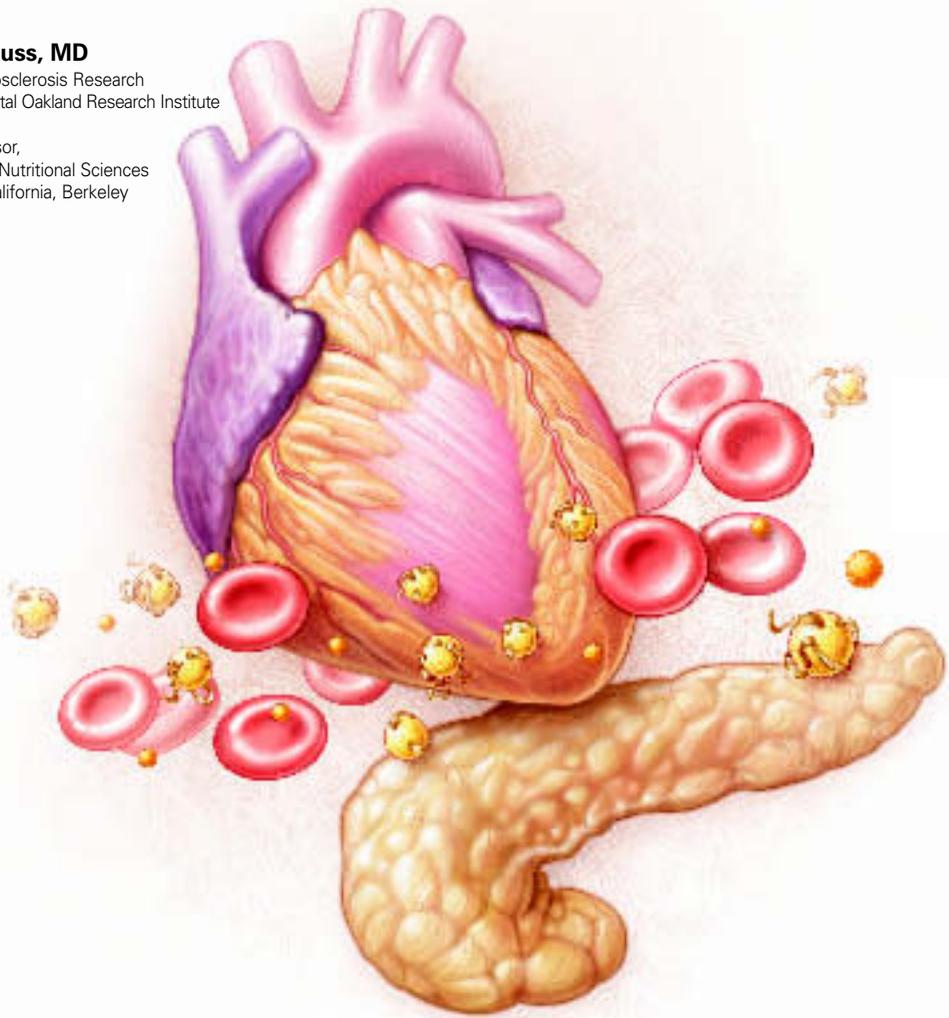


**Ronald Krauss, MD**

Director, Atherosclerosis Research  
Children's Hospital Oakland Research Institute  
Oakland, Calif  
Adjunct Professor,  
Department of Nutritional Sciences  
University of California, Berkeley



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## Metabolic syndrome: When and how to intervene

Ob/Gyns are in a position to intervene early enough to make a difference in diabetes and heart disease risk—and intervention does reduce risk.

