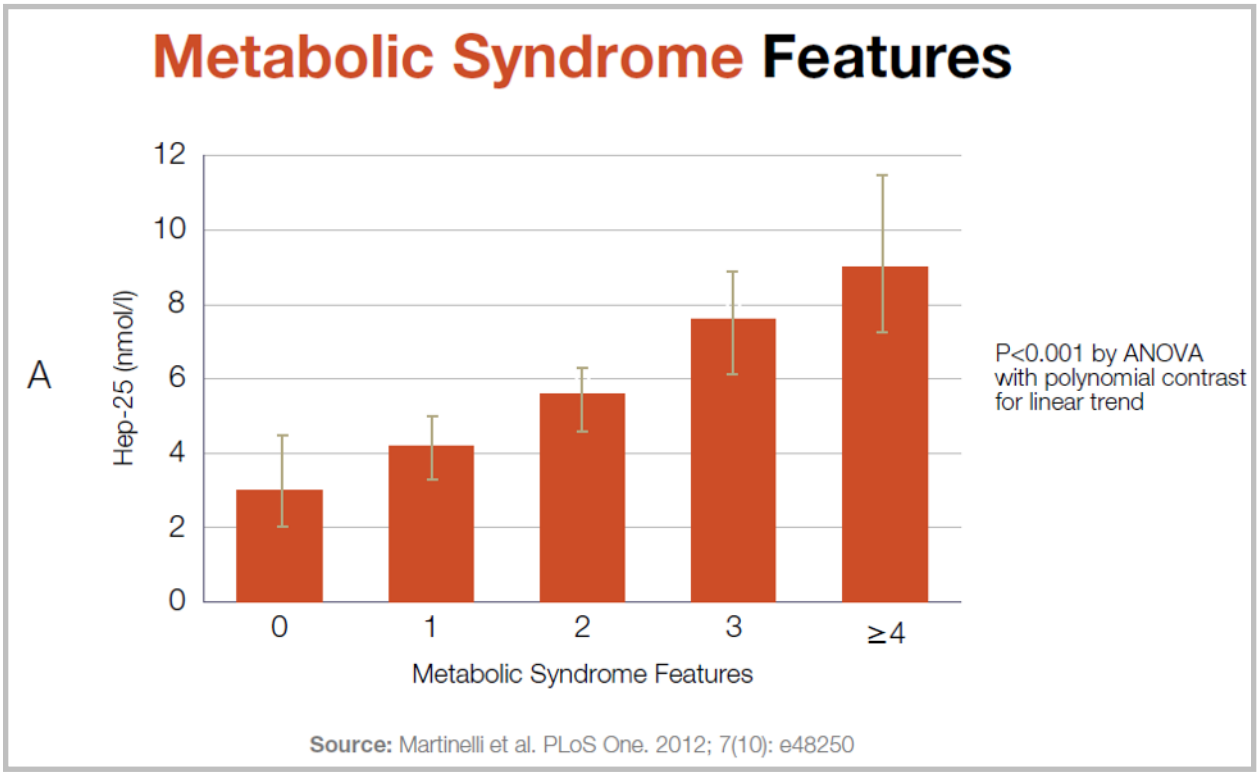
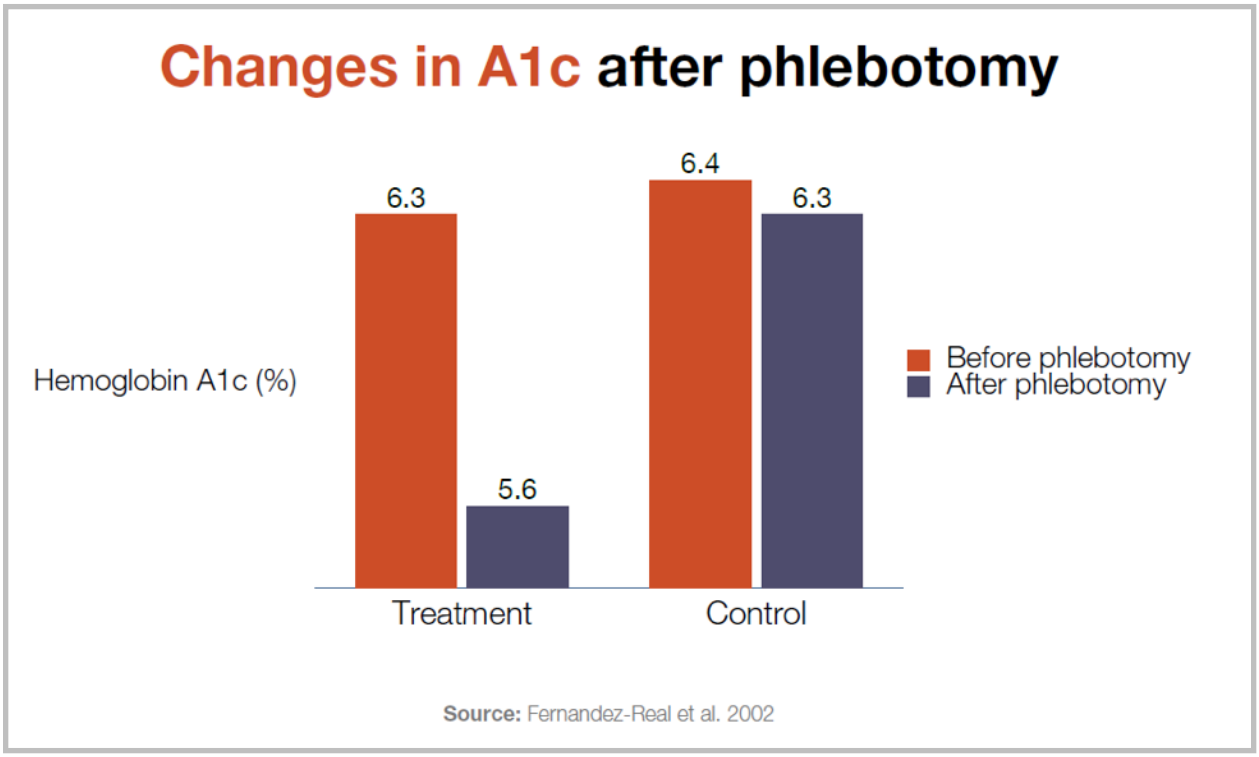
Another study found a linear increase in features of metabolic syndrome as hepcidin levels rose.

