Low Ankle-Brachial Pressure Index Predicts Increased Risk of Cardiovascular Disease Independent of the Metabolic Syndrome and Conventional Cardiovascular Risk Factors in the Edinburgh Artery Study

SARAH H. WILD, FRCPE[1]
CHRISTOPHER D. BYRNE, FRCP[2]
FELICITY B. SMITH, PHD[1]
AMANDA J. LEE, PHD[3]
F. GERALD R. FOWKES, FRCPE[1]

OBJECTIVE — To investigate whether a low ankle-brachial pressure index (ABI) predicts increased risk of cardiovascular disease (CVD) independent of the metabolic syndrome and conventional cardiovascular risk factors.

RESEARCH DESIGN AND METHODS — The Edinburgh Artery Study is a population-based cohort study in which subjects were followed up until their death or for ~15 years. Low ABI at baseline was defined as <0.9; subjects with ABI >1.4 ($n = 13$) were excluded from the analyses. We used a modified version of the definition of the metabolic syndrome published in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, replacing waist circumference criteria with BMI criteria. Data on relevant parameters were available for 1,467 men and women ages 55–74 years at baseline. Cox proportional hazards models were used to study cardiovascular morbidity and mortality before and after adjusting for potential confounding factors.

RESULTS — We determined that 25% of the study population had the metabolic syndrome and that a low ABI was more prevalent among people with than without the metabolic syndrome (24 vs. 15%; $P < 0.001$). During the follow-up period, there were 226 deaths from CVD and 462 nonfatal cardiovascular events. The hazard ratio (95% CI) for low ABI after adjusting for age, sex, baseline CVD, diabetes, smoking status, LDL cholesterol, and metabolic syndrome was 1.5 (1.1–2.1) for CVD mortality and 1.5 (1.2–1.8) for all CVD outcomes.

CONCLUSIONS — Low ABI is associated with increased risk of CVD independent of the metabolic syndrome and other major CVD risk factors.

Diabetes Care **29:637–642, 2006**

The ankle-brachial pressure index (ABI), which is the ratio of ankle to brachial systolic blood pressure, provides a simple measurement that can be performed in primary care settings without expensive or elaborate equipment or extensive training or experience. An ABI value <0.9 is widely acknowledged to indicate an abnormally low level (1). Several studies have shown that a low ABI is associated with increased risk of subsequent mortality in populations, including (2) and excluding (3–7) people known to have cardiovascular disease (CVD). A low ABI was shown to predict increased risk of fatal myocardial infarction in the Edinburgh Artery Study cohort (8) and increased risk of CVD mortality in other studies (3,4,6,7) independent of conventional risk factors.

In one systematic review (1), data on the relation between a low ABI and incident cardiovascular outcomes from prospective studies were examined. The researchers used weighted, rather than individual level, data so that adjustment for other risk factors was not possible. They determined that a low ABI has a high specificity and low sensitivity for subsequent cardiovascular outcomes (1). Their results indicated that a normal ABI alone might still be associated with increased risk of CVD, so that further information on other cardiovascular risk factors is required. The researchers concluded that further study of the incremental predictive role of a low ABI was required in studies that could adjust for conventional risk factors.

Depending on the definition used, the metabolic syndrome includes measures of general obesity (as reflected by BMI [kilograms divided by height in meters squared]), central obesity (as reflected by waist circumference or waist-to-hip ratio), dyslipidemia (as reflected by low HDL cholesterol and/or high triglyceride levels), hyperglycemia, high blood pressure, and resistance to the action of insulin. Several definitions of the metabolic syndrome exist, including that of the World Health Organization (WHO) (9), that defined in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) (10), and that of the International Diabetes Federation (IDF)

From the [1]Public Health Sciences, University of Edinburgh, Edinburgh, Scotland; the [2]Department of Endocrinology, Southampton General Hospital, Southampton, U.K.; and the [3]Department of General Practice and Primary Care, Foresterhill Health Centre, Aberdeen, Scotland.

