

Enlarged Waist Combined With Elevated Triglycerides Is a Strong Predictor of Accelerated Atherogenesis and Related Cardiovascular Mortality in Postmenopausal Women

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Background—Upward trends of obesity urge more effective identification of those at cardiovascular risk. A simple dichotomous indicator, enlarged waist (≥ 88 cm) combined with elevated triglycerides (≥ 1.45 mmol/L) (EWET), was shown to offer advantages in identifying individuals with atherogenic “lipid overaccumulation” compared with other indicators, including the metabolic syndrome defined by the National Cholesterol Education Program (MS-NCEP). Whether EWET offers superior disease and event prediction in postmenopausal women, however, remains unknown.

Methods and Results—A community-based sample of 557 women (48 to 76 years of age) were followed up for 8.5 ± 0.3 years to assess the utility of EWET and MS-NCEP in estimating the risk of all-cause and cardiovascular mortality and the annual progression rate of aortic calcification. At baseline, 15.8% of women had EWET and 17.6% had MS-NCEP. All-cause mortality and cardiovascular mortality were increased in carriers of the dichotomous indicators ($P < 0.001$). After adjustment for age, smoking, and LDL cholesterol, presence of EWET was associated with a 4.7-fold (95% CI, 2.2 to 9.8; $P < 0.001$) increased risk and presence of MS-NCEP was associated with a 3.2-fold (95% CI, 1.5 to 6.5; $P < 0.001$) increased risk for fatal cardiovascular events. Exclusion of women with prevalent diabetes did not change these trends; respective hazard ratios were 4.2 (95% CI, 1.9 to 9.3; $P < 0.001$) and 2.5 (95% CI, 1.1 to 5.5; $P < 0.05$). Among those who were discordant for EWET and MS-NCEP at baseline, those who had EWET alone ($n = 21$) had a higher annual progression rate of aortic calcification compared with those who had MS-NCEP alone ($n = 31$; $P < 0.05$).

Conclusions—The combined presence of EWET may be the best indicator of cardiovascular risk in postmenopausal women. Other components of the MS-NCEP add little medical value to screening in general practices. (*Circulation*. 2005;111:1883-1890.)

Key Words: atherosclerosis ■ diagnosis ■ lipids ■ obesity ■ women

Because two thirds of women who die suddenly of cardiovascular disease (CVD) have no previously recognized symptoms,¹ it is essential to find effective indicators of cardiovascular risk that could facilitate timely referral of those who would benefit the most from adequate prevention.

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Because of the heavy underrepresentation of postmenopausal women in previous cohorts investigating the epidemiology and pathophysiology of CVD,² major risk factors and hence targets of primary prevention are still incompletely understood. The notion that “lipid overaccumulation” has different relative importance for atherogenesis and CVD in the 2 genders arises from observations indicating that elevated triglycerides and decreased HDL cholesterol (HDL-C) are useful indicators of the risk of adverse outcomes in women but less so in men.^{3–5}

The Adult Treatment Panel III of the National Cholesterol Education Program (NCEP) has recently defined the meta-

bolic syndrome (MS) as a constellation of ≥ 3 of 5 components that for women were defined as follows: (1) enlarged waist (≥ 88 cm), (2) elevated triglyceride (≥ 1.69 mmol/L), (3) elevated blood pressure ($\geq 130/85$ mm Hg), (4) low HDL cholesterol (< 1.30 mmol/L), and (5) impaired fasting glucose (≥ 6.1 mmol/L).⁶ Initial studies revealed somewhat inconsistent results concerning the utility of MS-NCEP in predicting cardiovascular mortality, particularly in nondiabetic populations.^{7–10} The variation in predictive value could be explained by the fact that the diagnosis of MS-NCEP may be based on numerous combinations of the individual components; some may better correlate with the core pathogenic mechanisms driving atherothrombogenesis than others. In support, recent observations indicate that the obesity- and lipid-related components are better for identifying subjects with insulin resistance,^{11–13} an established indicator of atherogenic trends.^{14–16}

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Seminal works from the Quebec Cardiovascular Study group introduced "hypertriglyceridemic waist" (waist circumference ≥ 90 cm and triglycerides ≥ 2.0 mmol/L) as a marker of atherogenic metabolic profile in men and demonstrated its utility in estimating the 5-year risk for cardiovascular events.¹⁷⁻¹⁹ More recently, Kahn and Valdez²⁰ defined normative thresholds for waist circumference (≥ 88 cm) and triglycerides (≥ 1.45 mmol/L) in both sexes using data from the third National Health and Nutrition Survey (NHANES III). Their work further illustrated the possible advantages of using enlarged waist combined with elevated triglycerides (EWET), a simple dichotomous indicator, for identifying individuals with lipid overaccumulation. To date, however, no long-term prospective study has addressed the utility of EWET in estimating the annual progression rate of aortic calcification (AC), a surrogate marker of the atherosclerotic burden, and the risk of fatal outcomes in postmenopausal women.