**B**efore you ask why another set of risk factors deserves your attention, consider this: Metabolic syndrome is a veritable epidemic, affecting at least 1 of every 5 patients. Among 60- to 69-year-olds, almost half the population meets the diagnostic criteria.<sup>1</sup>

This risk are serious. Metabolic syndrome amplifies morbidity and mortality due to diabetes mellitus and cardiovascular

disease to such an extent that the National Cholesterol Education Program identifies it as a critical target of risk reduction, second only to reducing low-density lipoprotein (LDL) cholesterol.<sup>2</sup>

In our primary care capacity, Ob/Gyns are likely to be the first to identify metabolic syndrome and intervene—and intervention makes a difference. An aggressive approach to lipid lowering is critical.

IMAGE: RICH LARROCCO

However, solid evidence confirms that weight loss and physical activity eliminate some or all of the risk factors in many patients. There's the challenge. Notably, research reported in the *New England Journal of Medicine* found that, with a nutritionist's guidance, many patients who were counseled about these lifestyle changes reduced their risk of type 2 diabetes by 58% over 3 years.<sup>3</sup> (See page 54.)

This article reviews key studies linking metabolic syndrome to heart disease, diabetes, and death; and describes diagnostic and management fundamentals.

## ■ What defines metabolic syndrome?

Women with 3 or more of these factors have metabolic syndrome:

- Abdominal obesity; ie, waist circumference exceeding 35 inches (88 cm).
- Triglyceride level of 150 mg/dL or more.
- High-density lipoprotein (HDL) cholesterol below 50 mg/dL.
- Blood pressure 130/85 mm Hg or above.
- Fasting glucose of 100 mg/dL or above.<sup>2</sup>

Note that lipids should be measured when the patient is in a fasting state.

Women being treated for hypertension or diabetes can be presumed to meet the criteria for those components of metabolic syndrome.

Though the syndrome affects men and women equally overall, Hispanic and African-American women have a 26% and 57% higher incidence, respectively, than men of the same ethnic and racial background.<sup>1</sup>

## ■ Obesity and age drive full-blown syndrome

Insulin resistance, dyslipidemia, and other components of metabolic syndrome exist

because of intrinsic genetic susceptibility, which occurs to varying degrees throughout the population.

Some conditions cause this genetic susceptibility to blossom into the full-blown syndrome. Obesity is the driving force for much of this expression.

Age is a highly important factor. Prevalence of metabolic syndrome climbs sharply above the age of 40—in both men and women—so much so that the syndrome is close to becoming the common feature for older age groups (**FIGURE 1**).

## ■ Studies find link to diabetes, cardiovascular disease

What evidence do we have that this syndrome is associated with an increased risk of diabetes, heart disease, and death?

In a study of slightly more than 1,000 males with 10 years of follow-up, Lakka et al<sup>4</sup> found a 3.5-fold increased risk of cardiovascular disease mortality with metabolic syndrome. This risk is as high as or higher than the risk for cardiovascular disease in men with type 2 diabetes, which has been described in many other studies.

### Risk rises with number of components

A more recent study explored the impact of the number of components of meta-

### KEY POINTS

- **First-line therapies** for both lipid and nonlipid risk factors? Weight loss and regular exercise.
- **Reduce low-density lipoprotein (LDL) cholesterol** to less than 100 mg/dL when metabolic syndrome is present.
- **Lower the total of LDL and very-low-density lipoprotein (VLDL) cholesterol** to less than 130 mg/dL, especially in patients with borderline (150 to 199 mg/dL) or high (200 mg/dL or above) triglycerides.
- **When drug intervention is needed** to lower non-HDL cholesterol, use an LDL-lowering drug or add nicotinic acid or fibrate to reduce VLDL.

## INTEGRATING EVIDENCE AND EXPERIENCE

### With nutritionist counseling, glucose-impaired patients lost weight

Can lifestyle adjustments alone prevent type 2 diabetes to any great extent? Can anything be done to get overweight patients with impaired glucose to stick to a diet and exercise regimen?

Yes to both questions, according to researchers who conducted a randomized, controlled trial<sup>9</sup> of lifestyle changes among 522 middle-aged, overweight men ( $n = 172$ ) and women ( $n = 350$ ) with impaired glucose tolerance and a mean body mass index of 31.