Address correspondence and reprint requests to Dr. Sarah Wild, Public Health Sciences, University of Edinburgh, Teviot Pl., Edinburgh, EH8 9AG, Scotland. E-mail: sarah.wild@ed.ac.uk.

Received for publication 2 September 2005 and accepted in revised form 2 December 2005.

Abbreviations: ABI, ankle-brachial pressure index; ATP III, Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; CVD, cardiovascular disease; IDF, International Diabetes Federation; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

(11). The WHO definition also includes a measurement of insulin resistance that is not available in many large epidemiological studies.

The presence of the metabolic syndrome is associated with increased risk of CVD morbidity and mortality; the magnitude of the risk varies with the criteria for the metabolic syndrome, the definition of the outcome, and the population studied. The relative risk of the metabolic syndrome is generally highest for coronary heart disease mortality, intermediate for CVD mortality, and lowest (and not necessarily statistically significantly elevated) for all-cause mortality (12–15). The increased risk of CVD mortality associated with the metabolic syndrome has been shown to be independent of other conventional cardiovascular risk factors, including age, sex, LDL cholesterol levels, and smoking status (12–14,16,17). However, some studies have suggested that the metabolic syndrome does not add information beyond that offered by risk scores such as the Framingham equation (15,18).

Effective interventions to reduce CVD risk are available; thus it is important to identify high-risk individuals so they can be treated. Because the number of people at risk for CVD is high, the methods used to identify such individuals should be easily performed in primary care. Two such methods are the assessment of the presence or absence of the metabolic syndrome and the determination of a low ABI. The aim of this study was to investigate whether a low ABI is associated with increased risk of subsequent CVD independent of the metabolic syndrome and conventional cardiovascular risk factors.

RESEARCH DESIGN AND METHODS

— The Edinburgh Artery Study recruited 1,592 people (809 men and 783 women) ages 55–74 years in 1988 from a general northern European white population sample. Full details of recruitment, data collection at baseline in 1988–1989, methods of follow-up, and definitions of outcomes have been previously described (19,20). The study population was selected to provide a population-based sample by random identification of eligible individuals in 5-year age bands from 11 general practices across the city of Edinburgh that provide primary care for populations of varying socioeconomic status. The response rate was 65%. Respondents were found to be representative of the wider population, as comparisons with a random sample of 20% of nonrespondents did not detect substantial bias (19). Baseline data were collected during participants' attendance at a research clinic using a combination of questionnaire and examination data. Complete mortality follow-up was achieved by flagging for deaths at the National Health Service Central Registry in addition to being notified of deaths by general practitioners and family members. For this analysis, follow-up was undertaken until the date of death or for ~15 years until the end of April 2003. The study was approved by the Lothian Health Board Ethics Committee, and informed consent was obtained from each participant.

Participants completed a self-administered questionnaire at baseline that included the WHO angina and intermittent claudication questionnaires (21). Height and weight were measured using standard methods. Participants were asked to indicate whether they had received a diagnosis of diabetes from a doctor. Systolic blood pressure was measured in the right arm using a random zero sphygmomanometer with the subject in the supine position after a 10-min rest. The ankle systolic blood pressure at the posterior tibial artery was measured where possible in both legs using a random zero sphygmomanometer and a Doppler probe.

A fasting blood sample was collected from the antecubital vein using a tourniquet while the subject was recumbent. Glucose, total cholesterol, HDL cholesterol, and triglycerides were measured using a Cobas Bioanalyser (Roche, Welwyn Garden City, U.K.) and standard kits. Participants received an oral glucose tolerance test in the form of 75 g of glucose in 335 ml of Solripe Gluctoza Health Drink (Strathmore Mineral Water, Angus, U.K.); a further blood specimen was collected 2 h later for the measurement of glucose using the same method as for the fasting sample.

