Harvard Men's Health Watch

Cholesterol, the mind, and the brain

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It sounds like a no-brainer: The lower your cholesterol, the better your health. When it comes to coronary artery disease, conventional wisdom is truly wise; new guidelines call for reducing LDL ("bad") cholesterol levels to 70 mg/dL or lower for patients at the highest risk. But a man's heart and his head don't always agree. In fact, the relationships among cholesterol levels, psychological function, and neurologic disorders are complex and sometimes controversial. How do cholesterol levels and cholesterol-lowering drugs affect the mind and the brain?

Cholesterol in the brain

Despite its well-deserved notoriety as a cause of heart disease, cholesterol is essential for human health. It is the building block of steroid hormones, including the stress hormone *cortisol* and the male and female sex hormones, including *testosterone* and the *estrogens*. Cholesterol is also an essential component of the membranes that surround all human cells. More than simply holding cells together, these membranes have a crucial role in regulating cell function and allowing chemicals to pass into and out of cells.

Because cholesterol is so vital, the body does not rely on diet to provide it. In fact, most of the cholesterol in the blood is manufactured in the liver. Strict vegetarians who don't get any dietary cholesterol have admirably low blood cholesterol levels that reduce their risk of heart disease while providing plenty of cholesterol to keep their cells happy and their hormones flowing. Statin drugs reduce the liver's cholesterol production by targeting the enzyme *HMG-CoA reductase*; and by lowering blood cholesterol levels, they protect arteries from damage.

Most of the body's organs get the cholesterol they need from the blood. Similarly, when the body breaks down cholesterol, its components return to the liver for reprocessing. Some of the statin drugs' benefits depend on their ability to trick the liver into removing cholesterol from the blood.

The brain has a higher cholesterol content than any other organ. In fact, about 25% of the body's cholesterol is found in this small organ, which accounts for less than 2% of the body's weight. Most of the cholesterol is in the *myelin sheaths* that surround the *axons* of nerve cells, protecting the cells and facilitating the speedy transmission of the electrical impulses that govern thought, movement, and sensation.

The brain is highly dependent on cholesterol, but its cholesterol metabolism is unique. Because the *blood-brain barrier* prevents brain cells from taking up cholesterol from the blood, the brain must produce its own cholesterol. Like the liver, brain cells depend on HMG-CoA reductase to produce cholesterol. The brain's cholesterol is much more stable than the cholesterol in other organs, but when it breaks down, it is recycled into new cholesterol right in the brain.

Because of the blood-brain barrier, changes in blood cholesterol levels are not necessarily reflected in the brain itself. In addition, the barrier keeps many chemicals, including medications as well as toxins, away from the brain. Among the cholesterol-lowering statin drugs, some are largely excluded because they are water-soluble, while others that are fat-soluble can enter, at least to some degree (see table).

Scientists have learned a lot about cholesterol and the brain, but they still have a long way to go. The same is true for researchers who are puzzling out the relationships between cholesterol and cholesterol-lowering drugs and psychological function, stroke, and memory loss (*dementia*).

Statin drugs and the brain

Water-soluble; Excluded	Fat-soluble; May enter
Pravastatin (Pravachol)	Lovastatin (Mevacor and generics)
Fluvastatin (Lescol)	Simvastatin (Zocor and generics)
Rosuvastatin (Crestor)	Atorvastatin (Lipitor)

Cholesterol, mood, and behavior

Although doctors have wondered about a possible link between blood cholesterol levels and brain function for many years, interest really intensified after the introduction of *clofibrate* (Atromid-S) in the 1960s. The drug is effective at lowering cholesterol levels, but in the early days of treatment, patients taking it appeared to experience an increased risk of violent deaths due to accidents or suicide.

Clofibrate has long since been replaced by safer and more effective medications. But the question of a link between cholesterol, mood, and behavior persists.

One body of research asks if cholesterol levels correlate with mental function in the absence of cholesterol-lowering medications. A 1998 review of studies that examined the relationship between cholesterol levels and violence concluded that the data "consistently showed increased violent death and violent behavior in persons with low cholesterol levels." But that doesn't mean you should boost your cholesterol in a quest for peace. Only nine of the studies that contributed to this conclusion examined community-wide populations, while 12 studied criminals or psychiatric populations; differences in diet, smoking, exercise, body fat, alcohol use, and medication are among the factors that might affect the wider relevance of this research.

