

# Apolipoprotein B/Apolipoprotein A-I in Relation to the Metabolic Syndrome and Change in Carotid Artery Intima-Media Thickness During 3 Years in Middle-Aged Men

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**Background and Purpose**—The apolipoprotein B (apoB)/apolipoprotein A-I (apoA-I) ratio is a measure of the relationship between different lipoprotein particles and a powerful predictor of coronary death. The aim was to examine whether apoB/apoA-I was associated with the metabolic syndrome (MetS) at baseline and also with the future change in carotid artery intima-media thickness (IMT).

**Methods**—In 313 58-year-old men, carotid artery IMT was measured bilaterally by high-resolution B-mode ultrasound at baseline and after 3 years of follow-up. Serum apolipoprotein concentrations and the components of MetS were measured at study entry.

**Results**—ApoB/apoA-I showed statistically significant associations with body mass index, waist-to-hip ratio, high-density lipoprotein (HDL) cholesterol, triglycerides, low-density lipoprotein (LDL) particle size, insulin, and diastolic blood pressure. Two thirds of the patients with MetS had high apoB/apoA-I ratios ( $>0.90$ ) compared with one third of those without the syndrome ( $P<0.001$ ). The IMT change was associated with apoB, total cholesterol, LDL cholesterol, triglycerides, and inversely with HDL cholesterol and LDL particle size at entry, and there was a strong colinearity between these variables. The subjects with apoB/apoA-I above the first tertile (0.74) had a 20- $\mu\text{m}$ -higher (95% CI, 7 to 33) annual increase in IMT compared with those below this level after adjustment for blood pressure and smoking.

**Conclusions**—The apoB/apoA-I ratio was strongly associated with MetS and its components at baseline. ApoB/apoA-I at baseline was related to the change in carotid artery IMT during 3 years of follow-up. There was a strong colinearity between apoB/apoA and the atherogenic lipids. (*Stroke*. 2004;35:000-000.)

**Key Words:** apolipoproteins ■ atherosclerosis ■ intima-media thickness

High concentration of low-density lipoprotein (LDL) cholesterol is generally accepted as one of the strongest risk factors for atherosclerotic cardiovascular disease and mortality.<sup>1</sup> It is a measure of the mass of cholesterol in the LDL particle but provides no information on other lipoprotein particles or the atherogenicity of the LDL particles. Thus, also, very low-density lipoprotein (VLDL) particles contain cholesterol, and the size of LDL particles varies, with small LDL particles carrying an increased risk of cardiovascular disease. Each VLDL, intermediate-density lipoprotein, and LDL particle is covered by 1 apolipoprotein B (apoB) molecule. Hence, serum concentration of apoB yields the number of atherogenic particles.<sup>2</sup> Similarly, serum concentration of apoA-I, which is the protein covering the high-density lipoprotein (HDL) particle, is a measure of the HDL particle number. It follows that subjects with normal LDL

cholesterol may have an atherogenic dyslipidemia with many small LDL particles and a low HDL concentration.<sup>3</sup> It has been postulated that apoB may be superior to LDL concentration as a predictor of cardiovascular disease, and this has been confirmed in 4 prospective studies.<sup>4</sup> In several studies, the apoB/apoA-I ratio has been better than any cholesterol measure to predict cardiovascular risk.<sup>4</sup> Given the fact that insulin resistance is associated with hypertriglyceridemia, low HDL cholesterol, and small LDL particles,<sup>5</sup> the apoB/apoA-I ratio can be assumed to be associated with the metabolic syndrome.

We have shown previously that the metabolic syndrome (MetS) is associated with subclinical ultrasound-assessed atherosclerosis.<sup>6</sup> Whether or not the apoB/apoA-I ratio is associated with the presence of all features of MetS is, to our knowledge, unexplored, and therefore, we addressed that

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issue in the present study. The aim was also to investigate the relationship between the apoB/apoA-I ratio and the change in carotid artery intima-media thickness (IMT) during 3 years of follow-up in 58-year-old men.

## Materials and Methods

### Study Group

As described previously,<sup>6</sup> the design was a longitudinal study based on a stratified sampling of randomly selected and screened men (n=818), with the underlying aim to include men with different degrees of obesity and insulin sensitivity (n=391) to examine whether insulin resistance is associated with subclinical atherosclerosis.