Prevalent CVD at baseline was defined as stroke (recall of a doctor's diagnosis), angina (WHO questionnaire evidence and electrocardiographic ischemia or recall of a doctor's diagnosis), or myocardial infarction (two out of three of recall of a doctor's diagnosis, evidence from responses to the WHO questionnaire, and electrocardiographic evidence). Diabetes at baseline was defined using recall of a doctor's diagnosis and WHO 1999 criteria (fasting glucose ≥7 mmol/l or 2-h glucose ≥11.1 mmol/l) (8) applied to data collected during the oral glucose tolerance test. Smoking status was defined as self-report of current smoking at baseline.

Criteria used to define cardiovascular outcomes were adapted from international diagnostic criteria developed by the American Heart Association (22) and have been described in detail elsewhere (19). In brief, cardiovascular death was defined as postmortem evidence of acute myocardial infarction, cerebral infarction, or hemorrhage or from death certificates with an underlying cause of death in the range of CVD codes from ICD-9 (codes 410–414, 430–438, and 440–445) and ICD-10 (I21–25 and I60–73). Nonfatal cardiovascular outcomes included myocardial infarction, stroke or transient ischemic attack, angina, intermittent claudication, revascularization, and amputation. All possible cardiovascular outcomes were investigated using medical records, and only those that fulfilled the protocol criteria for a definite event were included in the analysis. Questionnaire and clinic measurement data were checked by clinic staff, coded, and entered onto a DBASE IV database. Double data entry was used and discrepant entries were checked against original records.

A low ABI was defined as ABI <0.9. Participants with an ABI >1.4 were excluded because of possible erroneously high levels due to arterial stiffness.

The ATP III criteria for the metabolic syndrome include the presence of three or more of the following: waist circumference ≥102 cm (men) or ≥88 cm (women); blood pressure 130/85 or treatment for hypertension; triglycerides >1.7 mmol/l (>150 mg/dl); HDL cholesterol <1.03 mmol/l (<50 mg/dl) (men) or <1.29 mmol/l (<50 mg/dl) (women); and fasting plasma glucose ≥6.1 mmol/l (>110 mg/dl) (9). Waist circumference was not available in the Edinburgh Artery Study, and therefore the waist circumference criteria used in the ATP III definition were replaced with cut points for BMI (28.8 kg/m^2 for men and 26.7 kg/m^2 for women), as in previous studies (16,22). The cut point for men was identified as being equivalent to a waist measurement of 102 cm in a regression analysis of a cross-sectional study (16). The criterion for women was developed from the Women's Health Study using the BMI value that corresponded to the same percentile cut point for a waist circumference

Table 1—*Characteristics of participants by presence or absence of low ABI (<0.9) and metabolic syndrome by ATP III criteria*