Therefore, the aim of the present study was to investigate the relative utility of EWET compared with the MS-NCEP criteria in estimating future risk of all-cause and cardiovascular mortality and the annual progression rate of AC. These questions were addressed in a community-based cohort of 557 postmenopausal women 48 to 76 years of age who were followed up for an average of 8.5 years.

Methods

During 1992 and 1993, 686 postmenopausal women living in the Copenhagen area were recruited via questionnaire surveys to participate in a study addressing the role of a number of metabolic risk factors in the pathogenesis of CVD and osteoporosis. Participants were followed up on average 8.5 years later. Information on individuals who died during the observation period was obtained via the Central Registry of the Danish Ministry of Health (follow-up rate, 100%). Although all survivors ($n=591$) were successfully contacted, 129 women who either relocated from the Copenhagen area or did not wish to participate provided no clinical data at the end of the study (follow-up rate, 78.2%). Baseline demographic characteristics and risk parameters of these women showed no significant differences compared with women included in the present analysis ($n=557$). All participants signed an approved informed consent, and the study was carried out according to the Helsinki Declaration II and good clinical practice. The local ethics committee approved the study protocols.

Baseline Examinations

Demographic characteristics and risk parameters collected at baseline were age, weight, height, body mass index (BMI), waist and hip circumferences, systolic and diastolic blood pressures, treated hypertension, treated diabetes, smoking, regular alcohol and daily coffee consumption, and weekly fitness activity. In addition, we measured fasting glucose and lipid profile (total cholesterol, triglycerides, HDL-C, LDL cholesterol (LDL-C), apolipoprotein (apo) AI, apoB, and lipoprotein a [Lp(a)]) using an automated blood analyzer (Cobas Mira Plus, Roche Diagnostic Systems, Hoffmann-La Roche). Threshold values for risk predefined for women were as described in the Introduction, and the presence of ≥ 3 components defined MS-NCEP.⁶ The combined presence of enlarged waist (≥ 88 cm) and elevated triglycerides (≥ 1.45 mmol/L) identified women with EWET.²³ Diabetes at baseline was defined by ongoing antidiabetic treatment or a fasting serum glucose >7.0 mmol/L.

Threshold values of other risk factors of cardiovascular relevance were as follows: BMI >27.5 kg/m², total cholesterol ≥ 6.20 mmol/L, LDL-C ≥ 4.20 mmol/L, and Lp(a) ≥ 30.0 mg/dL. Cutoff point of the

apoB/apoAI ratio (≥ 0.80) was defined according to results of the AMORIS trial.²¹

Outcome Variables

All-Cause and Cardiovascular Mortality

The primary end points of the study were all-cause and cardiovascular mortality. The 3 main disease groups considered in the present study were (1) cardiovascular death (*International Classification of Diseases*, ninth revision [ICD-9] codes 410 through 414 and 420 through 447, excluding 427.5), (2) death resulting from malignant proliferative diseases (ICD-9 codes 140 through 195 and 200 through 208), and (3) death resulting from other causes.

Annual Progression Rate of AC

Calcified deposits in the lumbar aorta (L1 through L4), a direct surrogate of the atherosclerotic burden, was visualized on lateral x-rays and graded on a scale of 0 to 24 to obtain severity scores, as first described by the Framingham study group.²² The annual progression rate of AC was calculated as the relative change in the severity score from baseline ($AC_{\text{follow-up}} - AC_{\text{baseline}}$) divided by the overall duration of the follow-up period (in years). This outcome parameter was collected from survivors only.

