



# LDL Cholesterol & Dementia Risk

*High LDL in Mid-life Raises the Risk of Dementia*

If you think keeping your low-density lipoprotein (LDL) cholesterol in check only matters for heart health, think again.

Last August, the *Lancet* standing Commission on Dementia Prevention, Intervention, and Care added high LDL in mid-life as a modifiable dementia risk factor to their previous list of 12 risk factors.

The news underscored the importance of identifying and treating high LDL in mid-life, especially as women have higher LDL cholesterol after menopause yet are less likely to be

prescribed cholesterol-lowering medication than men, leading to worse health outcomes.

Mind Over Matter® reviewed the evidence leading to the *Lancet* Commission's decision. We also spoke to leading experts to learn how high LDL cholesterol is linked to dementia and proven ways to lower it to protect brain health and heart health.

## LDL CHOLESTEROL

Cholesterol is a waxy substance your body uses to make cell membranes, vitamin D, and many hormones. Your liver makes

The *Lancet* standing Commission's 12 modifiable dementia risk factors are:

- less education;
- obesity;
- low social contact;
- hypertension;
- depression;
- excessive alcohol consumption;
- hearing impairment;
- physical inactivity;
- traumatic brain injury; and
- smoking;
- diabetes;
- air pollution.

all the cholesterol your body needs. The rest found in your blood comes from animal-based foods, such as meat, poultry, and dairy products, and a trace amount from plant-based foods.

Cholesterol is carried in your blood by lipoproteins, spherical particles made of fats (lipids) and proteins.

There are two main types of lipoproteins. LDL cholesterol is sometimes called “bad” cholesterol, but that’s not a fair nickname because it plays an essential role in transporting fats in your blood to various cells throughout your body.

The other primary lipoprotein is high-density lipoprotein (HDL), the “good cholesterol,” so named because it transports excess LDL in your blood back to your liver, where it is broken down and flushed from the body.

**TOO MUCH LDL CHOLESTEROL IS PROBLEMATIC. IT CAN CONTRIBUTE TO PLAQUE BUILDUP IN ARTERIES, INCREASING THE RISK OF CORONARY ARTERY DISEASE, CEREBROVASCULAR DISEASE, PERIPHERAL ARTERY DISEASE, HEART ATTACK, AND STROKE.**

Many factors cause high LDL cholesterol, including genetics, aging, eating a diet that’s high in saturated fats or trans fats and refined sugar, being overweight or obese, smoking, diabetes, kidney disease, and some medications.

As we age, LDL levels change, and so do sex-related differences. In early life, girls have higher LDL levels than boys. After 19 years of age, premenopausal women have lower LDL cholesterol levels than men.

However, after age 50 and coinciding with menopause, women experience a steep increase in LDL levels that surpasses men’s levels. LDL cholesterol levels gradually decline in older age. However, the drop is less pronounced and takes place later in women.

## LDL TARGETS

Your LDL cholesterol level is determined through blood work, typically as part of an annual wellness check-up.

**Canada** - Physicians use a risk calculator, such as the Framingham Risk Score (FRS), to determine your risk of developing cardiovascular disease in the next ten years. The FRS considers your cholesterol results, age, sex, and cardiovascular risk factors like diabetes, blood pressure, kidney disease, and smoking history. According to the Canadian Cardiovascular Society:

- **low risk:** FRS under 10%;
- **intermediate risk:** FRS of 10% to 19.9% and LDL cholesterol 3.5 mmol/L or higher; and
- **high risk:** An FRS of 20% or greater.

Treatment is not required for an FRS under 10%. For patients with an FRS in the intermediate- or high-risk categories, physicians discuss health behaviour changes and options for initiating treatment. If a first drug therapy does not sufficiently lower LDL cholesterol, your doctor may recommend adding on other treatments.

**United States** - For people without heart disease, the target LDL is 100 mg/dL or lower, and for people with heart disease, the target is 70 mg/dL or lower, according to the American Heart Association.

## EVIDENCE LINKING HIGH LDL TO DEMENTIA

The *Lancet* Commission reviewed the latest evidence and concluded, “Overall, high-quality, consistent, biologically plausible evidence exists that high LDL cholesterol in midlife is a risk factor for dementia.” ➡

High LDL cholesterol is one of the most significant risk factors for heart conditions and stroke in women, according to the Heart and Stroke Foundation of Canada.

Highlights of some of the study findings that formed the basis of their recommendation are as follows:

- every 1 mmol/L increase in LDL cholesterol was associated with an 8% increase in the incidence of dementia in adults under 65, according to a meta-analysis of health records for 1.1 million adults in the United Kingdom (U.K.) who were followed for more than a year. (*Alzheimer's Dementia (Amst.)*, 2023)
- an LDL cholesterol level of 3 mmol/L or higher was associated with a 33% increased risk of dementia, according to a population study of 1.2 million people. (*PLOS One*, 2023)
- an analysis of health records of more than 1.8 million people in a U.K. databank followed for about 7.4 years

The *Lancet* Commission's report stated that 45% of all dementia cases worldwide could be prevented or delayed by addressing these 14 modifiable risk factors across the human lifespan.