	Neither low ABI nor ATP III metabolic syndrome	Low ABI without ATP III metabolic syndrome	ATP III metabolic syndrome without low ABI	Low ABI and ATP III metabolic syndrome	*P*
n	936	167	273	91	—
Mean age (years)	64.4 ± 5.6	66.3 ± 5.6*	64.5 ± 5.5†	67.7 ± 5.1*†‡	<0.0001
Men	475 (51)	72 (43)	138 (51)	41 (45)	0.246
Mean BMI (kg/m^2)	24.7 ± 3.3	24.3 ± 3.5	28.8 ± 4.1*†	28.6 ± 4.1*†	<0.0001
Smoker at baseline	216 (23)	76 (46)*	53 (19)†	32 (35)*‡	<0.0001
Mean systolic blood pressure (mmHg)	139 ± 22	152 ± 28*	152 ± 21*	166 ± 24*†‡	<0.0001
Mean total cholesterol (mmol/l)	6.9 ± 1.3	7.3 ± 1.3*	7.2 ± 1.4*	7.3 ± 1.5*	<0.0001
Mean LDL cholesterol (mmol/l)	5.1 ± 1.2	5.5 ± 1.2*	5.6 ± 1.3*	5.6 ± 1.3*	<0.0001
Mean HDL cholesterol (mmol/l)	1.5 ± 0.4	1.5 ± 0.4*	1.2 ± 0.3*†	1.2 ± 0.3*†	<0.0001
Triglyceride (mmol/l)	1.21 (1.18–1.24)	1.36 (1.28–1.43)*	2.18 (2.06–2.28)*†	2.11 (1.92–1.31)*†	<0.0001
Diabetes (known and newly diagnosed)	37 (4.0)	9 (5.4)	58 (21.3)*†	27 (29.7)*†	<0.0001
History of myocardial infarction, angina, stroke, or intermittent claudication at baseline	56 (6.0)	38 (22.8)*	30 (11.0)*†	26 (28.6)*‡	<0.0001
Mean ABI	1.09 ± 0.11	0.75 ± 0.14*	1.08 ± 0.10*†	0.72 ± 0.17*‡	<0.0001
Deaths from all causes during follow-up	305 (33)	93 (56)*	106 (39)†	50 (55)*‡	<0.0001
Deaths from CVD during follow-up	109 (12)	40 (24)*	46 (17)*	31 (34)*‡	<0.0001
Fatal or nonfatal cardiovascular events during follow-up	381 (41)	95 (57)*	134 (49)*	64 (70)*†‡	<0.0001

Data are means ± SD, *n* (%), or geometric mean (transformed 95% CI). *P* values by ANOVA for continuous variables and χ^2 tests for categorical variables are given. *$P < 0.05$ vs. group with neither a low ABI nor the metabolic syndrome; †$P < 0.05$ vs. group with a low ABI without the metabolic syndrome; ‡$P < 0.05$ vs. group with the metabolic syndrome without a low ABI.

of 88 cm measured at the same time during follow-up (23).

Statistical analysis was performed using Stata software (Stata, College Station, TX). Geometric means and transformed confidence intervals are presented for triglyceride levels that were positively skewed. ANOVA was used to test for differences in baseline characteristics between groups defined by the presence or absence of a low ABI and the metabolic syndrome, with *t* tests and χ^2 tests used to determine differences between groups for continuous and categorical variables. Hazard ratios for CVD were estimated using Cox proportional hazards modeling for mortality and for all CVD with adjustment for age and sex in a basic model and adjustment for various other CVD risk factors in subsequent models. Likelihood ratio tests were used to compare full-adjusted models that included and excluded ABI to determine whether a low ABI contributed to the risk of CVD outcomes.

RESULTS — Of the 1,592 participants in the Edinburgh Artery Study, 8 had missing data for ABI, 13 had an ABI >1.4, 31 had data missing for one or more criteria of the metabolic syndrome, and 2 had data missing for both ABI and the definition of the metabolic syndrome. A further 71 had data missing on diabetes or smoking status at baseline. Data for the remaining 1,467 people were included in our analysis. Of this population, >17% had a low ABI and 25% had the metabolic syndrome, with 6% having both a low ABI and the ATP III–defined metabolic syndrome. Characteristics of the subgroups defined by the presence or absence of a low ABI and the metabolic syndrome are given in Table 1. Subjects with both a low ABI and the metabolic syndrome tended to have a more adverse cardiovascular risk factor profile. During the follow-up period, 554 people died, 226 from CVD. Just over half of the people that died of CVD (118 people) had a nonfatal cardiovascular event before death. A further 462 people had at least one nonfatal confirmed cardiovascular event but did not die from CVD during the study, giving a total number of cardiovascular events of 688.