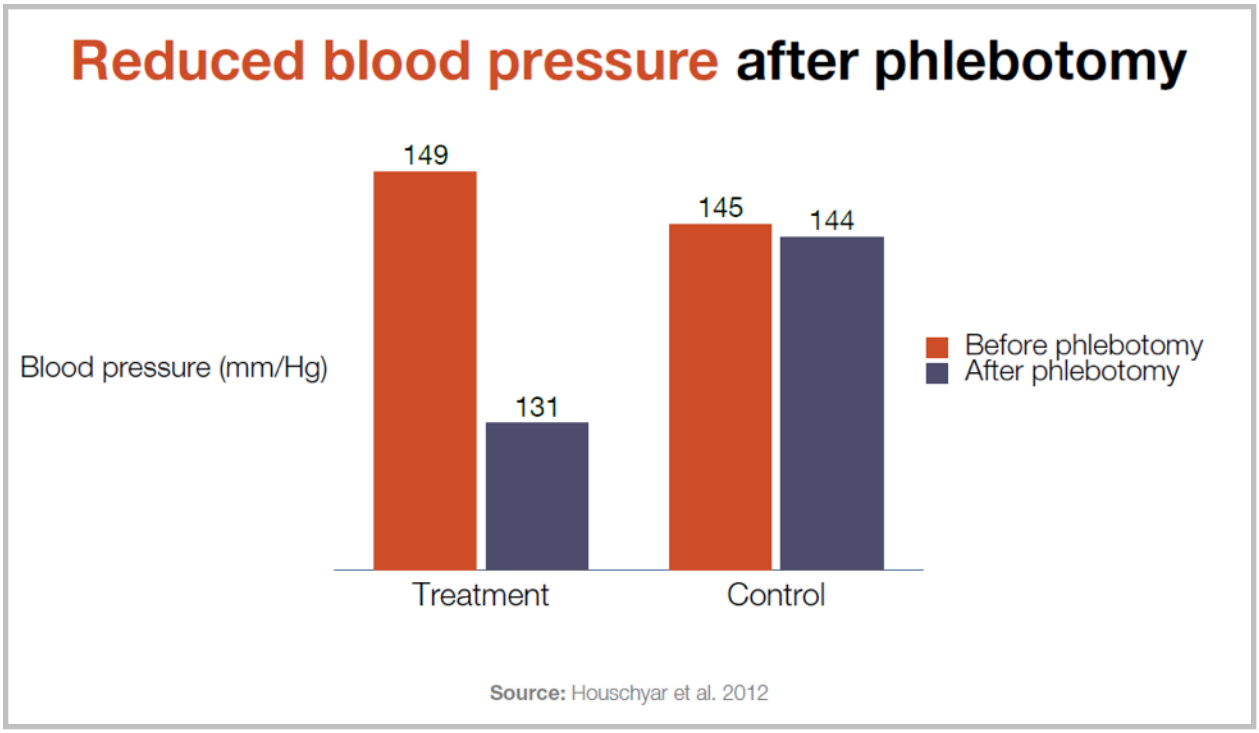


Hepcidin is the key iron regulatory hormone. It was discovered in 2000. It's produced by the liver in response to increased plasma or tissue iron to homeostatically down-regulate absorption and recycling of the metal. It acts by binding and inactivating its cell membrane receptor ferroportin, which is the only known cellular iron exporter. Hepcidin is also up-regulated by inflammatory cytokines, which is a response believed to contribute to host defense by subtracting iron from invading pathogens.

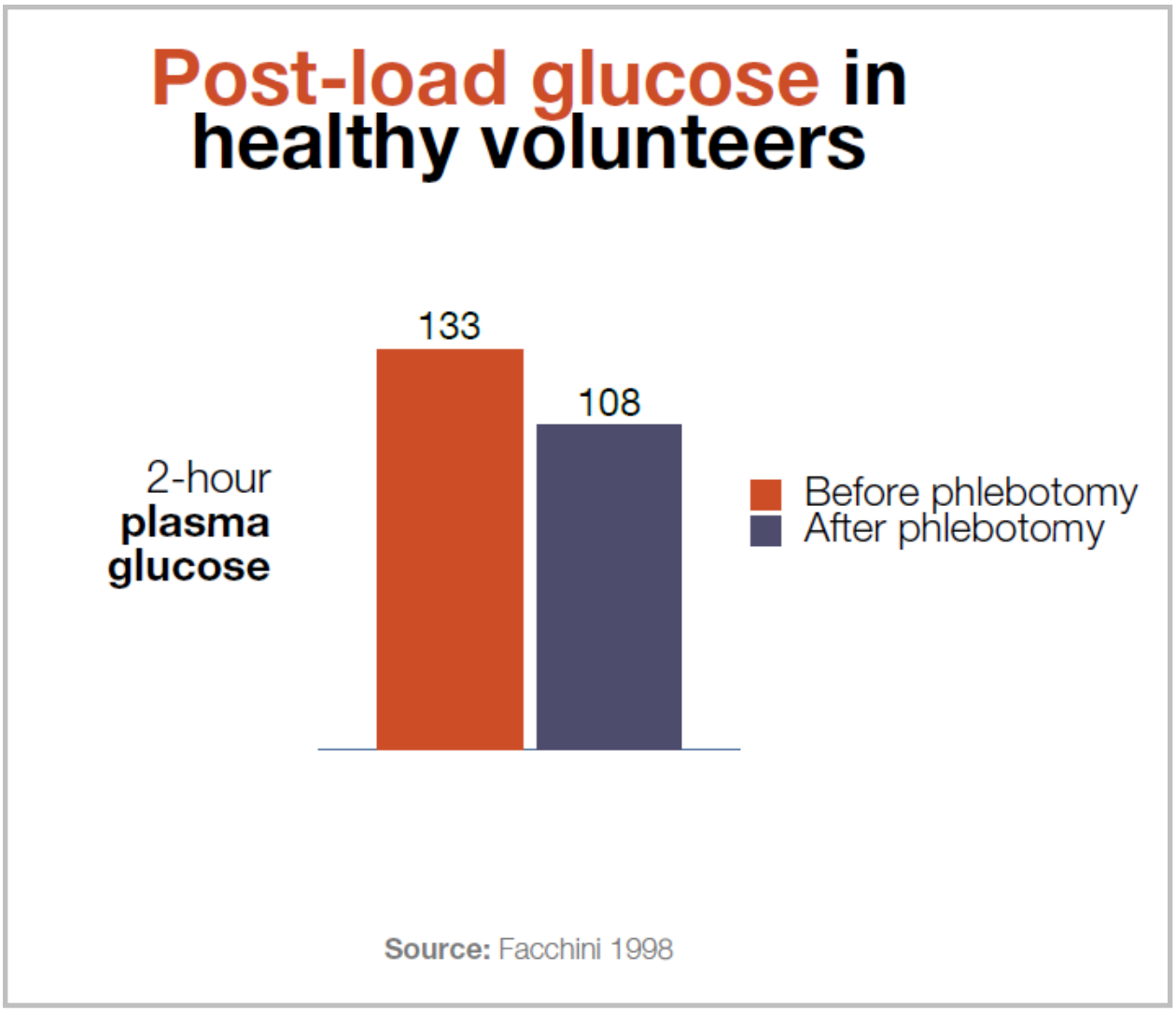
Other interesting lines of evidence supporting the connection between excess iron and metabolic syndrome include the observation that increased iron levels predict future diabetes. For example, frequent blood donors have lower rates of diabetes. People with elevated ferritin tend to have higher rates of hypertensive retinopathy, and those with hypertension have a higher prevalence of iron overload.