#### Chief intervention was nutritionist counseling

Nevertheless, getting the study participants to live healthier was a complex undertaking. The intervention group received individualized counseling to encourage them to:

- reduce their weight by 5% or more
- reduce fat consumption to less than 30%
- limit saturated fat intake to less than 10%
- eat 15 g or more of fiber per 1,000 kcal of intake
- exercise moderately for at least 30 minutes daily
- eat whole-grain products, fruits and vegetables, low-fat dairy products and meat, and vegetable oils rich in monounsaturated fatty acids.

Each person in the intervention group met with a nutritionist 7 times during the first year of the study and every 3 months thereafter. Dietary advice was based on 3-day diaries of food intake, completed quarterly.

Endurance exercise was recommended to increase aerobic capacity and improve cardiorespiratory function. In addition, progressive, individually tailored, circuit-type resistance training was offered to improve muscle strength. During the first year of the study, the rate of participation in these resistance training sessions ranged from 50% to 85%.

#### A very different picture for controls

In contrast to the individualized attention focused on the intervention group, controls received general oral and written information about diet and exercise at the beginning of the trial and at each annual visit, but no detailed counseling. They also completed a 3-day food diary at the beginning of the study and at each annual visit.

#### Risk of type 2 diabetes 58% lower

The percentage of patients in the intervention group who achieved a particular goal ranged from 25% (fiber consumption) to 86% (exercise). Net weight loss at the end of the second year was  $3.5 \pm 5.5$  kg in the intervention group versus  $0.8 \pm 4.4$  kg in the control group ( $P < .001$  for both comparisons).

While this weight loss was not dramatic, the differences between groups was substantial. For example, individuals who lost at least 5% of their baseline weight had an odds ratio for diabetes of 0.3 (95 percent confidence interval, 0.1 to 0.7).

Over the duration of the trial, the cumulative incidence of type 2 diabetes was 58% lower in the intervention group than in the control group ( $P < .001$ ).<sup>3</sup> When women were singled out, the incidence of diabetes was 54% lower in the intervention group than among controls.

The failure to make any changes in lifestyle led to an incidence of diabetes very near the 35% estimate for this high-risk population.

#### Patients willingly stuck to diet, exercise

The dropout rate was low, and the researchers concluded that patients with impaired glucose tolerance are "willing and able to participate in a demanding intervention program if it is made available to them."<sup>13</sup>

bolic syndrome present.<sup>5</sup> After controlling for age, family history of diabetes, alcohol intake, and cigarette smoking, investigators found a multivariate-adjusted relative risk of cardiovascular disease, compared with an absence of components, of 3.18, 3.48, 12.55, and 14.15 ( $P < .001$ ) for the presence of 1, 2, 3, and 4 or more components, respectively. The

corresponding relative risks of type 2 diabetes were 1.92, 4.36, 6.44, and 15.08 ( $P < .001$ ).

Another recent study used the coronary artery calcium score as a surrogate for cardiovascular disease.<sup>6</sup> This measure is increasingly recognized as a marker of underlying atherosclerosis. In both men and women, the amount of calcium in the

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coronary arteries increased with the number of metabolic syndrome components.

### Dyslipidemia is a critical component

Several studies have identified dyslipidemia as the key component of metabolic syndrome. That is not to say that other components are unimportant—only that lipid abnormalities appear to have the greatest impact.

In a trial from the Third National Health and Nutrition Examination Study (NHANES III),<sup>7</sup> the large dataset that has been studied extensively for this disorder, low HDL cholesterol and high blood pressure in the presence of overt diabetes appeared to account for much of the excess risk associated with metabolic syndrome. In fact, blood pressure, HDL cholesterol, and diabetes—but not metabolic syndrome per se—were significant multivariate predictors of prevalent CHD.<sup>7</sup>

### Twice the risk of myocardial infarction and stroke

Another recent study<sup>8</sup> found twice the risk of myocardial infarction and stroke when metabolic syndrome was present.