The inclusion criteria at entry were 58 years of age, male sex, and Swedish ancestry. Exclusion criteria were cardiovascular disease (myocardial infarction, angina pectoris, stroke, intermittent claudication, and aortic disease) or other established disease, treatment with cardiovascular drugs (ie, antidiabetic, lipid-lowering, antihypertensive, heart failure drugs, or drugs for angina pectoris), which might disturb the measurements performed in the study, or unwillingness to participate.

The present study reports on the 3-year follow-up examination that was performed to examine the change in carotid artery IMT and to relate these changes to the baseline characteristics. The mean follow-up time was 3.2±0.2 years. We were able to re-examine 342 patients, and 313 of those men had all requested data on apolipoproteins and ultrasound examinations available. Thus, the reasons for being excluded from the present analysis were death (n=4), having moved or refusal to participate (n=45), and incomplete data (n=29; see below).

The subjects received both written and oral information before they gave their consent to participate. The study was approved by the ethics committee at Sahlgrenska University Hospital.

### Measurements

All measurements were performed in the morning. Information on general health and smoking habits were obtained by a self-administered questionnaire. The total number of years of smoking was multiplied by the number of cigarettes smoked daily. The product was called "cigarette years."

Blood pressure was measured twice when the subject had been resting in the supine position for 20 minutes with appropriate cuff size in relation to arm size. Venous blood samples were drawn after a mean fasting period of 10 to 12 hours; serum was separated and frozen within 4 hours at -70°C.

### Biochemical Analysis

Cholesterol and triglyceride levels were determined by fully enzymatic techniques.<sup>7,8</sup> HDL cholesterol was determined after precipitation of apoB-containing lipoproteins with Mn-chloride and dextran sulfate. LDL cholesterol was calculated as described by Friedewald et al.<sup>9</sup> Apolipoproteins (apoA-I and apoB) were measured by a Konelab machine (ILS Laboratories). Using 2 different controls, the between-assay variation for repeated measurements have been shown previously to be 5.2% and 5.8% for apoA-I, and 2.5% and 3.2% for apoB, respectively. Corresponding figures within assay variation have shown to be 1.4% and 1.7% for apoA-I, and 1.4% and 1.4% for apoB, respectively. All lipid analyses were performed at the Wallenberg Laboratory. LDL particle size was determined by using gradient gel electrophoresis.<sup>6,10</sup>

### Ultrasonography

#### Intima-Media Thickness

Examination was performed with an ultrasound scanner (Acuson 128) with a 7-Mhz linear transducer aperture of 38 mm. The electrocardiographic signal (lead II) was simultaneously recorded to synchronize the image capture of the top of the R wave to minimize variability during the cardiac cycle. A 10-mm segment of the left and

right carotid arteries was scanned at the level of bifurcation, and images for IMT measurements were recorded from the far wall in the common carotid artery (CCA) and the carotid artery bulb. The software program gives the average thickness of the intima-media complex (IMT) on the left and right side for CCA and the carotid artery bulb, respectively. Hence, 4 variables are defined, namely IMT mean and maximum in CCA and carotid artery bulb. IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall. At the position of the thickest part of the wall (visually judged), a frozen longitudinal image was captured and recorded on videotape. A short sequence of real-time images was also recorded on videotape to assist in interpreting frozen images. Mean lumen diameter of the carotid artery was defined by the distance between the leading edges of the intima-lumen interfaces of the near and lumen-intima of the far wall. Images were measured in an automated analyzing system<sup>11</sup> based on automatic detection of the echo structures in the ultrasound image, with the option to make manual corrections by the operator. The interobserver variability for measurement of IMT in the CCA and the carotid artery bulb has been shown to be 5.3% and 6.0%, respectively.<sup>12</sup>

A composite measure of IMT in the carotid artery was calculated as the mean of the maximum IMT in the common carotid and the carotid artery bulb on the left and right side (composite IMT). The laboratory technician was blinded to the previous examination.

Comparison of baseline characteristics between men from whom it was possible to obtain follow-up data (n=313) and those it was not showed no statistically significant difference in apoB/apoA-I ratio (0.87±0.25 versus 0.92±0.24; n=60; P=0.18) or composite IMT (1.16±0.24 mm; 1.24±0.31 mm; n=61; P=0.17). The cardiovascular morbidity in the 2 groups of re-examined (n=313) and not re-examined (n=78) men at the time for follow-up were 5.4% versus 7.6% (NS).