Statistical Analysis

Baseline characteristics of survivors and nonsurvivors were compared by use of ANOVA or the Kruskal-Wallis test for parametric and nonparametric variables, respectively, followed by pairwise comparisons of the different groups with control subjects. Baseline characteristics of subjects stratified according to the EWET or MS-NCEP criteria were assessed with a Student *t* test or the Mann-Whitney test, as appropriate. Cumulative survivals were computed by Kaplan-Meier analysis and compared by use of the log-rank test. Unadjusted and adjusted (for age, smoking, and LDL-C) proportional hazards associated with selected risk factors were estimated by univariate or multivariate Cox regression analyses, respectively. The latter test was also used to identify independent contributors in the multicomponent models of MS-NCEP and EWET. The independent association between triglyceride (log transformed) and hip circumference was tested with partial correlation controlling for waist circumference. The estimated means of the annual progression rate of AC were obtained after adjustment for age, smoking, and LDL-C. Means were compared by use of the Kruskal-Wallis test, followed by pairwise comparison of groups of interest versus control subjects. Results are presented as mean \pm SD unless otherwise indicated. Differences and associations were considered statistically significant at values of $P < 0.05$. Data analysis was carried out with SPSS statistical analysis software (version 12.0).

Results

Causes of Death

Cause of death could be defined in 92 of the 95 cases. Thirty-six deaths (37.9%) were related to CVD (24 acute myocardial infarctions, 5 ischemic strokes, 4 hemorrhagic strokes, 2 ruptured aortic aneurysms, and 1 cardiac failure), 43 (45.3%) to malignant proliferative diseases, and 16 (16.8%) to other causes (5 chronic obstructive lung disease, 2 acute abdomens, 2 suicides, 1 diabetic nephropathy, 1 septicemia, 1 toxic nodose struma, 1 motoric neuron disease, 1 pulmonary embolism, and 3 unknown reasons).

Baseline Metabolic Risk Profile Associated With Cardiovascular Death

Table 1 summarizes baseline characteristics of women stratified according to cause of death compared with survivors. Women at risk for cardiovascular death had the highest BMI, the largest waist circumference, and highest waist-to-hip

TABLE 1. Baseline Characteristics and Cardiovascular Profile of Participants Stratified According to Cause of Death

Risk Factors at Baseline	Survivors (n=462)	CVD Mortality (n=36)	Cancer Mortality (n=43)	Other/Unknown* Mortality (n=16)	P, F Test
Age, y	60.4±7.1	66.3±5.8‡	66.0±6.8‡	63.1±8.2	<0.001
BMI, kg/m ²	25.3±4.1	27.3±5.9‡	25.0±4.4	23.9±4.2	0.020
Waist, cm	81.9±10.9	89.9±14.6‡	82.1±12.0	81.3±10.8	0.001
Waist-to-hip ratio	0.80±0.07	0.85±0.08‡	0.81±0.08	0.80±0.07	0.001
Systolic BP, mm hg	125±19	143±27‡	134±25‡	141±24‡	<0.001
Diastolic BP, mm Hg	76±10	78±11	76±11	80±9	0.233
Hypertension, %	19.9	44.4‡	30.2	50.0‡	<0.001
Diabetes,† %	2.4	16.7‡	4.7	6.3	<0.001
Glucose, mmol/L	5.42±1.11	6.00±2.20‡	5.59±1.41	5.80±1.88	0.042
Total cholesterol, mmol/L	6.50±1.20	7.45±1.35‡	6.40±0.98	6.48±0.98	<0.001
Triglycerides, mmol/L	1.22±0.63	1.96±1.33‡	1.39±0.87	1.36±0.66	<0.001
LDL-C, mmol/L	3.10±0.96	3.4±0.99‡	2.72±0.67‡	2.59±0.51‡	0.002
HDL-C, mmol/L	1.72±0.44	1.57±0.55	1.74±0.47	1.80±0.71	0.254
ApoB/apoA	0.57±0.17	0.73±0.23‡	0.57±0.18	0.50±0.15	<0.001
Lp(a), mg/dL	22.1±22.8	27.9±29.0	18.9±26.7	20.7±21.4	0.430
AC	1.6±3.0	5.7±4.0‡	3.8±4.2‡	1.5±2.3	<0.001
EWET, %	13.4	50.0‡	16.3	6.3	<0.001
MS-NCEP, %	19.9	44.4‡	25.6	31.3	0.005

BP indicates blood pressure. Results shown are mean±SD when appropriate.

*In 3 cases, the cause of death was unknown.

†Diabetes was defined by prevalent treated diabetes (n=8) or elevated fasting glucose ≥7.0 mmol/L (n=12).