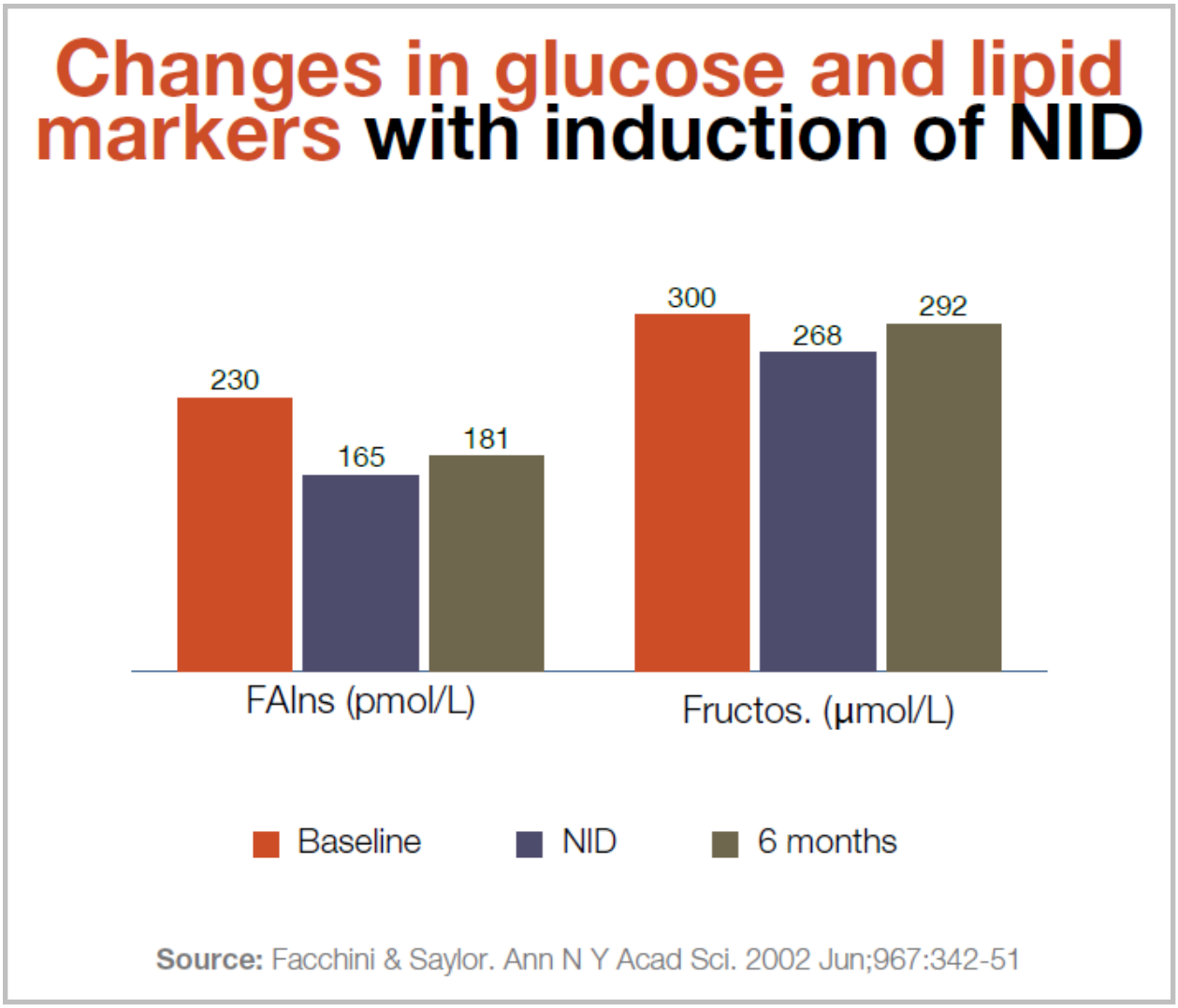
Of course, none of these associations prove causality. It could be that high blood sugar causes an increase in iron, right? But, actually, we have a significant amount of evidence that shows that reduction of iron levels restores normal glucose levels and normal insulin sensitivity. For example, in one trial with 25 patients—the chart here on this slide is from that trial—25 patients with high ferritin diabetes were separated into two groups. One group had three phlebotomies over a three-week period, and the other had no treatment. As you can see, those who had phlebotomies had significantly decreased hemoglobin A1c levels and C-peptide levels, as well as increased insulin sensitivity when compared to controls. This was especially striking given that these changes persisted for at least one year after the phlebotomies were finished.