### Definition of MetS

Glucose intolerance was defined as a fasting blood glucose level ≥5.6 mmol/L<sup>13</sup>. Insulin resistance was defined as a fasting plasma insulin level of ≥14.86 mU/L<sup>6</sup>. MetS according to the World Health Organization (WHO)<sup>13</sup> is defined as glucose intolerance or insulin resistance together with ≥2 of the following risk factors: (1) raised arterial (systolic/diastolic) pressure ≥140/90 mm Hg (either value); (2) raised triglycerides (≥1.7 mmol/L) or low HDL cholesterol (<0.9 mmol/L); (3) central body obesity waist-to-hip ratio (WHR) >0.90 or body mass index (BMI) >30 kg/m<sup>2</sup>; and (4) microalbuminuria (urinary albumin excretion rate ≥20 μg per minute).

In the definition of MetS according to the National Cholesterol Education Program (NCEP),<sup>14</sup> ≥3 of the following risk factors must be fulfilled: (1) a fasting blood glucose level ≥5.6 mmol/L; (2) raised arterial (systolic/diastolic) pressure ≥130/85 mm Hg (either value); (3) raised triglycerides (≥1.7 mmol/L); (4) HDL cholesterol <1.0 mmol/L; and (5) waist circumference >102 cm.

### Statistics

SPSS for Windows 10.0 was used for analyses. Characteristics of the subjects are described as means and SDs if nothing else is indicated. Serum concentrations of triglycerides were log transformed because of skewness before statistical analysis. Paired and unpaired Student *t* tests were used for comparison of continuous variables. Next, 95% CIs were calculated for the annual change in IMT. Nonparametric Spearman rank correlation test was used in the univariate correlation analysis. Linear regression was used to examine associations between apoA-I and apoB and other variables. Multiple regression was used to explore whether the association between the apoB/apoA-I ratio at entry and the annual increase in carotid IMT during follow-up was independent of other covariates. The apoB/A-I ratio was entered as a categorical variable with 3 levels (tertile 1 [reference] range 0.32 to 0.74; tertile 2 range >0.74 to 0.97; tertile 3 range >0.97 to 1.74). An apoB/apoA-I ratio >0.90 in males has been suggested as a level indicating increased cardiovascular risk.<sup>15,16</sup> The relationship between this cut-off value and the annual

**TABLE 1. Characteristics of Study Subjects at Entry (n=313)**

Characteristic	Mean±SD (Unless Otherwise Indicated)
BMI, kg/m	26.2±4.2
WHR	0.94±0.06
Present smoker, n (%)	63 (20)
Cigarette years, median (minimum to maximum value)	140 (0–2280)
Blood pressure	
Systolic, mm Hg	123±17
Diastolic, mm Hg	72±11
Heart rate, bpm	64±10
Serum cholesterol	
Total, mmol/L	5.98±1.09
HDL, mmol/L	1.28±0.36
LDL, mmol/L	4.05±0.97
Serum triglycerides, median, mmol/L (minimum to maximum value)	1.28 (0.41–9.89)
ApoA-I, g/L	1.43±0.23
ApoB, g/L	1.21±0.28
ApoB/apoA-I	0.87±0.25
LDL particle size, nm	26.4±0.7
Serum insulin, mU/L	9.56±5.02

BMI indicates body mass index; WHR, waist-to-hip ratio.

change in IMT were also examined.  $P<0.05$  (2-sided) was regarded as statistically significant.

## Results

The characteristics of the subjects at the study entry are presented in Table 1.