Investigators used logistic regression to estimate the association of the syndrome as a whole and each of its 5 component conditions separately with a history of myocardial infarction (MI), stroke, and either MI or stroke (MI/stroke).

Metabolic syndrome was significantly related in multivariate analysis to MI (odds ratio [OR], 2.01; 95% confidence interval [CI], 1.53 to 2.64), stroke (OR, 2.16; 95% CI, 1.48 to 3.16), and MI/stroke (OR, 2.05; 95% CI, 1.64 to 2.57).

Among the 5 component conditions of metabolic syndrome, the following were independently and significantly related to MI/stroke<sup>8</sup>:

- insulin resistance (OR, 1.30; 95% CI, 1.03 to 1.66),
- low HDL cholesterol (OR, 1.35; 95% CI, 1.05 to 1.74),
- hypertension (OR, 1.44; 95% CI, 1.00 to 2.08), and

**TABLE 1**

### ATP III classification of LDL, total, and HDL cholesterol (mg/dL)

LEVEL	STATUS
<b>LDL cholesterol</b>	
<100	Optimal
100–129	Near or above optimal
130–159	Borderline high
160–189	High
≥190	Very high
<b>Total cholesterol</b>	
<200	Desirable
200–239	Borderline high
≥240	High
<b>HDL cholesterol</b>	
<40	Low
≥60	High

LDL = low-density lipoprotein  
HDL = high-density lipoprotein

Source: NCEP.<sup>2</sup> Reprinted with permission

- high triglycerides (OR, 1.66; 95% CI, 1.20 to 2.30).

### Unique lipid triad

High triglycerides, small LDL particles, and low HDL form the characteristic lipid profile of women with metabolic syndrome. For classification of the different levels of cholesterol, see **TABLE 1**.

**High triglycerides heighten risk.** High triglyceride levels carry an increased, independent risk of cardiovascular disease, particularly in women. As levels exceed 200 mg/dL, that risk rises sharply (**FIGURE 2**).<sup>9</sup> Other studies, including a metaanalysis, have confirmed this finding.

**Low HDL cholesterol** is another independent risk factor for cardiovascular disease—one that is independent of standard risk markers such as LDL cholesterol. At high total cholesterol levels, the risk of cardiovascular disease increases, but that risk is even higher when HDL is low.<sup>10</sup>

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### FAST TRACK

**Lipid abnormalities appear to account for much of the excess risk of metabolic syndrome**

**TABLE 2**

**Comparison of LDL and non-HDL cholesterol goals for 3 risk categories**

RISK CATEGORY	LDL GOAL (MG/DL)	NON-HDL GOAL (MG/DL)
Coronary heart disease or risk equivalent (10-year risk for coronary heart disease >20%)	<100	<130
2 or more risk factors and 10-year risk ≤20%	<130	<160
0–1 risk factor	<160	<190

LDL = low-density lipoprotein  
 HDL = high-density lipoprotein  
 Source: NCEP.<sup>2</sup> Reprinted with permission

**FAST TRACK**

**C-reactive protein levels tend to be higher in women than in men**

**Small LDL cholesterol particles.** The characteristic LDL abnormality in patients with metabolic syndrome is not elevated levels, but a shift in size from larger to smaller LDL particles. In fact, the cardiovascular disease risk associated with small LDL particles is several times higher than the risk associated with the larger particles.

Smaller particles are more atherogenic than larger LDL particles despite their lower cholesterol content. The reasons:

They are cleared more slowly from plasma, taken up more readily by the artery wall, and more actively retained.

They are more rapidly oxidized, an important step in the atherogenic process.

At any level of LDL, there are more particles circulating.

Individuals tend to cluster into 2 groups based on LDL particle size: those with larger LDL particles, who usually have relatively lower triglyceride levels, and those with smaller LDL particles, who tend to have higher triglycerides. At triglyceride levels above 150 mg/dL—the cutoff for metabolic syndrome—individuals are more likely to have smaller LDL particles.