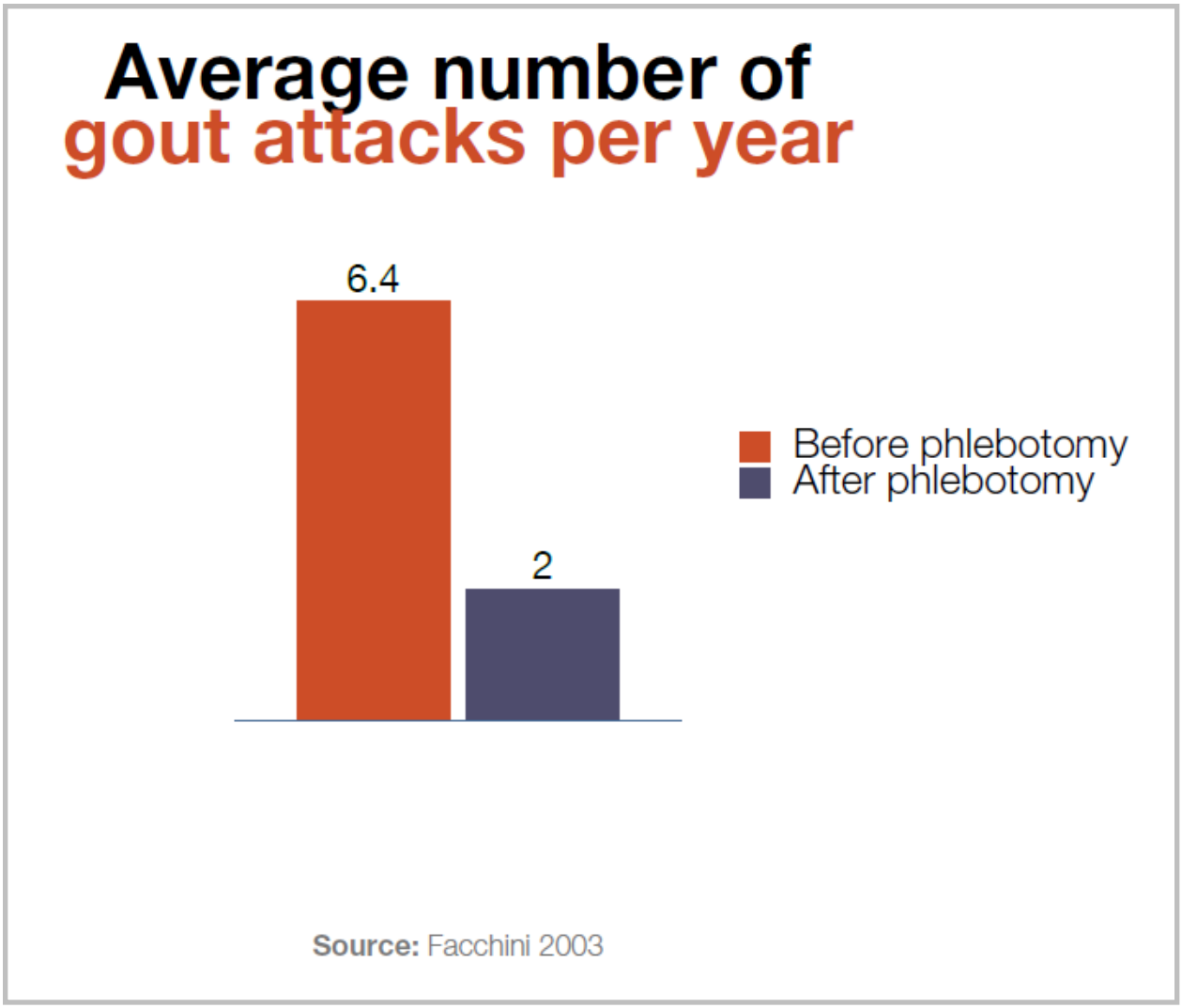
Here is another study of 64 patients with metabolic syndrome, and they found that phlebotomy, or removal of blood, which decreases iron levels, decreased blood pressure, resting heart rate, fasting glucose, hemoglobin A1c, and the LDL-to-HDL ratio.



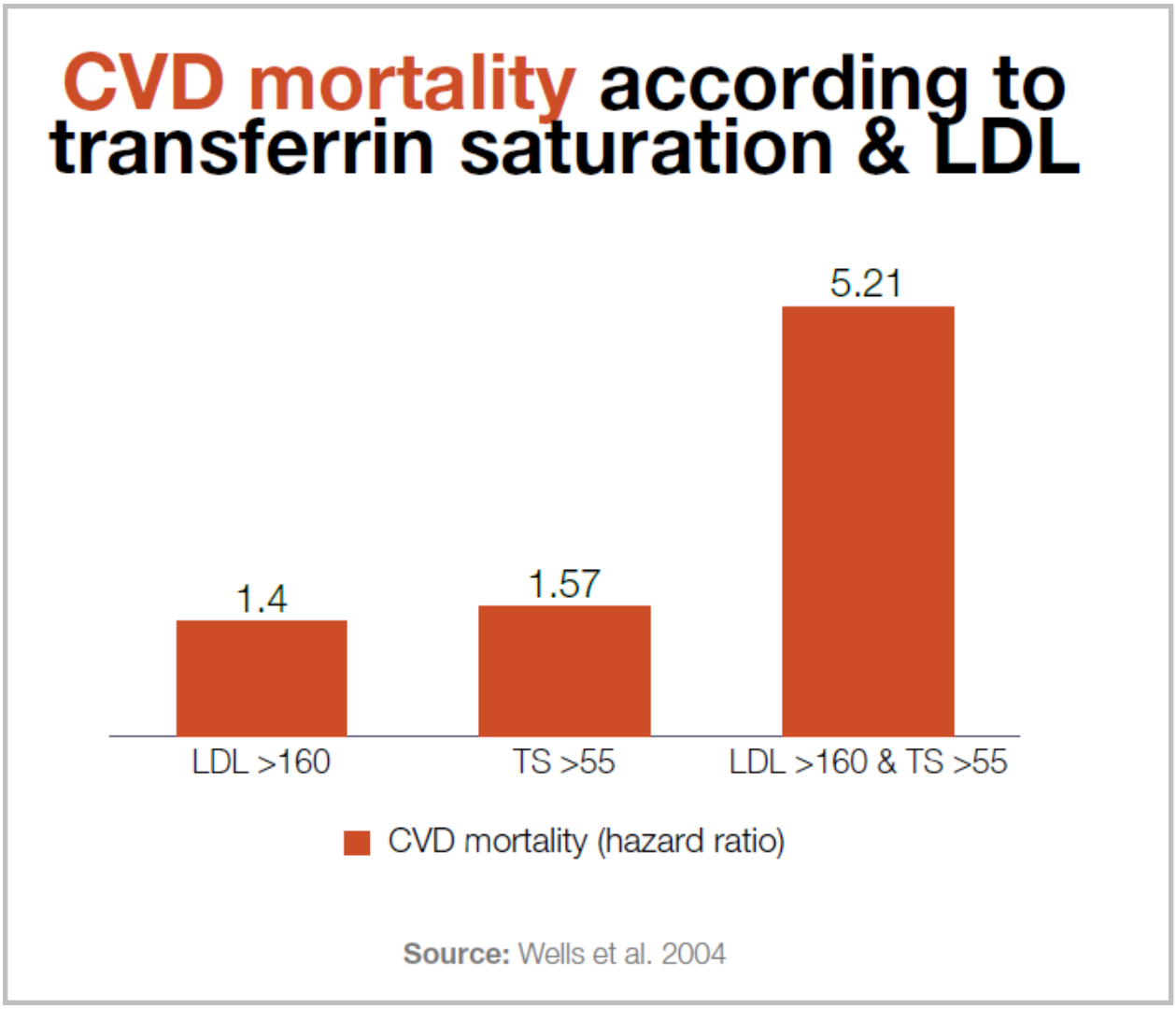
This effect isn't limited to patients with diabetes and impaired glucose tolerance. Even healthy volunteers with normal glucose and ferritin levels had decreased two-hour post-meal insulin one month after a single blood donation.