### ApoB/ApoA-I Ratio and MetS

As shown in Table 2, the apoB/apoA-I ratio was associated with all of the components of MetS: BMI, WHR, HDL cholesterol, triglycerides, LDL particle size, insulin, and diastolic blood pressure. Patients with increasing numbers of factors constituting MetS according to the WHO definition had a parallel increase in the apoB/apoA-I ratio (Figure 1). Of the men with an apoB/apoA-I ratio  $>0.90$ , 65% and 66%

**TABLE 2. Correlations (Spearman) Between Serum Concentration of apoB/apoA-I and Factors Characterizing the MetS at Study Entry in 313 58-Year-Old Men**

Characteristics	ApoB/ApoA-I	
	Correlation Coefficient	<i>P</i> Value
BMI, kg/m	0.22	0.000
WHR	0.28	0.000
Diastolic blood pressure, mm Hg	0.14	0.012
Serum insulin, mU/L	0.30	0.000
HDL cholesterol, mmol/L	−0.60	0.000
Serum LDL particle size, nm	−0.62	0.000
Serum triglycerides, mmol/L	0.57	0.000

BMI indicates body mass index; WHR, waist-to-hip ratio.

fulfilled the criteria for MetS, according to the WHO and NCEP classifications, respectively, compared with 35% and 34% of the subjects below the cut-off value of 0.9 ( $P=0.001$  and  $P<0.001$ ).

### ApoB/ApoA-I Ratio and Change in Carotid Artery IMT

The composite IMT was  $1.16±0.24$  mm at study entry and  $1.21±0.27$  at follow-up (95% CI, 28 to 68  $μm$ ;  $P<0.001$ ). As shown in Table 3, the annual change in IMT was univariately associated with the following characteristics at entry: serum concentration of apoB, total cholesterol, LDL cholesterol, and inversely to HDL cholesterol and LDL particle size. These associations were stronger after adjustment for baseline IMT, and serum triglycerides at baseline were also found to be associated with the annual change in IMT.

Figure 2 shows the tertiles of apoB/apoA-I and corresponding annual changes in IMT, demonstrating a nonlinear association.

In a statistical model with annual change in IMT as dependent variable and baseline IMT, apoB/apoA-I tertiles, smoking, and diastolic blood pressure as independent variables, subjects with apoB/apoA-I above the first tertile (0.74) had a 20- $μm$ -higher (95% CI, 7 to 33  $μm$ ) annual increase in IMT compared with those below this apoB/apoA-I ratio ( $R^2=0.05$ ;  $P=0.008$ ). Adding HDL, LDL, and LDL particle size separately or together to the model did not increase *r*-square (data not shown).

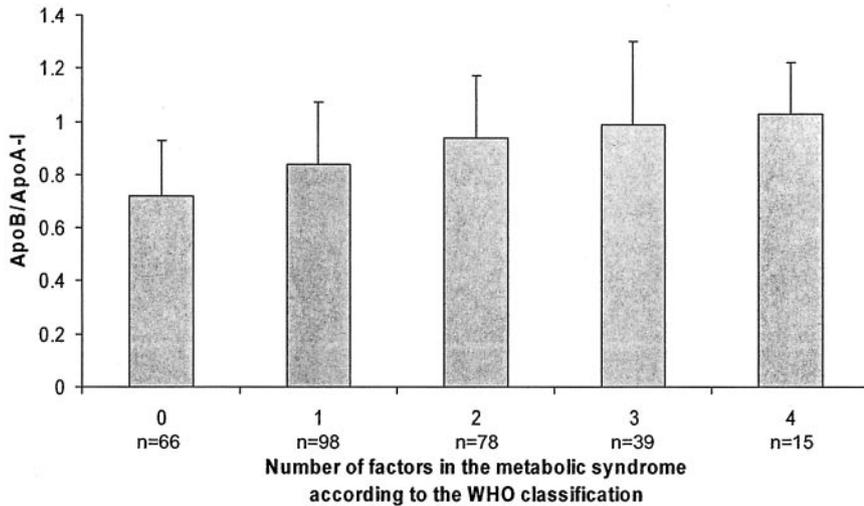
The apoB/A-I ratio correlated to total cholesterol ( $r=0.56$ ), HDL cholesterol ( $r=-0.58$ ), LDL cholesterol ( $r=0.66$ ), triglycerides ( $r=0.57$ ), and LDL particle size ( $r=-0.58$ ; all  $P<0.001$ ). A correlation matrix showed that these lipid variables also showed statistically significant intercorrelations (data not shown).