‡P<0.05 vs survivors.

ratio. Furthermore, these women had the highest total cholesterol, triglycerides, LDL-C, and ratio of apoB to apoAI and the lowest HDL-C. Importantly, compared with survivors, only these women showed significantly increased frequency of clustering of risk factors (EWET, MS-NCEP, and type 2 diabetes). Finally, severity scores of AC were also the highest in women at risk for fatal CVD events.

Baseline Metabolic Profile of Women Stratified According to the EWET or MS-NCEP Criteria

The number of women fulfilling the MS-NCEP or EWET criteria was 98 (17.6%) and 88 (15.8%), respectively. Sixty-seven women with MS-NCEP (68.4%) also fulfilled the criteria of EWET.

Those with MS-NCEP (63.6±6.7 versus 60.8±7.4 years; P<0.001) or EWET (63.4±6.8 versus 60.9±7.4 years; P<0.001) were older compared with their respective control subjects, but there were no differences between carriers of the dichotomous indicators. Similar results were found for overall obesity. Thus, BMIs in women with and without MS-NCEP were 29.9±4.5 and 24.3±3.5 kg/m², respectively (P<0.001), whereas in those with and without EWET, BMIs were 30.0±4.2 and 24.5±3.7 kg/m² (P<0.001), respectively. Ever smoking showed no significant differences in any comparisons. Women with EWET (44.3% versus 54.8%; P<0.05) or MS-NCEP (41.8% versus 55.6%; P<0.01) were less likely to be regular consumers of alcoholic beverages

compared with respective control subjects, but again there were no differences between carriers.

At baseline, there were 8 women with prevalent diabetes and 12 with a fasting glucose ≥7.0 mmol/L. The distribution of these women between those with or without MS-NCEP was 14.3% versus 1.3% (P<0.001); between women with or without EWET, it was 10.2% versus 2.3% (P=0.002).

To assess the relative advantages and drawbacks of the 2 dichotomous indicators, we compared their efficacy in identifying individuals with changes in metabolic parameters exceeding threshold for risk (Table 2). In general, carriers of either EWET or MS-NCEP had more pronounced alterations in all 5 components of the MS-NCEP criteria compared with their respective control group. Women with MS-NCEP had higher systolic and diastolic blood pressures, and impaired fasting glucose was more frequent among carriers versus control subjects (56.0% versus 42.0%; P<0.05). As expected, EWET was better for identifying women with enlarged waist (100% versus 89.9%) and triglycerides levels >1.45 mmol/L (100% versus 79.0%). No statistically significant differences were found in other lipid and lipoprotein components such as LDL-C, total cholesterol, apoB/apoAI, and Lp(a).

Finally, AC was more severe in women with EWET (3.2±4.2 versus 1.9±3.2; P=0.008) or MS-NCEP (3.4±4.4 versus 1.7±3.0; P<0.001) compared with their respective control group, but there were no differences in severity scores between carriers of the dichotomous indicators.

TABLE 2. Utility of the Dichotomous Indicators in Identifying Individuals With the Different Metabolic Variables Exceeding Threshold for Risk

	EWET– (n=469)	EWET+ (n=88)	MS-NCEP– (n=459)	MS-NCEP+ (n=98)	EWET+ vs MS-NCEP+
Triglycerides					
Mean, mmol/L	1.09±0.45	2.32±1.04*	1.09±0.45	2.18±1.08*	NS
>1.69, %	8.5	71.6*	7.7	68.0*	
>1.45, %	14.9	100*	17.3	79.0*	
Waist					
Mean, cm	79.6±9.4	97.5±8.6*	79.0±9.1	97.0±10.3*	NS
≥88 cm, %	15.9	100*	16.2	90.7*	
Systolic BP					
Mean, mm Hg	125±20	139±22*	124±19	145±20*	0.05
≥130 mm Hg, %	40.7	62.5*	37.2	76.0*	
Diastolic BP					
Mean, mm Hg	76±10	79±10†	75±10	82±10*	0.04
≥85 mm Hg, %	24.1	39.8†	21.7	49.0*	
Glucose					
Mean, mmol/L	5.32±0.84	6.33±2.39*	5.25±0.68	6.54±2.37*	NS
≥6.1 mmol/L, %	11.0	42.0*	7.2	56.0*	
HDL-C					
Mean, mmol/L	1.79±0.45	1.34±0.30*	1.80±0.45	1.36±0.35*	NS
<1.30 mmol/L, %	10.4	47.7*	8.3	53.0*	
LDL-C					
Mean, mmol/L	2.96±0.90	3.74±0.97*	2.99±0.93	3.76±1.06	NS
≥4.20 mmol/L, %	7.2	32.9*	8.5	33.0*	
ApoB/apoA					
Mean	0.55±0.16	0.73±0.20*	0.55±0.15	0.73±0.20*	NS
≥0.80, %	7.0	30.7*	6.7	30.9*	
Total cholesterol					
Mean, mmol/L	6.43±1.12	7.28±1.38*	6.42±1.13	7.22±1.35*	NS
≥6.20 mmol/L, %	56.5	76.1†	55.8	77.0*	
Lp(a), mg/dL					
Mean, mg/dL	21.9±22.2	24.1±29.1	22.2±22.8	22.4±26.0	NS
≥30.0 mg/dL, %	24.9	26.1	26.0	24.7	