Iron depletion to near-iron deficiency, which means getting ferritin levels to the point where the patient is nearly iron deficient, decreased fasting and post-meal glucose, hemoglobin A1c, fructosamine, and lipid markers in healthy volunteers with normal iron levels and no mutations commonly associated with iron overload. These effects were largely reversed by a six-month period of iron repletion with re-institution of iron sufficiency.

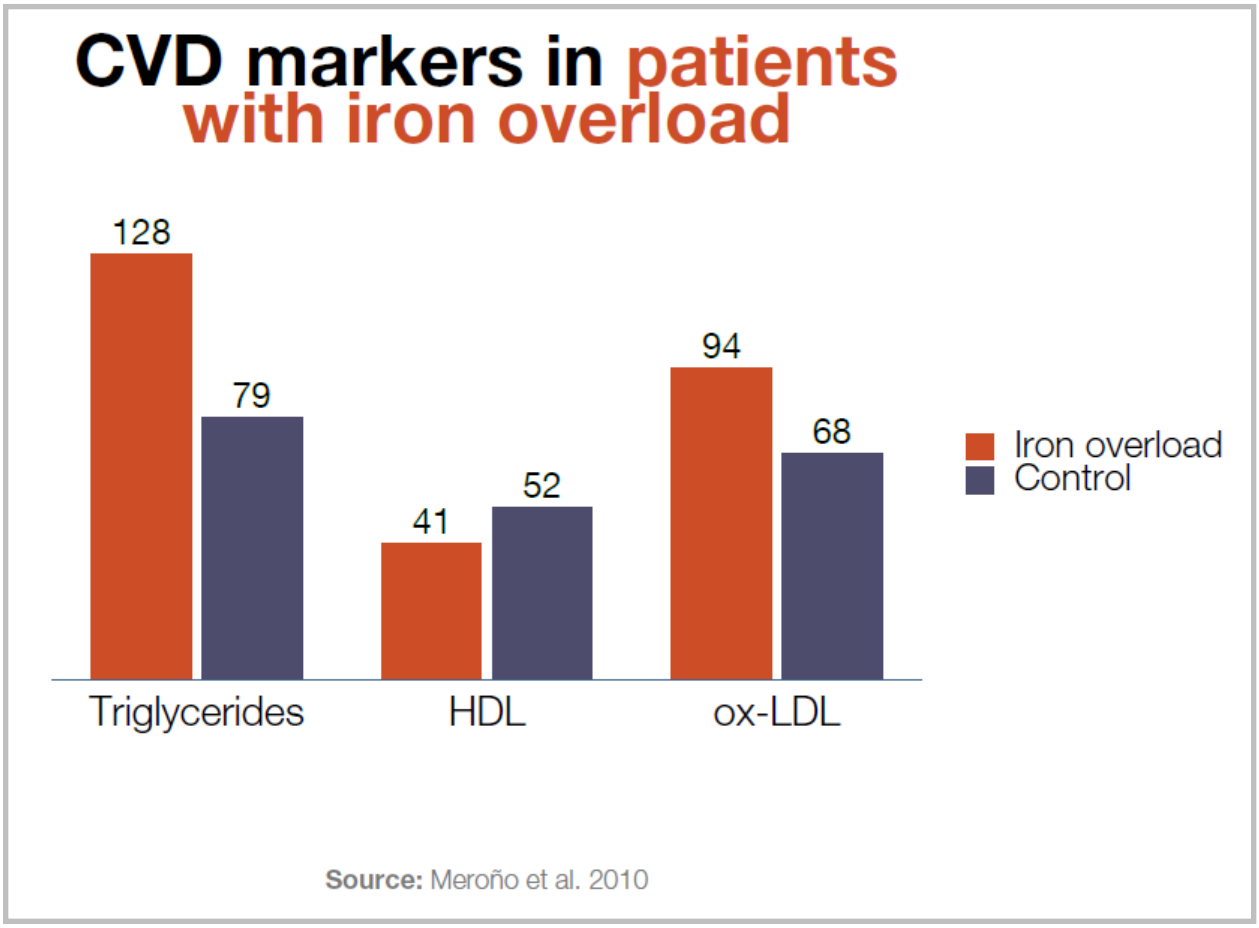


Another study of patients with gout but without iron overload found that induction of near-iron deficiency reduced the average number of gout attacks from 6.4 to two. Near-iron deficiency prevented relapse in 58 percent of patients with gout and significantly reduced the frequency and severity of gout in 48 percent of the patients.