Using a suggested cut-off value of 0.90 for the apoB/apoA-I ratio, subjects with a value above that limit had a more pronounced annual change in carotid artery IMT than those with a ratio below the cut-off value (mean difference 18  $μm$ ; 95% CI, 7 to 29  $μm$ ). The apoB/apoA-I ratio was ( $0.86±0.23$ ;  $n=17$ ) in the small group with cardiovascular events and ( $0.87±0.25$ ;  $P=0.82$ ) in the group with no events ( $n=296$ ).

## Discussion

Our data showed that the apoB/apoA-I ratio was associated with MetS and with the change in carotid artery IMT during 3 years of follow-up. Findings were very consistent because all major factors in the syndrome correlated to apoB/apoA-I, subjects with an increasing number of risk factors in the syndrome had a parallel increase in the apoB/apoA-I ratio, and two thirds of the men fulfilling WHO or NCEP criteria for MetS had an apoB/apoA-I ratio above a level that indicates elevated coronary risk.<sup>15,16</sup>

No previous study of the relationship between the apoB/apoA-I ratio and MetS was identified. In the Insulin Resistance Atherosclerosis Study, plasma apoB correlated positively to BMI, waist circumference, triglycerides, diastolic blood pressure, and fasting insulin, and negatively to HDL cholesterol, LDL size, and insulin sensitivity.<sup>3</sup> Similar corre-



**Figure 1.** The association between number of factors constituting MetS according to the WHO classification and the apoB/apoA-I ratio (mean±SD) in 296 58-year-old men. *P*<0.001 for trends.

lations to apoB were found in our study, although associations were weaker overall than those obtained with the apoB/apoA-I ratio (data not shown).

In principle, subjects with a high apoB/apoA-I ratio have many apoB particles and few apoA-I particles. Increased production of small dense LDL particles in subjects with MetS is related to an increased influx of fatty acids to the liver, insulin resistance and hyperinsulinemia, increased secretion of VLDL particles, diminished activities of lipoprotein lipase, prolonged residual time of lipoprotein particles in the circulation, and lipid transfer from VLDL to LDL, followed by lipid hydrolysis resulting in small LDL particles containing little cholesterol.<sup>2,17</sup> With the exception of blood pressure, associations between the apoB/apoA-I ratio and the factors of MetS can be understood in the context of these underlying mechanisms, although many details still are not known. We also found that the apoB/apoA-I ratio was associated closely with small LDL size. Considerable evidence indicates that small LDL particles are atherogenic and related to the development of cardiovascular disease.

In the second part of this study, we prospectively examined the change in a composite measure of carotid artery IMT. It is an established measure of atherosclerotic disease and

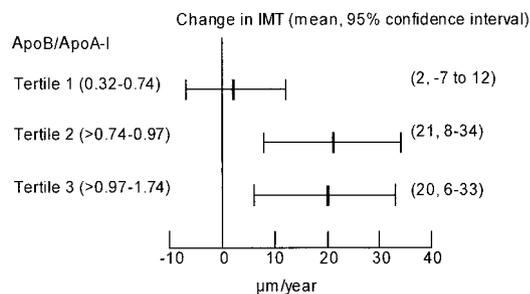
predicts future cardiovascular disease.<sup>18–21</sup> The ultrasound method has been well established in our hands for many years. Our research group has developed a computerized reading system that is associated with a very high reproducibility for measuring IMT.<sup>11</sup> The present results showed that apoB/apoA-I ratios above the first tertile (0.74) at baseline were associated with a rapid increase in IMT, a result that remained after adjustment for other cardiovascular risk factors at entry, such as smoking or blood pressure. These findings support observations in other studies using clinical end points. Thus, several studies have shown that the apoB/apoA-I ratio is associated with the risk of future cardiovascular disease even after adjustment for usual risk factors.<sup>4</sup> A cut-off value of 0.90 has been suggested as an indicator of increased risk.<sup>15,16</sup> In the present study, men with an apoB/apoA-I ratio >0.90 had also a faster growth of IMT than those below this level.