BP indicates blood pressure. Data shown are mean±SD when appropriate.

* $P<0.001$; † $P<0.01$.

Body Fat Distribution in Women With EWET or MS-NCEP

After adjustment for the influence of waist circumference, circulating triglycerides showed an inverse correlation with hip circumference ($r=-0.18$, $P<0.001$). Accordingly, women in the lowest tertiles of waist circumference (<76 cm) and triglycerides (<0.89 mmol/L) had the lowest waist-to-hip ratios, whereas women in the highest tertiles of waist circumference and triglycerides (>86 cm and 1.35 mmol/L, respectively) had the highest waist-to-hip ratios (linear trend $P<0.001$). Furthermore, all women with EWET but only 69.4% of women with MS-NCEP belonged to the group defined by the upper tertiles of triglyceride and waist circumference.

Clinical Outcomes

Kaplan-Meier Survival Curves

Analysis of Kaplan-Meier curves indicated significantly decreased survival rates among carriers of the dichotomous indicators compared with their respective control subjects (Figure 1). Similar trends characterized the survival curves when the analysis was focused on cardiovascular death, but no separation of the curves was apparent when the analysis was focused on death resulting from malignant proliferative disease or other causes (data not shown).

When the analysis focused on cardiovascular death, survival rates among women with EWET or MS-NCEP were 79.1% (difference from control, 17.2%) and 83.6% (difference from control, 11.8%), respectively. Fifty percent (18 of

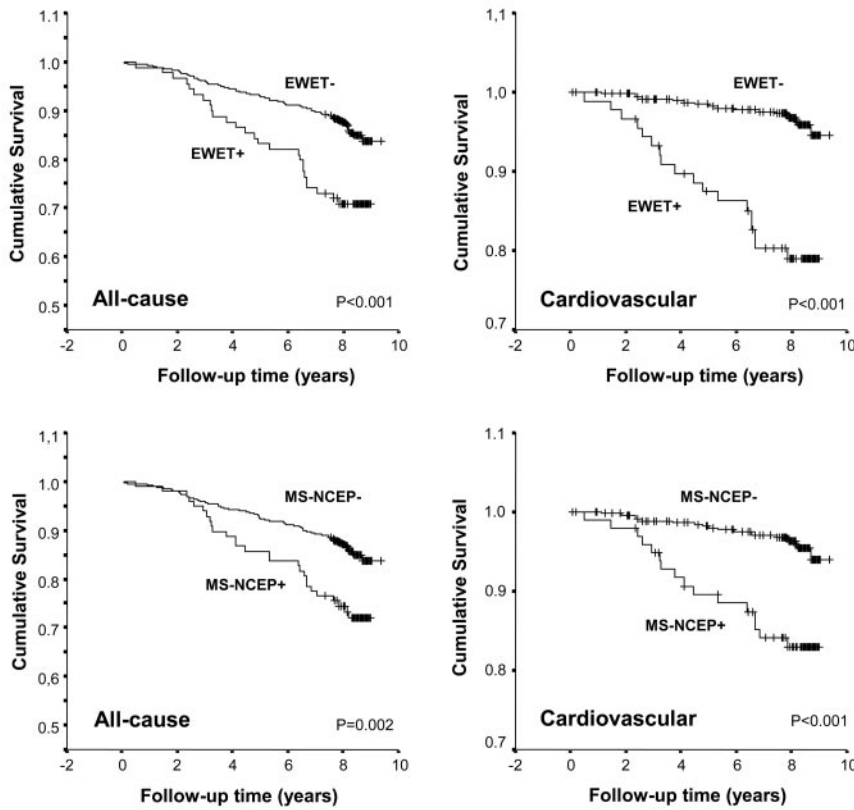


Figure 1. Kaplan-Meier curves indicating all-cause and cardiovascular event rates in women with (n=88) or without (n=469) EWET or with (n=100) or without (n=433) MS-NCEP.