Tables 2 and 3 show hazard ratios for cardiovascular mortality and for combined fatal and nonfatal CVD derived from Cox proportional hazards models of increasing complexity. A low ABI was a statistically significant risk factor for CVD mortality independent of the metabolic syndrome and conventional cardiovascular risk factors: hazard ratio 1.53 (95% CI 1.13–2.07; $P = 0.006$). The hazard ratio for the metabolic syndrome for CVD mortality did not achieve conventional levels of statistical significance after full adjustment for other CVD risk factors (1.30 [0.97–1.75]; $P = 0.07$), and the hazard ratio was further attenuated by the addition of a low ABI to the model (1.26 [0.94–1.70]; $P = 0.13$). The addition of a low ABI to the model with the outcome of CVD mortality and independent variables of age, sex, metabolic syndrome, LDL cholesterol, baseline CVD, known or newly diagnosed diabetes, and smoking status at baseline significantly improved the fit of the model ($P = 0.007$, change in −2 log likelihood 7.2 with one degree of freedom [df]). A low ABI was also a statistically significant risk factor for the combined outcome of fatal and nonfatal CVD independent of the metabolic syndrome and conventional cardiovascular risk fac-

Table 2—*Cardiovascular disease mortality associated with a low ABI (<0.9) and the metabolic syndrome after adjusting for other factors*

	Low ABI	Metabolic syndrome
Model 1: Age and sex	2.19 (1.64–2.91)	1.66 (1.26–2.18)
Model 2: Age, sex, and baseline cardiovascular disease	1.85 (1.37–2.48)	1.44 (1.08–1.90)
Model 3: Age, sex, baseline LDL cholesterol, smoking status, cardiovascular disease, and known and newly diagnosed diabetes	1.56 (1.15–2.11)	1.30 (0.97–1.76)
Model 4: Model 3 variables and metabolic syndrome (for low ABI as the independent variable) or low ABI (for metabolic syndrome as the independent variable)	1.53 (1.13–2.07)	1.26 (0.94–1.70)

Data are adjusted hazard ratios (95% CI).

tors (hazard ratio 1.46 [1.20–1.76]; $P < 0.0001$). The statistical significance of the metabolic syndrome as a risk factor for all CVD independent of a low ABI and conventional risk factors was borderline (hazard ratio 1.20 [1.00–1.43]; $P = 0.05$). Adding a low ABI to a model with all CVD as the outcome with adjustment for all other factors mentioned above significantly improved the fit of the model ($P = 0.002$, change in −2 log likelihood 14.3 with 1 df).

CONCLUSIONS — We have shown that a simple measure of preclinical atherosclerosis, a low ABI, is associated with an increased risk for CVD independent of the metabolic syndrome and conventional cardiovascular risk factors. This measurement could be applied in clinical practice to identify patients at high risk of CVD. The excess risk of CVD associated with the metabolic syndrome was of borderline statistical significance after adjusting for conventional cardiovascular risk factors and a low ABI; this may have been due to the limited power of this study to detect an independent effect of the metabolic syndrome.

The IDF recently released a worldwide consensus definition of the metabolic syndrome, stated as a waist circumference ≥94 cm (men) or ≥80 cm (women) and two or more of the following factors: fasting plasma glucose 5.6 mmol/l and the same blood pressure and lipid criteria as for the ATP III definition of the metabolic syndrome (10). In our study, data for the general population ages 55–74 years in the Health Survey for England 1999 were used to generate BMI cut points in place of the waist cutpoints used in the IDF definition for the metabolic syndrome that had similar sensitivity and specificity to those used as proxy measurements for the ATP III criteria (S.H.W., unpublished observations). These values were 26.2 kg/m^2 for men and 24.2 kg/m^2 for women. Using the modified IDF criteria, over a third (34%) of the study population had the metabolic syndrome compared with 25% using the modified ATP III criteria. The hazard ratios for fatal and all CVD for a low ABI adjusted for age, sex, metabolic syndrome, and cardiovascular risk factors were similar for the ATP III– and IDF-defined metabolic syndrome (data not shown but available from S.H.W.). The adjusted hazard ratios for fatal and all CVD for the metabolic syndrome were generally lower for the IDF definition than for the ATP III definition.