Because of a strong colinearity between apoB/apoA-I, LDL, HDL, triglycerides, and LDL particle size, we could not clarify whether the effect of apoB/apoA-I on the change in IMT was independent of the effects of the lipid variables. The value of apoB/apoA-I might be that it gives an overall measure of cardiovascular risk, capturing atherogenic lipid

**TABLE 3. Associations Between Entry Characteristics and Annual Change in Composite Carotid Artery During 3 Years of Follow-Up**

Entry Characteristics	Annual Change in Composite Mean-Max IMT (n=313) Regression Coefficient (95% CI)	
	Univariate	Adjustment for Baseline IMT
Current tobacco smoking, yes/no	0.005 (−0.009 to 0.018)	0.003 (−0.010 to 0.17)
Diastolic blood pressure, mm Hg	0.000 (−0.001 to 0.000)	0.000 (0.000 to 0.001)
ApoA-I, g/L	−0.016 (−0.040 to 0.008)	−0.016 (−0.040 to 0.008)
ApoB, g/L	0.029 (0.009 to 0.048)**	0.032 (0.013 to 0.052)**
Total cholesterol, mmol/L	0.005 (0.000 to 0.010)*	0.006 (0.001 to 0.011)*
HDL cholesterol, mmol/L	−0.02 (−0.033 to −0.003)*	−0.02 (−0.034 to −0.004)**
LDL cholesterol, mmol/L	0.007 (0.001 to 0.013)*	0.008 (0.002 to 0.013)**
Log serum triglycerides, mmol/L	0.024 (−0.002 to 0.050)	0.029 (0.002 to 0.056)*
LDL particle size, nm	−0.011 (−0.019 to −0.002)**	−0.012 (−0.020 to −0.004)**

\**P*<0.05; \*\**P*<0.01.



**Figure 2.** The association between tertiles of the apoB/apoA-I ratio at entry and the annual change in composite carotid artery (IMT) during 3 years of follow-up in 313 men, originally 58 years of age.

factors such as many small LDL particles, low HDL cholesterol, hypertriglyceridemia, and other major components of MetS. To clarify this further, a larger study is needed.

We selected men of the same age and ethnic background with different degrees of obesity and insulin sensitivity and excluded those with prevalent cardiovascular disease. On one hand, this approach had the disadvantage that the cohort was not representative of the general population. On the other hand, confounding factors such as age, sex, and concomitant cardiovascular disease or treatments were kept constant, and the subjects were selected in a structured way from a population sample. Hence, results represent subjectively healthy men with varying degrees of obesity. Loss of subjects to the follow-up examination might have biased the results. However, the men lost to follow-up did not differ at study entry in apoB/apoA-I ratio and IMT or cardiovascular morbidity at the time for follow-up from the re-examined men.

We conclude that in this cohort of middle-aged men, the apoB/apoA-I ratio was closely associated with the factors constituting MetS including a small LDL particle size. The apoB/apoA-I ratio was associated with the change in carotid artery IMT independent of diastolic blood pressure and smoking. There was a strong colinearity between apoB/apoA-I and lipid variables. Results support the concept that the apoB/apoA-I ratio is a powerful predictor of atherosclerotic disease.

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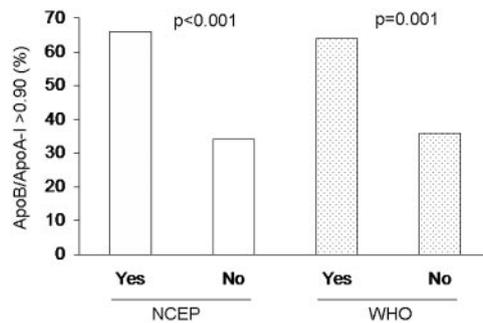
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# Correction

In the October issue of *Stroke*, the article entitled, “Apolipoprotein B/Apolipoprotein A-I in Relation to the Metabolic Syndrome and Change in Carotid Artery Intima-Media Thickness During Three Years in Middle-Aged Men” by Wallenfeldt et al<sup>1</sup> there was an error concerning data in the Results section. The following sentence and the figure replace the last sentence in the first column on page 2250 (paragraph title ApoB/ApoA-I Ratio and MetS):

As shown in the Figure, two thirds of the patients with MetS had high apoB/apoA-I ratios (>0.90) compared to one third of those without the syndrome.



The proportion of 58-year-old men (n=313) with an ApoB/ApoA-I ratio >0.90 by occurrence of the metabolic syndrome according to the National Cholesterol Education Program (NCEP) or World Health Organisation (WHO) definitions.

<sup>1</sup>[Correction for Vol 35, Number 10, October 2004. Pages 2248–2245.]  
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