36) of all cardiovascular deaths was explained by EWET and 44.6% (16 of 36) by MS-NCEP. Of the 16 deaths explained by MS-NCEP, 14 (87.5%) also could have been predicted by EWET.

Of the remaining 18 deaths that could not be explained by EWET, 2 showed elevated blood pressure and glucose combined with enlarged waist, 4 showed elevated blood pressure combined with an additional component, 1 showed elevated triglycerides combined with low HDL-C, 9 showed

only elevated blood pressure, and 2 showed no alteration in any of the components.

Relative Risk of Adverse Outcome

When assessed on an individual basis with univariate Cox regression models, all components of MS-NCEP and EWET were associated with increased all-cause and cardiovascular mortality ($P < 0.05$). Table 3 summarizes hazard ratios (HRs) associated with the individual components and the composite

TABLE 3. Adjusted Relative Risk for All-Cause and Cardiovascular Mortality Associated With Individual Components and Composite Traits

	High-Risk Thresholds	All Women, HR (95% CI)		Without Women With Prevalent Diabetes, HR (95% CI)	
		All-Cause Mortality	CVD Mortality	All-Cause Mortality	CVD Mortality
MS-NCEP					
Triglycerides	≥1.69 mmol/L	1.9 (1.2–3.1)†	3.1 (1.4–6.2)‡	1.7 (1.0–2.8)*	2.4 (1.0–5.2)*
Waist	≥88 cm	1.4 (0.9–2.2)	2.7 (1.3–5.5)†	1.3 (0.8–2.1)	2.5 (1.2–5.3)*
Glucose	≥6.1 mmol/L	1.7 (1.1–2.8)*	2.5 (1.3–5.1)†	1.4 (0.8–2.4)	1.9 (0.8–4.3)
BP	≥130/85 mm Hg	1.7 (1.1–2.7)*	1.8 (0.8–3.9)	1.6 (1.0–2.6)*	1.5 (0.7–3.4)
HDL	<1.30 mmol/L	1.8 (1.0–3.2)*	3.1 (1.1–6.7)*	1.7 (1.0–3.2)	2.7 (1.1–6.5)*
Composite MS-NCEP	≥3 Components	1.8 (1.1–3.0)*	3.2 (1.5–6.5)‡	1.6 (0.9–2.6)	2.5 (1.1–5.5)*
EWET					
Waist	≥88 cm	1.4 (0.9–2.2)	2.7 (1.3–5.5)‡	1.3 (0.8–2.1)	2.5 (1.2–5.3)*
Triglyceride	≥1.45 mmol/L	2.1 (1.3–3.3)‡	3.7 (1.8–7.5)‡	1.9 (1.2–3.0)†	2.8 (1.3–6.0)‡
Composite EWET	Both components	2.2 (1.3–3.6)†	4.7 (2.2–9.8)‡	2.2 (1.2–3.7)†	4.2 (1.9–9.3)‡

BP indicates blood pressure. Results were obtained after adjustment for age (continuous), smoking (categorical), and LDL-C (continuous).

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.

traits independent of age, smoking, and LDL-C. Each component except waist circumference was associated with increased risk of all-cause death; the highest HR was associated with elevated triglycerides (2.1; 95% CI, 1.4 to 3.1; $P<0.001$). With regard to cardiovascular mortality, all components except elevated blood pressure indicated increased risk; once again, elevated triglycerides posed the highest relative risk (4.3; 95% CI, 2.2 to 8.3; $P<0.001$). When HRs associated with the individual components are compared with those associated with the composite traits, the relative risk associated with the diagnosis of EWET but not MS-NCEP exceeded those posed by the respective individual components. Exclusion of women with prevalent diabetes at baseline ($n=8$) had moderate influence on HRs, with continuing higher relative risk accompanying the diagnosis of EWET (Table 3). In multivariate Cox proportional-hazard models, we assessed the independent contribution of individual components of MS-NCEP and EWET to the risk for cardiovascular mortality. In the 5-component model of MS-NCEP, independent contributors were triglycerides, HDL, and elevated blood pressure ($P<0.05$). In the 2-component EWET model, both triglycerides ($P<0.01$) and waist circumference ($P<0.05$) were significant contributors. Exclusion of women with prevalent diabetes at baseline did not change the pattern and significance level of independent contributions in the models (data not shown).

