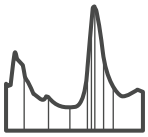
Labs to Identify High-density Lipoprotein (HDL) Risk

Learn which lab tests can help you better understand HDL and cardiovascular (CV) risk





HDL-C testing | HDL-P testing | HDL mapping | HDL-size and density | Surrogate markers

HDL-Cholesterol (HDL-C)

What does this test measure?	• This blood test measures the amount of cholesterol present within the HDL particles (HDL-P) in circulation.
Why would I test?	• In large cohort studies, very low levels of HDL-C were associated with increased risk of developing cardiovascular disease (CVD).[1-6] • HDL-C is closely linked with insulin resistance and is often part of an atherogenic dyslipidemia phenotype.[7] Finding low HDL-C can add to a picture of general metabolic risk.
What should I know?	• The relationship between HDL-C and CV risk is not linear (i.e., higher HDL-C is not more protective). • In a large cohort of 24,510 men and women, HDL-C levels above 75 mg/dL for men and 90 mg/dL for women did not provide any additional cardioprotective effects.[8] In a Japanese cohort, HDL-C greater than or equal to 90 mg/mL in both men and women was associated with increased CV mortality risk,[9] a finding echoed in a Northern European cohort, where it was found that HDL-C greater than or equal to 116 mg /dL for men and 135 mg /dL in women was linked with greater risk of CV mortality.[10] • In a cohort of 1,764,986 men who were United States veterans followed for ~10 years, a U-shaped curve was identified with HDL-C and all-cause mortality. Individuals at both ends of the curve (low and very high) were seen to be at greater risk of all-cause mortality.[11] • Clinical studies with cholesterol ester transfer protein (CETP) inhibitors failed to reduce CV risk despite raising HDL by 40-133%.[12-14] • Large cohort studies have shown that individuals with high HDL-C due to genetic variation are not protected against CVD.[15] • These newer data suggest that HDL-C measurement alone is not sufficient to understand CV risk. Additionally, HDL-C does not provide any information on HDL function. Studies show HDL can be dysfunctional when HDL-C are below or within normal values.[16]
Normal reference ranges?*	• Women: 50-90mg /dL • Men: 40-90mg /dL • Values > 90-135mg /dL for women and > 90-116mg /dL for men have been associated with increased CV risk[9,10]

*Reference ranges may differ between clinical laboratories

HDL-Particle Number	
What does this test measure?	• This blood test measures the number of HDL particles in circulation.
Why would I test?	• Data from multiple cohort studies has demonstrated that HDL-P is superior to HDL-C in assessing CVD.[17,18]
What should I know?	• The JUPITER trials showed HDL-P is a greater predictor of residual risk than HDL-C, cholesterol efflux capacity, or apoAI, when using potent statins as a therapy.[17,19] • Clinical cohort studies measuring HDL-P by both nuclear magnetic resonance (NMR) or Ion Mobility Spectrometry, have shown that HDL-P is inversely related to risk of developing heart disease.[20] • HDL-P was shown to correlate with cholesterol efflux capacity (spearman correlation coefficient of 0.39; $p < 0.0001$).[17]
Normal reference ranges?*	• Women and men: > 7,000 nmol/L[13,14]

*Reference ranges may differ between clinical laboratories

HDL Mapping

What does this test measure?

- HDL Mapping provides information on the 5 different subspecies of HDL molecules from pre-β-1 (small discoid particles with low levels of cholesterol and high capacity to accept cholesterol) through α-4, α-3, α-2, and α-1 particles, which get progressively larger and more spherical as they accumulate more cholesterol.

Why would I test?

- Lower levels of the larger α-1 particles are associated with the development of cardiovascular disease. Functional smaller pre-β-1 particles have a greater ability to accept cholesterol from peripheral cells through ABCA-1.[20] Larger particles (α-1) are responsible for efflux of cholesterol through SR-BI (from peripheral cells or to the liver).[21] Both components provide insights into the reverse cholesterol transport process and, HDL particle size may not be as important as initially thought.[21,22]

What should I know?

- In male participants of the Framingham offspring study, higher levels of the lipid-poor pre-β-1 HDL particles and lower levels of cholesterol-rich larger α-1 HDL particles were correlated with coronary heart disease risk.[22] These results suggest that maturation of pre-β-1 HDL particles into larger cholesterol-rich particles was impaired, which resulted in inadequate reverse cholesterol transport.[23]
- In the HDL-Atherosclerosis Treatment Study using a niacin-simvastatin combination, participants with the greatest increase in α-1 HDL particles halted progression of arterial stenosis.[24]
- In a group of subjects with raised triglycerides, pre-β-1 concentration was reduced compared to healthy controls.[21] However, the function and capacity for cholesterol efflux was significantly increased in the group with high triglycerides.[22]
- In subjects with type 2 diabetes, pre-β-1 concentrations were increased compared with controls; however, their HDL function was impaired.[25]
- These results in total indicate that the size and concentration of different HDL subspecies is not as clear cut as initially thought. All subspecies play an important role in reverse cholesterol transport, and subspecies function is important to understand.