The advantages of this study were its long follow-up period and the high number of fatal and nonfatal outcomes. Work before the start of this study showed that a single measurement of ABI is suitable for most epidemiological studies (24). The limitations of this study were those common to many cohort studies with lengthy follow-up, such as the use of baseline data only, which does not allow for adjustment for regression dilution bias or changing prevalence of risk factors. It was not possible to validate reports of doctor diagnoses of myocardial infarction, stroke, or intermittent claudication in the baseline data. Self-report of angina or myocardial infarction appears to be reasonably valid in men (25) but less accurate in women (26) when comparisons are made against medical records. In this study, further information from questionnaires and electrocardiographic findings were used to define CVD in addition to self-report of a doctor's diagnosis.

Patterns of cardiovascular risk factors have changed in recent years, and it is likely that the distribution of the metabolic syndrome components have changed. In a contemporary cross-sectional study, a lower prevalence of hypertension and hypercholesterolemia might be expected than was observed in this population at baseline in 1988–1989. However, the current prevalence of the metabolic syndrome may be similar to the 1988–1989 level because of the increasing prevalence of central obesity

Table 3—*Fatal and nonfatal cardiovascular disease associated with low ABI (<0.9) and metabolic syndrome after adjusting for other factors*

	Low ABI	Metabolic syndrome
Model 1: Age and sex	1.85 (1.55–2.22)	1.39 (1.18–1.64)
Model 2: Age, sex, and baseline cardiovascular disease	1.64 (1.36–1.98)	1.31 (1.11–1.54)
Model 3: Age, sex, baseline cardiovascular disease, LDL cholesterol, smoking status, and known and newly diagnosed diabetes	1.47 (1.22–1.78)	1.21 (1.02–1.45)
Model 4: Model 3 variables and metabolic syndrome (for low ABI as the independent variable) or low ABI (for metabolic syndrome as the independent variable)	1.46 (1.20–1.76)	1.20 (1.00–1.43)

Data are adjusted hazard ratios (95% CI).

and dysglycemia, and there is evidence to suggest that the prevalence of the metabolic syndrome is increasing (27). At present it is not clear whether certain combinations of metabolic syndrome components confer different risks from other combinations. Smoking habits have also shown secular changes, which is likely to affect the prevalence of a low ABI. Although waist circumference measurements were not available for Edinburgh Artery Study data, we were able to use a proxy measure of BMI that has been shown to reflect central obesity in other populations, one of which was a cohort of Scottish men (16,23).

A previous cross-sectional study reported no independent effect of the metabolic syndrome on the prevalence of CVD beyond that associated with the individual components of the syndrome and diabetes (28). This finding may have been influenced by survival bias, and it contrasts with those of a cohort study that found the metabolic syndrome was a stronger predictor of coronary heart disease, CVD, and total mortality than its individual components (13). Moreover, in a prospective study of subjects with newly diagnosed type 2 diabetes, one of us (C.D.B.) has shown that there is a progressive decrease in survival over ~5 years with the presence at diagnosis of each additional feature of the metabolic syndrome defined by ATP III criteria (29). Based on data from the Framingham offspring cohort study of 3,323 men and women (mean age 52 years) with 8 years follow-up, it has been estimated that the metabolic syndrome (as defined using ATP III criteria) contributes almost half of the population-attributable risk for diabetes and ~25% of all incident CVD (30).

In summary, a low ABI can be used to identify individuals at increased risk of CVD and thus provides information on risk beyond that provided by a prevalence of conventional cardiovascular risk factors and the presence of the metabolic syndrome (whether defined using ATP III or IDF criteria). ABI can easily be measured in a primary care setting and could be used as part of the assessment of cardiovascular risk in individuals if further research confirms its cost-effectiveness.

