-2.29 |
| Multivariate model 2[‡] | 1.15 | 0.50-2.67 | 1.96 | 1.01-3.65 | 1.47 | 0.96-2.24 |
| Comparison (n=574)[1] | (n=19) | | (n=27) | | (n=83) | |
| Age-adjusted model | 3.01 | 1.22-7.43 | 3.86 | 1.81-8.24 | 1.77 | 1.11-2.83 |
| Multivariate model 1[2] | 2.28 | 0.75-6.92 | 3.50 | 1.36-8.97 | 1.99 | 1.12-3.54 |
| Multivariate model 2[3] | 2.11 | 0.66-6.74 | 3.36 | 1.27-8.87 | 1.93 | 1.08-3.46 |
| Ranch Hand (n=469)[1] | (n=18) | | (n=29) | | (n=79) | |
| Age-adjusted model | 1.38 | 0.49-3.93 | 2.06 | 0.95-4.51 | 1.84 | 1.12-3.03 |
| Multivariate model 1[2] | 0.50 | 0.13-1.94 | 1.07 | 0.39-2.95 | 1.05 | 0.55-2.00 |
| Multivariate model 2[3] | 0.46 | 0.12-1.80 | 1.05 | 0.38-2.93 | 1.05 | 0.54-2.04 |

1. Number and percent of veterans with metabolic syndrome: Entire cohort 169 (16.2%), Comparison 102 (17.7%), Ranch Hand 67 (14.3%).
2. Adjusted for age, smoking (pack-years), family history of CVD, and triglycerides.
3. Adjusted for age, smoking (pack-years), alcohol consumption (drink-years), family history of CVD, triglycerides, white blood cells count, and military occupation.