Normal reference range*

Men	**Optimal**	**Borderline mg/dL**	**Increased Risk**
α-1	> 35.0	25.0-35.0	< 25.0
α-2	> 55.0	45.0-55.0	< 45.0
α-3	< 20.0	20.0-25.0	> 25.0
α-4	< 20.0	20.0-25.0	> 25.0
Preβ-1	< 20.0	20.0-25.0	> 25.0

Women	**Optimal**	**Borderline mg/dL**	**Increased Risk**
α-1	> 45.0	35.0-45.0	< 35.0
α-2	> 65.0	55.0-65.0	< 55.0
α-3	< 20.0	20.0-25.0	> 25.0
α-4	< 20.0	20.0-25.0	> 25.0
Preβ-1	< 20.0	20.0-25.0	> 25.0

*Reference ranges may differ between clinical laboratories

HDL Subclasses

What does this test measure?	• HDL subclasses measure the concentration of larger, more buoyant HDL2b and the smaller, less buoyant HDL3 in circulation.
Why would I test?	• Concentrations of HDL2 and HDL3 have been associated with reduced risk of cardiovascular disease.[26] • In more recent studies, higher levels of HDL3 were associated with reduced risk of developing arterial stiffness and reduced risk of developing coronary heart disease.[27]
What should I know?	• The literature supporting the link between HDL2, HDL3, and cardiovascular disease is mixed. A review of 80 studies highlights this variability, wherein several studies report a link between higher HDL2 and reduced cardiovascular risk; other studies report that higher HDL3 concentrations drive risk reduction.[26]
Normal reference range?*	• HDL-2 Cholesterol: 9-38 mg/dL • HDL-3 Cholesterol: 22-35 mg/dL

*Reference ranges may differ between clinical laboratories

Myeloperoxidase (MPO)

What does this test measure?	• This test measures levels of circulating a pro-oxidant protein expressed in and secreted from proinflammatory immune cells.
Why would I test?	• Circulating MPO is linked with increased risk of developing CVD and to greater risk of adverse events following a myocardial infarction (MI).[28,29] • HDL particles and the apoA-I proteins on HDL can be modified by MPO, causing them to become dysfunctional.[30]
What should I know?	• Several human studies implicate MPO in the development of atherosclerotic plaques.[31] • In a study of ~3,300 men and women, circulating MPO concentrations at baseline predicted the risk of development of coronary artery disease over an 8-year follow-up.[32] • Circulating MPO levels predict adverse outcomes following MI.[28,29] • MPO-modified apoA-I recovered from human atherosclerotic plaque showed impaired cholesterol efflux capacity and had potent proinflammatory activity on endothelial cells.[33] • Elevated circulating levels of MPO-modified apoA-1 was associated with increased CV risk in humans.[33] • In HDL isolated from healthy people, exposure to a pro-oxidant metabolite of MPO led to a reduction in HDL function as seen by a reduction in cholesterol efflux capacity and a failure to activate endothelial nitric oxide (eNOS).[34] Additionally, MPO-modified HDL increased the expression of vascular inflammation markers.[34]
Normal reference range?*	< 470pmol/L* cardiovascular risk; other studies report that higher HDL3 concentrations drive risk reduction.

*Reference ranges may differ between clinical laboratories

High-Sensitivity C-Reative Protein (hsCRP)

What does this test measure?	• This is a high-sensitivity assay to assess the concentration of C-reactive protein in circulation.
Why would I test?	• hsCRP is a biomarker of inflammation and, increased circulating concentrations are associated with an increased risk for developing cardiovascular disease.
What should I know?	• An inflammatory environment is associated with HDL dysfunction. In individuals participating in the the PREVEND (Prevention of Renal and Vascular End-stage Disease) study, higher hsCRP concentrations correlated significantly with lower cholesterol efflux capacity.[35]
Normal reference range?*	• < 1.0 mg /L is optimal

*Reference ranges may differ between clinical laboratories

Circulating ApolipoproteinA-I (apoA-I)

What does this test measure?	• This test measures the concentration of apoA-I in circulation.
Why would I test?	• apoA-I is the major protein on HDL and is involved in the transport of cholesterol from peripheral cells into the HDL particle.
What should I know?	• The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial showed HDL-P is a greater predictor of residual risk than HDL-C, cholesterol efflux capacity, or apoA-I, when using potent statins as a therapy.[17,19] • MPO-modified apoA-I recovered from human atherosclerotic plaque showed impaired cholesterol efflux capacity and had potent proinflammatory activity on endothelial cells.[33] • Elevated circulating levels of MPO-modified apoA-I was associated with increased CV risk in humans.[33]
Normal reference range?*	• Men: > 160 mg/dL • Women: > 180 mg/dL