References

1. Doobay AV, Anand SS: The sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. *Arterioscler Thromb Vasc Biol* 25:1–7, 2005
2. Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV: Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. *BMJ* 313:1440–1444, 1996
3. McKenna M, Wolfson S, Kuller L: The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis* 87:119–128, 1991
4. Vogt MT, Cauley JA, Newman AB, Kuller LH, Hulley SB: Decreased ankle/arm blood pressure index and mortality in elderly women. *JAMA* 270:465–469, 1993
5. Vogt MT, McKenna M, Wolfson SK, Kuller LH: The relationship between ankle brachial index, other atherosclerotic disease, diabetes, smoking and mortality in older men and women. *Atherosclerosis* 101:191–202, 1993
6. Newman AB, Tyrrell KS, Kuller LH: Mortality over four years in SHEP participants with a low ankle-arm index. *J Am Geriatr Soc* 45:1472–1478, 1997
7. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, Powe NR, Siscovick D: Ankle-arm index as a predictor of CVD and mortality in the Cardiovascular Health Study: the Cardiovascular Health Study Group. *Arterioscler Thromb Vasc Biol* 19:538–545, 1999
8. Lee AJ, Price JF, Russell MJ, Smith FB, van Wijk MC, Fowkes FG: Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. *Circulation* 110:3075–3080, 2004
9. World Health Organization: Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva, World Health Organization, 1999
10. 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* 285: 2486–2497, 2001
11. Alberti KGMM, Zimmet P, Shaw J, the IDF Epidemiology Task Force Consensus Group: The metabolic syndrome: a new worldwide definition. *Lancet* 366:1059–1062, 2005
12. 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* 24:683–689, 2001
13. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT: The metabolic syndrome and total and CVD mortality in middle-aged men. *JAMA* 288:2709–2716, 2002
14. 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, CVD, and all causes in United States adults. *Circulation* 110:1240–1245, 2004
15. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, Ballantyne CM, Heiss G: The metabolic syndrome and 11-year risk of incident CVD in the atherosclerosis risk in communities study. *Diabetes Care* 28:385–390, 2005
16. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J: Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 108:414–419, 2003
17. Ford ES: The metabolic syndrome and mortality from CVD and all-causes: findings from the National Health and Nutrition Examination Survey II Mortality Study. *Atherosclerosis* 173:309–314, 2004
18. Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM: Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or CVD? *Diabetes Care* 27:2676–2681, 2004
19. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ: Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 20:384–392, 1991
20. Leng GC, Lee AJ, Fowkes FG, Whiteman M, Dunbar J, Housley E, Ruckley CV: Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 25:1172–1181, 1996
21. Rose GA, Blackburn H: Cardiovascular survey methods. *Monogr Ser World Health Organ* 56:1–188, 1968
22. Gillum RF, Fortmann SP, Prineas RJ, Kottke TE: International diagnostic criteria for acute myocardial infarction and acute stroke. *Am Heart J* 108:150–158, 1984
23. Ridker PM, Buring JE, Cook NR, Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. *Circulation* 107:391–397, 2003
24. Fowkes FG, Housley E, Macintyre CC, Prescott RJ, Ruckley CV: Variability of ankle and brachial systolic pressures in the measurement of atherosclerotic peripheral arterial disease. *J Epidemiol Community Health* 42:128–133, 1988
25. Lampe FC, Walker M, Lennon LT, Whincup PH, Ebrahim S: Validity of a self-reported history of doctor-diagnosed

angina. *J Clin Epidemiol* 52:73–81, 1999
26. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, Hennekens CH, Speizer FE: Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol* 123: 894–900, 1986
27. Ford ES, Giles WH, Mokdad AH: Increasing prevalence of the metabolic syndrome among U.S. adults. *Diabetes Care* 27:2444–2449, 2004
28. Alexander CM, Landsman PB, Teutsch SM, Haffner SM: NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 52:1210–1214, 2003
29. Guzder RN, Gatling W, Mullee MA, Byrne CD: The impact of metabolic syndrome criteria on CVD risk in people with newly diagnosed type 2 diabetes. *Diabetologia* Dec 10, 2005 [Epub ahead of print]
30. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C: Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 109:433–438, 2004