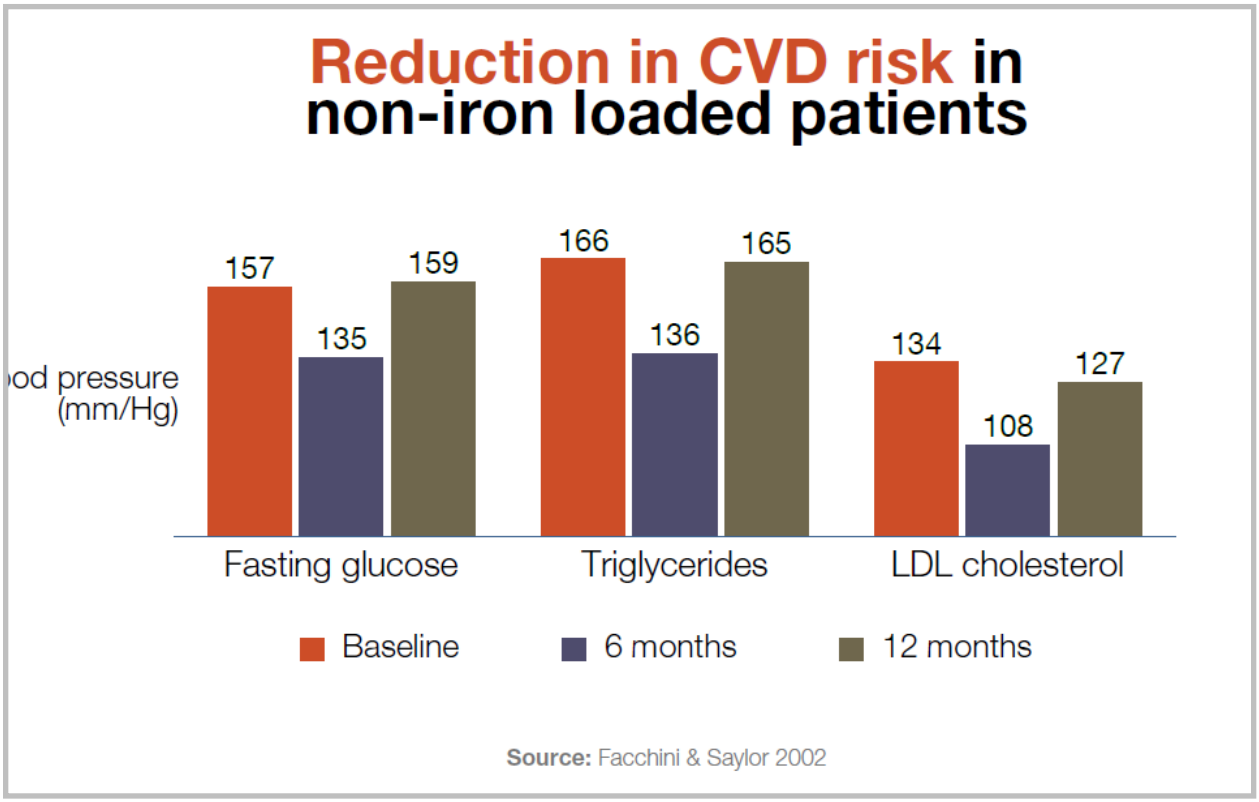


Iron overload is also associated with an increased risk of death from cardiovascular disease, even in healthy people. According to a study of 3,410 U.S. adults, 27 percent of them had LDL levels above 160 mg/dL, and 1.64 percent had transferrin saturation levels above 55 percent. Now, if they only had elevated LDL or transferrin saturation, their relative risk of death from cardiovascular disease was 1.4 or 1.57, respectively, but if both LDL and transferrin saturation were elevated, their relative risk was 5.21, so a hugely significant difference. In other words, if you have LDL above 160 and transferrin saturation above 55 percent, you have a fivefold higher risk of death from cardiovascular disease compared to those with LDL below 160 and transferrin saturation below 55 percent. You also have a 3.8-fold higher risk of death from all causes.

The likely mechanism for this link is that iron oxidizes lipids and free fatty acids. Free fatty acid oxidation reduces glucose uptake and causes gluconeogenesis in the liver, which leads to insulin resistance. Iron is also a catalyst that promotes free radical production and contributes to oxidative damage and inflammation.



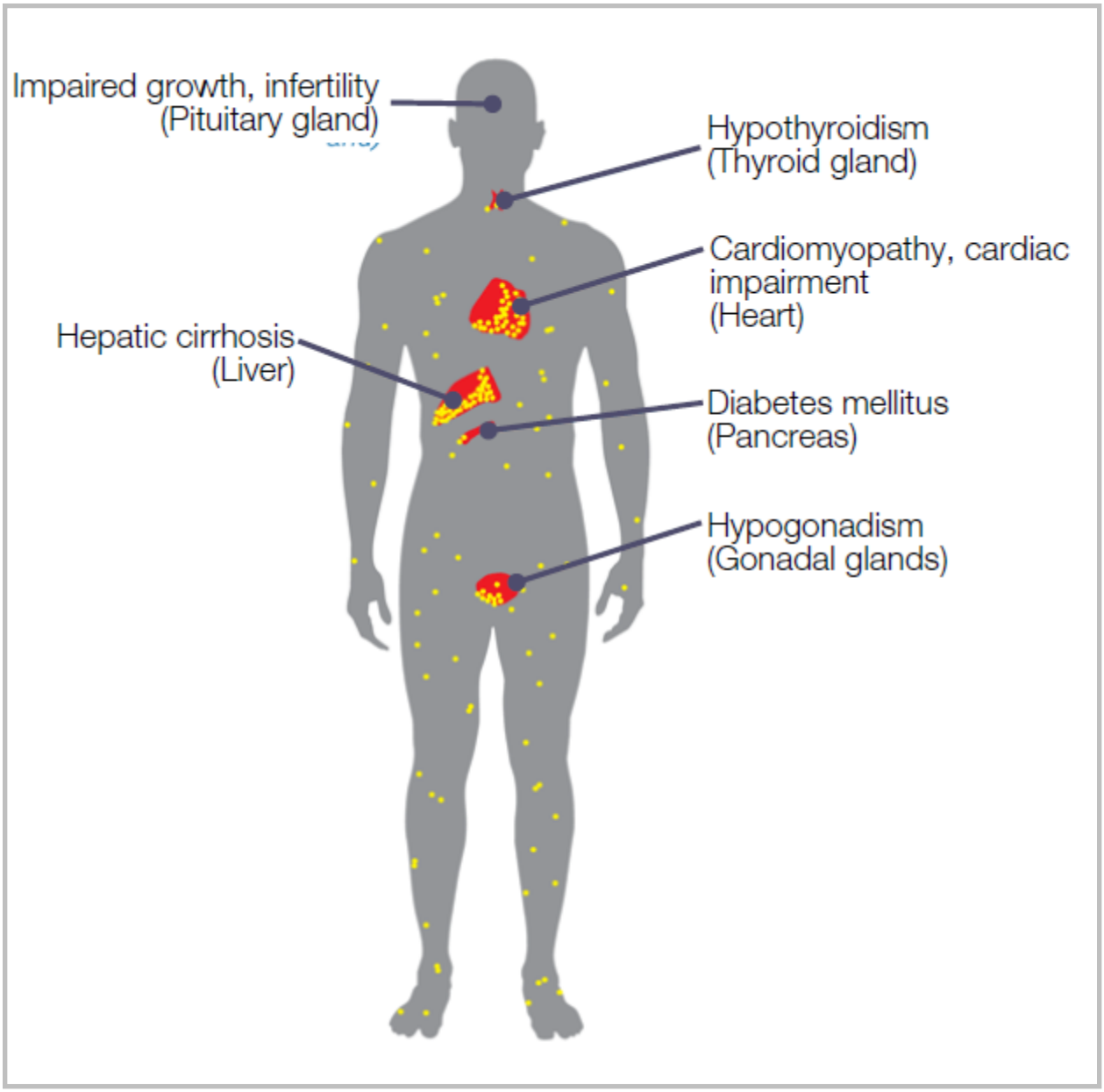
This may explain why iron overload leads to increased levels of oxidized LDL. One study of 40 male patients found that those with high iron levels had 40 percent higher levels of oxidized LDL along with higher levels of other markers associated with cardiovascular disease such as CETP, Lp-PLA2, and triglycerides and then lower levels of HDL and reduced activity of antioxidant enzymes.



Even people at high risk of cardiovascular disease who are not iron loaded benefit from iron reduction. A study of 31 carbohydrate-intolerant people with normal iron levels found that inducing near-iron deficiency with phlebotomy increased HDL levels and reduced fasting glucose, total and LDL cholesterol, triglycerides, and fibrinogen. These effects were reversed after six months of iron repletion when their iron levels returned to normal, as you can see here on this slide.