The relationship between cholesterol and depression or suicide is also complex. For example, studies from France and Canada linked low cholesterol levels to an increased incidence of suicide, and research from the Netherlands and Turkey reported an association between low cholesterol levels and depression. On the other hand, data from Hawaii found the reverse: High cholesterol levels were connected with an increased risk of suicide.

Since so many lifestyle and health factors influence both the body's metabolism and the mind's function, it's not surprising that population-based observational studies have produced conflicting results. Randomized clinical trials of cholesterol-lowering medications avoid many of these pitfalls, and here the results are reassuring. Placebo-controlled trials of lovastatin and simvastatin (which can cross into the brain) and of pravastatin (which does not) have not identified any adverse effects on cognitive function or psychological well-being. In fact, the long-term use of statin drugs has been associated with reduced risks of anxiety, hostility, depression, and suicide, perhaps because of the improved physical health that results from these medications. Similarly, a meta-analysis of 19 trials of cholesterol-lowering interventions found no effect on the risk of death from suicide, accidents, or violence. And men who claim that a heart-healthy diet will drive them over the edge should note that dietary interventions that lower cholesterol are as psychologically friendly as medications.

Cholesterol and mortality

The lower your cholesterol, the better. It's an article of faith nearly on the same pedestal as motherhood and apple pie. Then along came a series of studies that found an increased death rate among people with the very lowest cholesterol levels. An investigation of 3,572 elderly men in Hawaii is but one example. Men with the lowest cholesterol levels (81""167 mg/dL) had a 35% higher death rate than those with the highest levels (210""382 mg/dL). In similar studies, cancer was responsible for most of the excess deaths in people with very low cholesterol levels.

Before you toss out your Lipitor and toss down a Big Mac, consider the basis for this association. It's not that low cholesterol causes cancer, but the reverse. In fact, many studies show that elderly people have very low cholesterol levels because they smoke, abuse alcohol, are malnourished, or have chronic illnesses. Smoking accounts for the apparent link between low cholesterol and cancer.

All these factors should reassure older people that low cholesterol levels are safe. And in younger people, low readings are very good news indeed; for example, an investigation of 3,277 healthy businessmen who were 30""45 years old when they entered the study in 1964""73 found that low cholesterol levels predicted better survival and better physical function and quality of life over the next four decades.

When it comes to cholesterol and longevity, less really is more.

Cholesterol and stroke

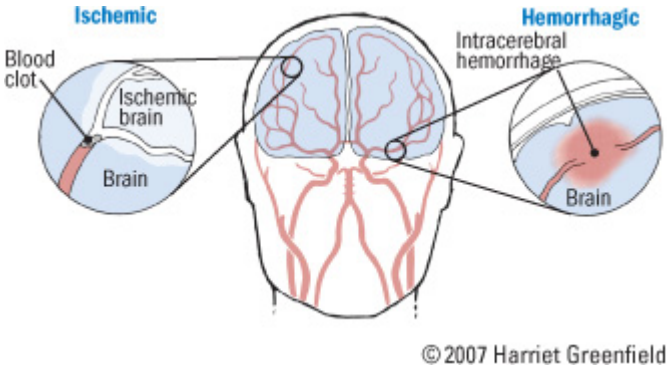
Heart disease and stroke, the first and third leading killers of American men, are linked so often that they may seem to be a single disease. Indeed, high blood pressure, smoking, diabetes, obesity, and lack of exercise increase the risk of both heart attack and stroke. It's a familiar list of cardiovascular risk factors, but the most familiar villain of all is not on the list. Cholesterol is clearly a central culprit in heart disease, but its relationship to stroke is complex and even controversial.

Many studies from around the world have failed to implicate cholesterol as a cause of stroke. Back in 1995, a major meta-analysis evaluated 45 studies that included some 450,000 individuals and 13,397 strokes during an average period of over 16 years. When age, sex, and blood pressure were taken into account, there was no link between cholesterol and stroke; people with higher cholesterol levels were no more vulnerable than people with normal or low levels.