*Reference ranges may differ between clinical laboratories

Research tests	
Paraoxonase (PON)	
What does this test measure?	• This test measures PON protein concentration associated with HDL. • Tests can also measure the activity of PON.
Why would I test?	• PON is a protein with antioxidant capacity that protects low-density lipoprotein (LDL) from oxidation.[29,30,36]
What should I know?	• Antioxidant activity of PON decreases with age.[37,38] • Several preclinical studies suggest that PON1 may play a role in supporting cholesterol efflux capacity.[39] • In the PREVEND study (n=6,029 people followed over 9 years), increased PON activity was associated with increased risk of developing CVD.[42] However, PON activity did not provide additional improvement in risk assessment beyond what traditional biomarkers could predict.[42] • In subjects with high HDL-C and hsCRP, decreased PON activity is associated with incident CVD risk.[41]
Normal reference range?	• Research tool

Cholesterol Efflux Capacity	
What does this test measure?	• This test commonly measures the movement or efflux of cholesterol from macrophages or foam cells into HDL.
Why would I test?	• Cholesterol efflux capacity is a measure of HDL function and is considered a surrogate marker of reverse cholesterol transport.[42] Cholesterol efflux capacity is inversely associated with the development of CVD and survival following MI.[35,43,44]
What should I know?	• In the PREVEND study (n=8592 with a follow-up of 12 years), a comparison of cases with cardiovascular disease compared with healthy controls with identical HDL-C and apoA-I levels, cholesterol efflux capacity from foam cells was significantly lower in cases.[35] Cholesterol efflux capacity was inversely associated with incident cardiovascular events.[35] • In a generally healthy population of men participating in the Health Professionals Follow-up Study, baseline cholesterol efflux capacity predicted the risk of developing cardiovascular disease.[45] However, controlling for baseline HDL-C removed the predictive power of cholesterol efflux capacity, indicating this test might not improve clinical decision making.[37] • In patients hospitalized with acute MI (n=1609), higher cholesterol efflux capacity was a strong predictor of survival.[46] Patients with higher cholesterol efflux capacity experienced a markedly lower rate of mortality after 6 years.[36] • The JUPITER trials showed HDL-P is a greater predictor of residual risk than HDL-C, cholesterol efflux capacity, or apoAI, when using potent statins as a therapy.[10,12]
Normal reference range?*	• Varies depending on method and cell type used • Research tool

HDL-Apolipoprotein E (apoE) content	
What does this test measure?	• This measures the concentration of the apoE on HDL particles.
Why would I test?	• In a study of 3696 men and women, higher apoE reduced the risk of developing coronary heart disease.[38] Those in the highest quintile of HDL-apoE had a 35% reduction in risk.[38]
What should I know?	• Only ~4% of HDL contains apoE.[38] • Tracer studies in humans show that presence of apoE on HDL leads to faster clearance through the liver, with this more rapid metabolism thought to reflect enhanced reverse cholesterol transport.[38] • apoE protective properties are blocked by the presence of apoCIII on the HDL particle.[47] This is thought to delay HDL metabolism and clearance, reflecting slowed reverse cholesterol transport.[38]
Normal reference range?*	• Research tool

HDL-Apolipoprotein CIII (apoCIII) content	
What does this test measure?	• This test measures the concentration of the apoCIII on HDL particles.
Why would I test?	• Increased apoCIII content of HDL is associated with an increased risk of developing coronary heart disease.[39]
What should I know?	• 6-8% of HDL particles have apoCIII present.[39] • The presence of apocIII on HDL appears to block protective properties of apoE. This is thought to delay HDL metabolism and clearance, reflecting slowed reverse cholesterol transport.[38] • The MESA (Multi-Ethnic Study of Atherosclerosis) study (n= 5675 men and women aged 52-72 years followed for up to 13 years) and DCH (Danish Diet, Cancer, and Health) study (n= 3642 men and women aged 51-64 years followed for up to 16 years) cohorts demonstrated higher apoCIII content of HDL increased the risk of developing cardiovascular disease.[39] • In nested case-control cohorts from the Nurses' Health Study and the Health Professionals Follow-Up Study higher levels of HDL without apoCIII lowered the risk of developing coronary heart disease.[40] • In a study of subjects with (n=140) and without (n=99) coronary artery disease, the apoCIII content of HDL was inversely correlated with cholesterol efflux capacity, indicating the presence of apoCIII impacts HDL-mediated cholesterol efflux capacity and HDL function.[41]
Normal reference range?*	• Research tool

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