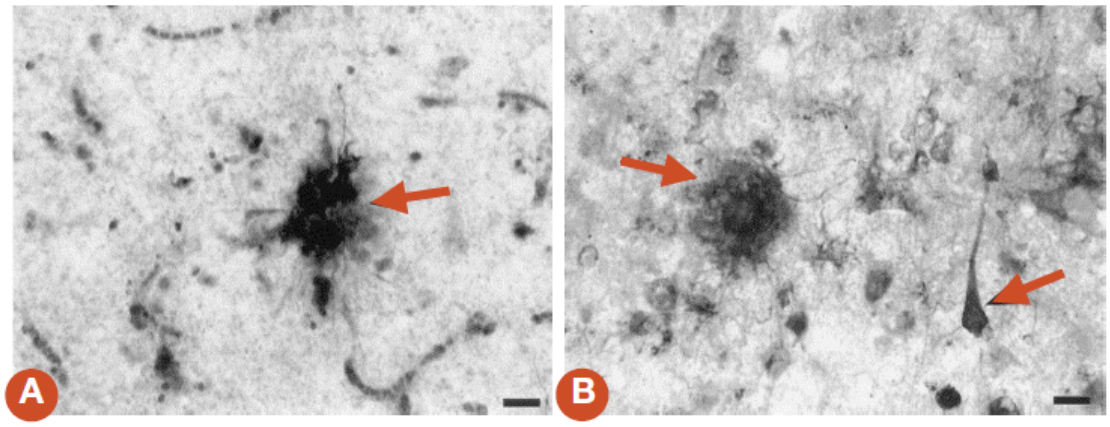
Some researchers believe that iron status explains the difference in heart disease rates observed between men and women. We've known for some time that premenopausal women have lower rates of heart disease than men, but that advantage disappears when women enter menopause. The early hypothesis, as I'm sure you know, is that estrogen was to blame, that there is some protective effect of estrogen. Women go into menopause, and their estrogen levels go down, and that's why they start to get heart disease at the same rate as men. When this was tested clinically, it went terribly wrong. Postmenopausal women who were given estrogen in all of the HRT trials actually experienced a doubled risk of heart disease.

The iron hypothesis suggests that the beneficial effect of iron depletion is what explains the difference. Men begin accumulating iron from the day that they are born. Women don't acquire it because of menstruation and childbirth.



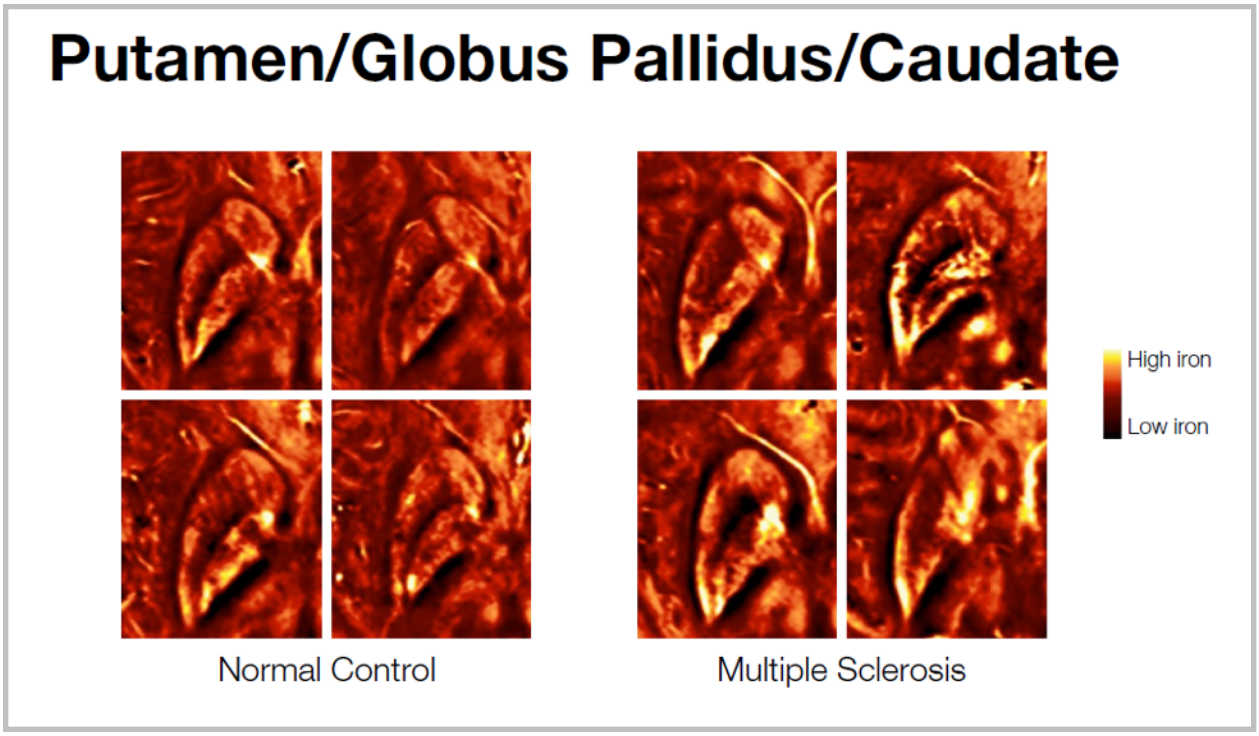
Women with diabetes, lupus, and PCOS have similar rates of heart disease to men. What do these diseases have in common? They are all associated with increased iron levels.