With the benefit of hindsight, it's now clear that two factors account for this apparent paradox. First, there are two major types of strokes, *hemorrhagic* and *ischemic* (see figure). Hemorrhagic strokes are less common but more cataclysmic; they occur when a blood vessel in the brain bursts, spilling blood into the brain or the surrounding fluid. Ischemic strokes, on the other hand, result from the blockage of a blood vessel in the brain. Heart attacks also result from blockages; in fact, the lack of oxygen-rich blood is responsible for both heart attacks and ischemic

strokes. The huge 1995 international study lumped both types of strokes together. But most of the studies that analyze the types of strokes separately come to different conclusions. The landmark MRFIT study is an example. It evaluated 12,866 American men who were 35 to 57 years old when they volunteered to participate. Ten years later, when the results were in, high cholesterol levels indeed predicted an increased risk of ischemic strokes, but low cholesterol levels increased the risk of hemorrhagic stroke, perhaps because of underlying chronic illnesses or alcohol abuse.

Anatomy of a stroke



Ischemic strokes, the most common type, result from the blockage of an artery. Improving your cholesterol can reduce your risk.

Hemorrhagic strokes result from bleeding into the brain. Cholesterol is not to blame.

The second explanation is that there are two types of blood cholesterol. It turns out that high HDL ("good") cholesterol levels protect against ischemic strokes without affecting the risk of hemorrhagic strokes one way or the other. As in the case of heart disease, though, LDL cholesterol is a culprit, and high levels increase the risk of ischemic stroke.

Now for the $64,000 question: Will lowering LDL cholesterol protect against stroke as well as heart attack? Here, too, it's not simple. Interventions that rely on diet or nonstatin drugs have not been effective. In contrast, a meta-analysis of 65 trials involving over 200,000 patients reported that statin therapy reduced the risk of fatal and nonfatal strokes by 18%. Patients without heart disease benefit as much as those with heart disease. And there is more good news: Statin therapy does not increase the risk of hemorrhagic stroke, and it appears to improve recovery in patients with ischemic strokes.

For strokes as well as heart attacks, LDL cholesterol is a villain, HDL cholesterol a hero.

Cholesterol, cognitive function, and Alzheimer's disease

There are two major forms of severe cognitive impairment, or dementia: *vascular dementia* and *Alzheimer's disease*. Although there is reason to suspect that cholesterol may play a role in both, the data are preliminary and the evidence is mixed.

Vascular dementia results when blood vessel damage deprives brain cells of vital oxygen. As brain cells die, mental function suffers. Cholesterol has a major role in vascular health "" but is it linked to cognitive function? Some studies link high total cholesterol levels to an increased risk of cognitive impairment, but other research reports just the opposite. More research is needed to sort this out, but even now, investigations of HDL cholesterol and mental function have consistently reported that high levels appear to help preserve mental function in older people.

Alzheimer's disease is even more complex. Scientists have learned that much of the damage is caused by deposits of a sticky protein called *beta-amyloid* in critical areas of the brain. In some clinical studies, high blood cholesterol levels appear to accelerate the formation of beta-amyloid plaques. People with the genetic trait that increases the level of a particular cholesterol transport protein (*APOE4*) have a greatly increased risk of late-onset Alzheimer's.

In practical terms, the urgent question is whether cholesterol-lowering drugs can reduce the risk of Alzheimer's disease. Hopes were raised in 2000 and 2001, when several observational studies reported that people who took statins had a dramatically lower risk of Alzheimer's disease than people who did not take them. But these were *retrospective* studies that began with Alzheimer's patients and healthy elders; they looked back to see if previous statin therapy seemed to affect the likelihood of dementia. Next came *prospective* studies, which began with a group of mentally intact people. Researchers then observed them over time to see whether patients on statins enjoyed protection. Unfortunately, these newer investigations are negative, and a trial of statin therapy in patients who already had Alzheimer's failed to show important benefits. But additional research is under way; until the results are in, it's too early for firm conclusions on the relationship between cholesterol, cognitive function, and statin therapy.

Perspectives

It took decades for scientists to establish the basic interactions between cholesterol and atherosclerosis, and new research adds to the fine print every year. The brain is our most complex organ, and researchers are only starting to make progress studying brain cholesterol, which leading scientists have called a "long secret life behind a barrier." Even now, we have learned that cholesterol-lowering drugs do not increase the risk of violent behavior and suicide and that the statin drugs reduce the risk of stroke, in patients both with and without heart disease. And don't forget that the last chapter on cholesterol and dementia has yet to be written.

All in all, the cholesterol story is heartening news for the brain.

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