Estimated % reduction in dementia cases if each risk factor is eliminated by stage of life:\*

#### EARLY LIFE

Less education	5%
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#### MID-LIFE

High LDL cholesterol	7%**
Hearing loss	7%
Depression	3%
Traumatic brain injury	3%
Physical inactivity	2%
Diabetes	2%
Smoking	2%
Hypertension	2%
Obesity	1%
Excessive alcohol consumption	1%

#### LATE LIFE

Vision loss	2%**
Social isolation	5%
Air pollution	3%

\*Adapted from: *Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission.*

\*\* New in 2024

showed that having a higher LDL level at the beginning of the study was associated with a 5% increased risk of all-cause dementia for each additional 1 mmol/L. The risk of a dementia diagnosis within ten years and later was 10% greater for people under 65 than for people who were older than 65 at the beginning of the study. (*Lancet Healthy Longevity*, 2021)

## THE LINK BETWEEN HIGH LDL & DEMENTIA

Heart health and brain health are intertwined, but how does having a high LDL raise the risk for dementia? The common denominators are vascular disease and inflammation.

Vascular disease is any condition that affects how well blood vessels carry blood throughout your body and brain. A buildup of excess LDL cholesterol in your arteries can cause atherosclerosis, a narrowing that, over time, can become a blockage that causes heart attack or stroke. Ongoing inflammation is part of the atherosclerosis process.

Vascular dementia is a decline in cognitive function caused by reduced or blocked blood flow to the brain. It is the second-most common subtype of dementia after Alzheimer's disease (AD), representing about 15% to 20% of dementia cases in North America and Europe.

"Most people show some degree of vascular damage over time as they age, even when they don't have cognitive deficits," said Dr. Betsy Mills, Assistant Director of Aging and Alzheimer's Prevention at the Alzheimer's Drug Discovery Foundation.

**“HOWEVER, GROWING EVIDENCE SHOWS THAT VASCULAR DISEASE PROCESSES AND INFLAMMATION ARE MAJOR FACTORS IN MOST FORMS OF DEMENTIA, INCLUDING ALZHEIMER'S.**

"As scientists developed blood biomarkers for Alzheimer's disease, they discovered that cognitive impairment in people with Hispanic or African American ethnicities appears to be driven by vascular-related disease processes more so than amyloid beta deposition," added Dr. Mills.

The *Lancet* Commission report identified lowering high LDL cholesterol as one way to decrease vascular damage and prevent and delay dementia.

"High LDL cholesterol is a proven cardiovascular risk factor," said Dr. Christopher Labos, a Montreal-based cardiologist, epidemiologist, and co-host of the award-winning *The Body of Evidence* podcast. "Anything that decreases the risk of

cardiovascular disease and stroke is also going to lead to a lower risk of vascular dementia.”

## “HIGH LDL CHOLESTEROL IN MID-LIFE IS AN IMPORTANT DEMENTIA RISK FACTOR THAT ALL WOMEN SHOULD KNOW ABOUT.

“We already knew that vascular disease plays a role in dementia and cognitive impairment, but the *Lancet* Commission’s news underscores that it’s a major driver. We can’t yet prevent amyloid plaques and tau tangles, but we can take steps to prevent vascular damage, and that’s huge,” continued Dr. Mills.

## HOW TO LOWER HIGH LDL

The good news is that there are steps you can take to lower high LDL and reduce your risk of dementia and heart disease.

### DIET AND EXERCISE STRATEGIES

Harvard Medical School recommends the following diet modifications to help bring down your LDL:

#### Eliminate trans fats and limit saturated fats.

Eliminate trans fats by avoiding foods with “partially hydrogenated” ingredients. Limit foods high in saturated fats, such as red meat, shrimp, lobster, high-fat dairy products, and butter, to small portions every couple of weeks. Note that it’s OK to have as many as four egg yolks weekly and egg whites as often as you wish.

**Consume more polyunsaturated and monounsaturated fats.** Plant-based oils, like olive, canola, and sunflower oil, are good sources of these healthy fats. Seeds, nuts, avocados, soybeans, and fatty fish, including salmon, trout, tuna, herring, and mackerel, are also excellent sources.

**Eat a rainbow of fruits and veggies.** Colourful fruits and vegetables contain fibre as well as cholesterol-blocking substances called sterols and stanols.

**Avoid added sugars and refined grains.** Avoid added sugars by spotting sugar, corn syrup, or words ending in “ose” near the top of ingredient lists. Choose whole grain foods as a good source of fibre over those containing refined flour or white rice.