What is the risk associated with smaller particles? A study from 2001 by St. Pierre and colleagues<sup>11</sup> showed that, at any level of triglycerides, LDL cholesterol, or apolipoprotein B (another LDL-related risk marker), the risk of coronary heart disease associated with small LDL particles is more than 3 times the risk associated with larger LDL particles.

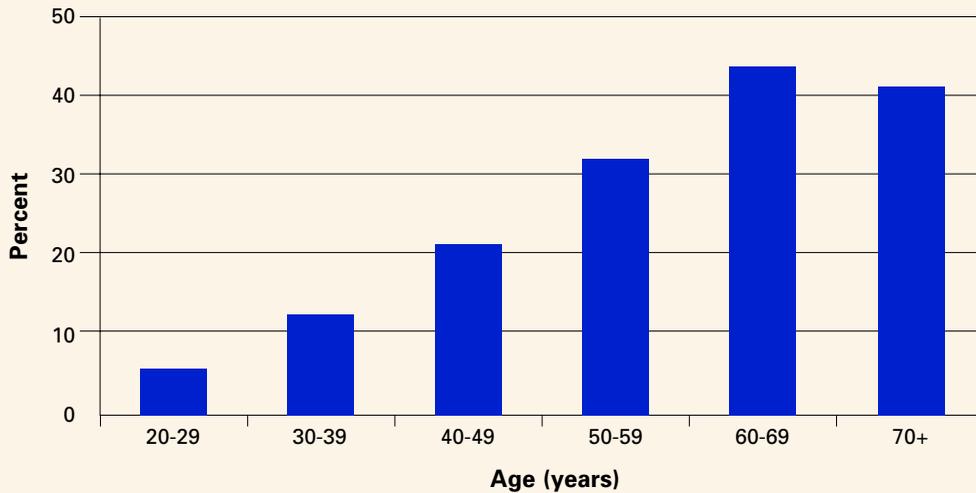
**C-reactive protein is an important marker**

C-reactive protein is an important marker of the inflammation linked to heart disease. Elevated C-reactive protein also is associated with insulin resistance and adiposity. The trigger for the liver’s production of C-reactive protein is a cytokine released in large part by adipose tissue and endothelial cells.

Because a standardized, highly sensitive assay to measure plasma C-reactive protein is now available, there is a movement to include it in the definition of metabolic syndrome. As a recent study shows, the level of C-reactive protein rises with the number of components of metabolic syndrome.<sup>12</sup> Levels tend to be higher in women than in men.

In addition, as Ridker et al<sup>13</sup> and others have shown, as the levels of C-reactive protein rise from low (<1 mg/L) to high (>3 mg/L), so does the risk of cardiovascular disease.

Moreover, high C-reactive protein levels add to the risk associated with standard cholesterol-based risk factors. Thus, adding plasma C-reactive protein to standard lipid screening may help predict the risk of cardiovascular disease in women with high as well as low cholesterol levels.<sup>13</sup> For example, if an individual has both elevated C-reactive protein and the metabolic syndrome, the relative risk of cardiovascular disease is more than twice the risk in women with high C-reactive protein alone.

**FIGURE 1****Incidence of metabolic syndrome rises with age**

Data from the Third National Health and Nutrition Examination Survey show the rising incidence of metabolic syndrome with age; incidence peaks among 60- to 69-year-olds. Source, Ford ES, et al<sup>1</sup>

### ■ First-line therapies are weight loss, exercise

According to ATP III<sup>2</sup>, the aims of managing metabolic syndrome are:

- to reduce causes of the syndrome, such as obesity and inactivity, and
- to treat lipid and nonlipid risk factors.

Weight reduction and increased physical activity should reduce both lipid and nonlipid risk factors and should be encouraged in all patients with the syndrome.