Annual Rates of the Progression of AC

At baseline, 53.1% of women had no calcified deposits at radiographs (severity score, 0), whereas others revealed severity scores ranging from 1 to 17. The estimated mean in the overall population regardless age, smoking habits, and LDL-C was 2.1 ± 1.4 . After the same adjustments, presence of at least 1 calcified deposit in the lumbar aorta (severity score >0) was associated with a markedly increased risk for cardiovascular mortality (adjusted HR, 6.4; 95% CI, 2.2 to 18.8; $P=0.001$). The annual progression rate of AC adjusted for age, smoking, and LDL-C status at baseline was significantly higher in women with EWET, MS-NCEP, or both compared with control subjects ($P<0.01$). When women with MS-NCEP with or without simultaneous fulfillment of the EWET criteria were compared, a significantly higher progression rate was apparent in the former group ($P<0.01$) (Figure 2).

Discussion

This is the first long-term prospective study in a community-based, gender-specific population that suggests that EWET is a strong indicator of atherogenic trends and related cardiovascular risk in postmenopausal women. The relative advantages of EWET compared with the 5-component MS-NCEP criteria include a somewhat higher sensitivity and an easier accessibility in general practices. Therefore, inclusion of this diagnostic test in the daily routine procedures of primary care settings not only could facilitate identification of high-risk individuals but also might promote savings for healthcare systems in an era with upward trends in obesity and type 2 diabetes, both of which forecast an epidemic of CVD among elderly women in the upcoming decade.^{23,24}

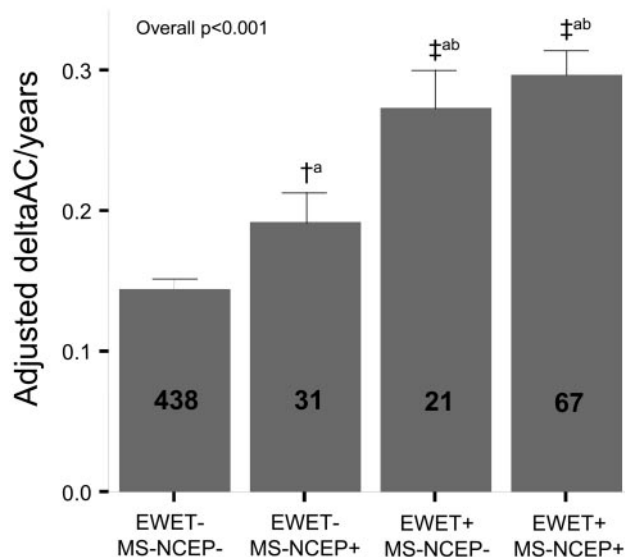


Figure 2. Annual progression rate of AC during 8.5-year observation period in postmenopausal women with MS-NCEP, EWET, or both diagnostic criteria. Results shown are mean \pm SEM obtained after adjustment for age, smoking habits, and LDL-C at baseline. Scatterplots indicate nonskewed distribution of annual progression rate of AC (dAC/years). Numbers in bars indicate number of women in each group. † $P<0.01$, † $P<0.001$ vs control subjects (a) and women with MS-NCEP+ only (b).

The NCEP recently concluded that a constellation of lipid and nonlipid risk factors contributes to the pathogenesis of CVD.⁶ Our results are in line with this conclusion and showed frequent clustering of risk factors in women at risk for cardiovascular death. Generally, these women were more likely to be overweight or obese and had increased upper-body fat deposition combined with the relative lack of gluteal fat mass. This phenotype of obesity, which is in line with previous observations,²⁵ was frequently associated with impaired fasting glucose, elevated triglycerides, and decreased HDL. In the present study, each of these parameters was associated with increased risk for cardiovascular mortality. These observations emphasize that central obesity and related lipid overaccumulation are important risk factors for CVD in postmenopausal women.

With the 5-component MS-NCEP criteria, metabolic alterations do not necessarily involve elevated triglycerides. Indeed, whereas all women with EWET had by definition a triglyceride value >1.45 mmol/L, only 79% of women with MS-NCEP had a similar alteration in triglyceride. In terms of other lipid fractions, the 2 dichotomous indicators were equally effective in capturing those individuals with values that exceed the threshold for risk. Given that hypertriglyceridemia in women seems to pose an increased risk for cardiovascular mortality independently of other lipid fractions, including HDL-C,^{26,27} the relatively higher sensitivity of EWET in identifying individuals with this important lipid alteration might also offer advantages in terms of estimating future risk of manifest CVD.