Ensuring you get enough moderate-to-vigorous exercise on an ongoing basis can also lower LDL by boosting HDL cholesterol. According to the Canadian Cardiovascular Society, half an hour to one hour of moderate-to-vigorous intensity exercise daily can raise HDL by 5% to 10%.

## EXAMPLES OF EXPECTED BENEFITS OF HEALTH BEHAVIOUR CHANGES TO LOWER LDL\*

	% reduction in LDL cholesterol
Reduced saturated fats/dietary cholesterol:	
200 mg or less daily (7% or less of total food energy)**	12-16%
300 mg or less daily (10% or less of total food energy)**	10-12%
Portfolio dietary pattern	8-14%
Weight loss of 5-10% of body weight	11-12%
Dietary pattern with plant sterols/stanols 1-2 g daily	6-12%
Viscous fibre: 10 g or more daily (oats, barley, psyllium, pectin)	5-10%
Pulses: more than 1 serving or 130g daily (beans, peas, chickpeas, lentils)	5%
Low glycemic index dietary pattern	5%
Nuts: more than 30 g daily	5-7%
Soy protein: more than 30 g daily	3-5%
DASH dietary pattern	3%

*\*Adapted from the 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults.*

*\*\*National Cholesterol Education Program Step Diet*

*Before making changes to your diet, consult with your healthcare provider.*

Note that both diet and exercise are essential: a large study of several controlled trials found that dietary changes lowered LDL while exercise alone did not. However, adding aerobic exercise enhanced the lipid-lowering effect of a heart-healthy diet, according to Harvard Medical School.

Dr. Labos gives patients with a borderline intermediate-risk FRS an opportunity to decrease their LDL cholesterol with diet and exercise modifications first.

“A heart-healthy diet and sufficient cardiovascular exercise are important for everyone, whether or not they require cholesterol-lowering medication,” Dr. Labos said. ➔

Set nutrition and exercise goals and track your progress with Women Brain Health Initiative's BrainFit™ mobile app, a unique habit tracker designed to help you prolong cognitive vitality.

**“However, the reality is that it's very hard to bring down a high LDL with diet and exercise alone. You may be able to lower it by 10% to 15%, but not much more, because most cholesterol produced in the body is determined by genetics.**

#### MEDICATION OPTIONS

There are several medications that effectively suppress the production of excess LDL cholesterol.

Statins are a proven effective class of oral drugs for lowering LDL cholesterol. They work by blocking an enzyme your body needs to make cholesterol. Some common examples are atorvastatin (Lipitor®), rosuvastatin (Crestor®), and simvastatin (Zocor®).

Meta-analyses of observational studies have shown statins have a beneficial impact on dementia risk, according to the *Lancet* Commission. For example, a meta-analysis of 36 cohort studies found that statin use was associated with a 20% lower risk of all-cause dementia and a 32% lower risk of AD compared with untreated high LDL, with no difference between women and men. The study was published in *European Journal of Preventive Cardiology* in 2022.

**“Recently, statins have become a focus of Alzheimer's and dementia research due to their anti-inflammatory and antioxidant properties in addition to their cholesterol-reducing benefit,” said Dr. Mills.**

The side effects of statins may include muscle soreness and short-term brain fog, but these do not occur in most people and can be addressed by switching to a different statin or another medication type, Dr. Labos advised.

Beyond statins, other medication options for lowering LDL cholesterol include ezetimibe, PCSK9 inhibitors, and bempedoic acid.

Ezetimibe is an oral drug that helps prevent the absorption and storage of cholesterol in the liver and improves the cholesterol clearance from your blood. It may be prescribed alone or as an ingredient in a combination medication.

PCSK9 inhibitors, such as alirocumab (Praluent®) and evolocumab (Repatha®), are given by injection every three months. They prevent the breakdown of LDL receptors, especially in the liver, so more LDL receptors work to reduce your LDL cholesterol.

Bempedoic acid (Nexletol®) is an oral non-statin medication that reduces the amount of cholesterol made by the liver. Nexlizet®, made by the same manufacturer, combines bempedoic acid and ezetimibe in the same medication.

#### KEEP IN MIND

“It is important for women to realize their dementia risk increases starting in mid-life because it usually takes decades to develop. Menopause seems to be a tipping point where the seeds of cardiovascular and dementia-related disease processes get planted, and damage starts building up,” Dr. Mills said.

**“High LDL is a warning sign that vascular damage and inflammation may be occurring, and women should take action to mitigate their future risk of developing dementia.**

“High LDL cholesterol is bad for men. It's bad for women. It's bad for everyone,” Dr. Labos said. “The fact that women are under-treated for high LDL cholesterol is a detriment to their heart health and brain health. More women should pay attention to the increased risks associated with high LDL cholesterol and discuss treatment options with their physicians.” 🌐