**Weight loss** enhances efforts to lower LDL cholesterol and reduces the impact of all risk factors for metabolic syndrome.<sup>2</sup>

**Physical activity** can reduce the risk of cardiovascular disease by improving cardiovascular fitness and coronary blood flow. Regular physical activity reduces very-low-density lipoprotein (VLDL) cholesterol levels, increases HDL cholesterol, and can lower LDL levels in some individuals. It also may help reduce blood pressure and insulin resistance.

ATP III recommends regular physical activity as a key component of managing high serum cholesterol.<sup>2</sup> For more information on these interventions, see “Integrating evidence and experience,” on page 54.

### ■ Why aggressive lipid lowering?

The current goal is reducing LDL cholesterol to less than 100 mg/dL when metabolic syndrome is present. Even lower levels, eg, less than 70 mg/dL, may be advisable when both cardiovascular disease and metabolic syndrome are present.<sup>14</sup>

A broader measure of atherogenic lipoproteins is total cholesterol minus HDL cholesterol. This measure incorporates some of the triglyceride-rich lipoproteins involved in atherosclerosis. The target is less than 130 mg/dL (**TABLE 2**).<sup>2</sup> All people with borderline (150 to 199 mg/dL) or high (200 mg/dL or above) triglycerides should be managed to achieve this goal. Weight reduction and physical activity are critical, even with drug therapy.

#### When to use drug therapy

Pharmacologic intervention to lower non-HDL cholesterol may involve use of an LDL-lowering drug or the addition of nicotinic acid or fibrate to reduce VLDL.

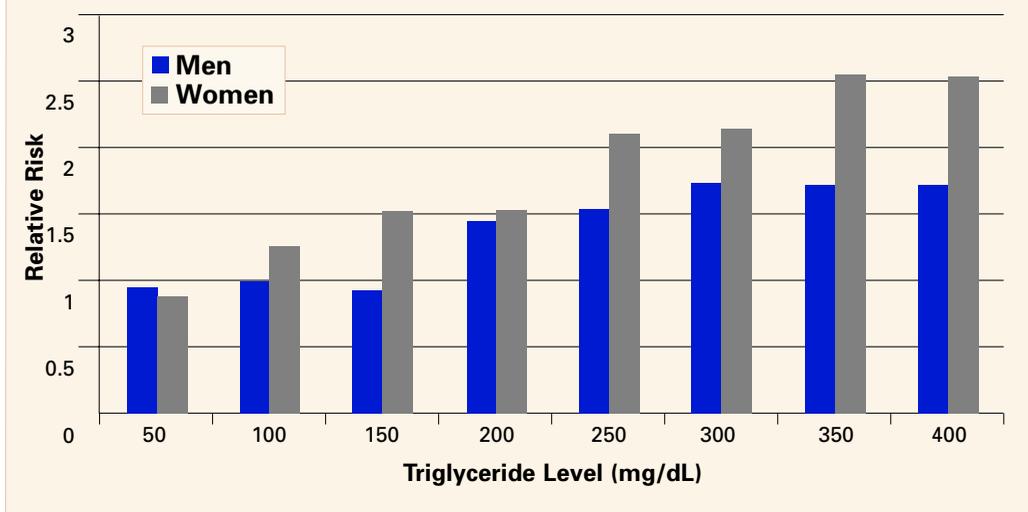
**When triglyceride levels are extremely high** (500 mg/dL or higher), the primary goal of therapy is preventing acute pancreatitis. This may require a combination of low-fat

#### FAST TRACK

**Reduce LDL cholesterol to less than 100 mg/dL in women with metabolic syndrome**

**FIGURE 2**

**Risk of coronary heart disease rises with triglyceride level**



Data from the Framingham Heart Study show a sharply increased risk of coronary heart disease when triglyceride levels are high, especially in women. Source: Castelli et al<sup>9</sup>

diet, weight loss, regular physical activity, and a triglyceride-lowering drug.<sup>2</sup> Once triglyceride levels decline to less than 500 mg/dL, the emphasis can return to reducing cardiovascular risk.