Although the number of cardiovascular deaths was relatively small for proper comparison of the relative efficiency of the 2 indicators in identifying women at risk, EWET

explained more fatal events than did MS-NCEP (50.0 versus 44.6%). Moreover, 87.5% of deaths explained by MS-NCEP involved the presence of EWET, which provides support for the previously raised notion^{11–13,20} that enlarged waist and elevated triglycerides may be the best to identify women at cardiovascular risk. Interestingly, enlarged waist and elevated triglycerides had an apparent additive impact on cardiovascular risk, indicated by higher HR associated with the composite trait compared with its individual components, which was not true for MS-NCEP. Thus, these findings suggest the relative superiority of EWET in estimating cardiovascular risk in postmenopausal women.

Previous observations indicate that direct measurement of the ratio of central to peripheral fat mass by dual-energy x-ray absorptiometry is a better predictor of the rate of atherogenesis than overall obesity per se.²⁸ Findings from the present study draw attention to a close association between the presence of EWET and the waist-to-hip ratio, an anthropometric estimate of body fat distribution; waist circumference is proportional to the degree of upper-body adiposity, whereas triglycerides are inversely proportional to the degree of lower-body adiposity. Accordingly, women with MS-NCEP that does not involve EWET may have normal to only moderately altered waist-to-hip ratios. In support, all women with EWET but only 69.4% of women with MS-NCEP belonged to the group in the highest tertiles of waist circumference and triglycerides and thus with the highest waist-to-hip ratio. The impact of body fat distribution on atherogenesis was indicated by greater annual changes in AC scores of women with MS-NCEP involving EWET compared with those with MS-NCEP not involving EWET. Thus, EWET seems to be a simple estimate of the relative presence of central and peripheral fat compartments, which is an established predictor of atherogenesis and cardiovascular risk in postmenopausal women.^{16,28–32}

Adipocytes may be distinguished for subcutaneous and visceral adipocytes, the latter being more sensitive to lipolytic stimuli and less sensitive to antilipolytic stimuli.³³ Excessive intra-abdominal fat mass is associated with increased release of free fatty acids into the circulation, which in turn can inhibit glucose uptake and oxidation by muscle and other organs. Increased secretion of insulin may temporarily compensate for these alterations, but the chronic presence of triggering mechanisms may lead to dysfunction of these cells, thereby promoting type 2 diabetes. In addition, excessive fluxes of free fatty acids will lead to cellular accumulation in various organs, particularly in the liver, muscle, and pancreas (lipotoxicity), which has direct implications for the propagation of insulin resistance and impaired β -cell function.^{34,35} Excess free fatty acids may also provide substrate for hepatic triglyceride and triacylglycerol-rich lipoprotein production,³⁶ whereas their enhanced clearance may contribute to depletion of circulating HDL-C.³⁷ Deposition of lipid products in the intima of arteries is a critical step in initiating atherogenesis.³⁸

Numerous studies^{16,28,32,39–42} draw attention to the active role of peripheral fat mass in the modulation of metabolic and cardiovascular risk in postmenopausal women. Excessive lower-body adiposity, even in generally obese women with excessive upper-body adiposity, can provide protective effects against lipid overaccumulation, insulin resistance, type

2 diabetes, and atherogenesis. With regard to the underlying mechanisms, recent observations indicate that in generally obese women, constitutive adiponectin secretion from subcutaneous adipocytes is sustained and proportional to the degree of peripheral adiposity, whereas secretion from visceral adipocytes is blunted.^{16,43,44} Adiponectin has an established role in the maintenance of peripheral insulin sensitivity and thus glucose and triglyceride homeostasis.⁴⁴ In the present study, we found an independent inverse association between triglyceride and hip circumference, an anthropometric estimate of peripheral fat mass, which seems to be in line with this emerging concept.

In summary, our study suggests that EWET is a simple diagnostic tool that could facilitate the identification of postmenopausal women at increased risk for accelerated atherogenesis and related adverse outcomes. Further evaluation of EWET as a universally applicable screening tool in primary care units and general practices is warranted. In addition, intervention studies are needed to test the hypothesis that decreases in waist circumference and serum levels of triglycerides confer beneficial effects in terms of reducing cardiovascular risk in postmenopausal women.

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