**When LDL cholesterol is very high.** LDL cholesterol levels of 190 mg/dL or higher, usually signify genetic hypercholesterolemia.<sup>2</sup> Early detection—preferably, in young adults—is crucial to prevent coronary heart disease, and a combination of drugs usually is necessary to reduce LDL cholesterol levels. Otherwise, aim for the goals in **TABLE 2**.

**Benefits of statins.** In a post hoc analysis of data from the Scandinavian Simvastatin Survival Study, which enrolled patients with elevated LDL cholesterol and coronary heart disease, those with the triad of elevated LDL cholesterol, low HDL cholesterol, and elevated triglycerides were more likely than patients with isolated high LDL cholesterol to have other characteristics of the metabolic syndrome. They also had a greater risk of coronary heart disease on placebo and received greater benefit with simvastatin therapy.<sup>15</sup>

**Fibrates and HDL cholesterol.** In a subgroup analysis from the Department of Veterans

Affairs High-Density Lipoprotein Intervention Trial, investigators explored the efficacy of gemfibrozil in men with coronary heart disease, HDL cholesterol levels of 40 mg/dL or below, and LDL cholesterol of 140 mg/dL or less.<sup>16</sup>

Participants were given 1,200 mg of gemfibrozil daily and followed for an average of 5.1 years. The drug was most effective in those with diabetes, reducing death from coronary heart disease by 41% (hazard ratio, 0.59; 95% confidence interval, 0.39–0.91;  $P < .02$ ).

Among men without diabetes, gemfibrozil was most effective for those in the highest quartile for fasting plasma insulin (risk reduction 35%;  $P < .04$ ).

Among those who had coronary heart disease and low HDL cholesterol, the drug reduced major cardiovascular events.

**Nicotinic acid** improves each of the common lipid abnormalities found in metabolic syndrome.<sup>17</sup> Early concern that it can precipitate or worsen diabetes has largely been disproved, although some data suggest that it can slightly aggravate insulin resistance and elevate blood glucose. ■

The author reports no relevant financial relationships.

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**FAST TRACK**

**When LDL is 190 mg/dL or higher, use a combination of LDL-lowering drugs**

## INTEGRATING EVIDENCE AND EXPERIENCE

**When it comes to cognitive function, is metabolic syndrome a “brain drain”?**

A recent prospective observational study<sup>14</sup> found a link between metabolic syndrome and cognitive impairment in the elderly, particularly when inflammation also was present.

Hypertension, diabetes, and other cardiovascular and metabolic risk factors are thought to play a role in the development of Alzheimer’s disease and vascular dementia.

Researchers followed 2,632 elderly men and women over 5 years (mean age: 74), documenting metabolic syndrome in 1,016. Those with metabolic syndrome were more likely to have cognitive impairment (26% versus 21%; multivariate-adjusted relative risk [RR], 1.20; 95% confidence interval [CI], 1.02–1.41) than were those without the syndrome.

Investigators also documented high inflammation in the study population, defining it as

higher-than-median serum levels of both interleukin 6 ( $\geq 2$  pg/mL) and C-reactive protein ( $\geq 2$  mg/L). They then assessed its relationship to cognitive decline.

**Those with both metabolic syndrome and high inflammation** had an increased likelihood of cognitive impairment, compared with those without metabolic syndrome (multivariate-adjusted RR, 1.66; 95% CI, 1.19–2.32).

**Those with metabolic syndrome and low inflammation** had a low likelihood of impairment (multivariate-adjusted RR, 1.08; 95% CI, 0.89–1.30).

These findings held true even after adjusting for demographics, comorbidities, and health habits. It remains to be seen whether attempts to prevent metabolic syndrome or lower inflammation also limit cognitive impairment.

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## FAST TRACK

## Metabolic syndrome is linked to cognitive decline in the elderly

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