This is your brain on iron

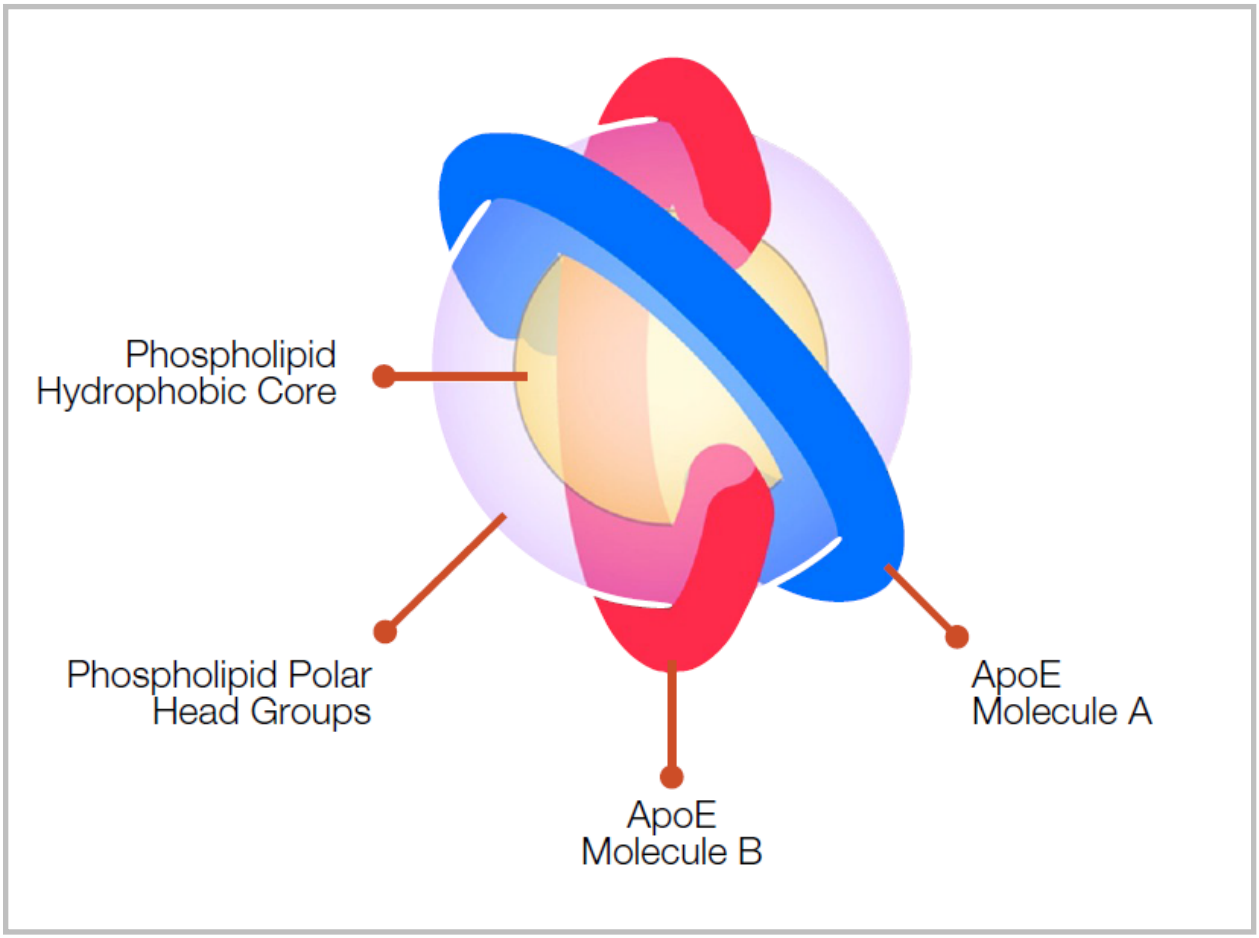


Iron in **neuritic plaques** in Alzheimer's diseased brains

In addition, iron is associated with an increased risk of cardiovascular and endocrine disorders. Iron causes oxidative stress and neuronal damage in the central nervous system. Brain iron levels increase with age, even without mutations that cause excess iron storage. Excessive iron has been found in the brain of Parkinson's patients and in the plaque of patients with Alzheimer's.



Iron overload in the brain has been observed in other conditions involving the central nervous system, including MS, ALS, Huntington's disease, stroke, and cerebral hemorrhage. Studies have shown that the iron chelator desferrioxamine can slow the progression of dementia.



The role of iron in the oxidation of LDL is likely the common mechanism behind its role in heart disease and neurocognitive disorders, and this is especially true in carriers of APOE4. We know that carriers of APOE4 are at increased risk for both cardiovascular and neurodegenerative disease. APOE4 carriers have also been shown to be more susceptible to oxidative damage and have higher levels of oxidized LDL. This suggests that people with APOE4 are more vulnerable to the harmful effects of oxidative stress, and it may explain the higher rates of cardiovascular disease and Alzheimer's in patients with iron overload.

Prevalence of symptoms of iron overload

Symptom	Reported
Extreme fatigue	46%
Joint pain	44%
Impotence (or loss of libido)	26%
Skin bronzing	26%
Palpitations	24%
Depression	21%
Abdominal pain	20%

Source: Iron Disorders Institute 2004

Okay, so now that you have a better grasp of the scope of this problem, how often it's misdiagnosed, and how serious it can be, let's talk a little bit about diagnosis. The signs and symptoms of iron overload are nonspecific, and this is another reason why it is often missed. The number one sign is extreme and unexplained fatigue. The number two sign is joint pain. The number three sign is impotence, loss of libido, or some kind of sexual dysfunction. Then we have skin bronzing, palpitations, depression, and abdominal pain. None of those are specific to iron overload, and they look a lot like just common symptoms that you see in practice.

Reference ranges for iron markers

Marker	Men	Pre-menopausal women	Post-menopausal women
Serum iron	40–155 ug/dL	40–155 ug/dL	40–155 ug/dL
Serum ferritin	30–400 ng/mL	15–150 ng/mL	15–150 ng/mL
Transferrin saturation	15–55%	15–55%	15–55%
TIBC	250–450 ug/dL	250–450 ug/dL	250–450 ug/dL
UIBC	150–375 ug/dL	150–375 ug/dL	150–375 ug/dL
sTfR	12.2–27.3 nmol/L	12.2–27.3 nmol/L	12.2–27.3 nmol/L

Let's talk a little bit about serum markers for iron overload. Here are the laboratory reference ranges for iron markers, and you'll recall these from the iron deficiency presentation. This slide is the same. Note that serum iron levels are not accurate for iron overload, just as they are not particularly accurate for iron deficiency, but they are even less so for iron overload because serum iron can be low when the patient has hemochromatosis.

Functional ranges for iron markers

Marker	Men	Pre-menopausal women	Post-menopausal women
Serum iron	40–135 ug/dL	40–135 ug/dL	40–135 ug/dL
Serum ferritin	30–200 ng/mL	30-100 ng/mL	30-100 ng/mL
Transferrin saturation	17–45%	17-45%	17-45%
TIBC	275–425 ug/dL	275-425 ug/dL	275-425 ug/dL
UIBC	175–350 ug/dL	175-350 ug/dL	175-350 ug/dL
sTfR	14.5-25 nmol/L	13-25 nmol/L	14.5-25 nmol/L

I've listed the functional ranges again for iron markers on this slide. They're the same from the iron deficiency presentation as well. The Iron Disorders Institute recommends achieving serum ferritin levels below 100 ng/mL during treatment and then maintaining serum ferritin in a range of 25 to 75 ng/mL for optimal risk reduction. However, 200 for men and 100 for women is recommended as a cutoff for screening. There is still a little bit of controversy and disagreement on this, so I have chosen to make 200 the upper limit for men and 100 the upper limit for women along with the Iron Disorders Institute, but, of course, we're always paying attention to all of the other markers in the iron panel as well. I'm going to give you an algorithm to follow for determining who is at risk.

Iron saturation should be below 45 percent, according to several studies. That would be the lowest screening value that could be used to identify people at risk of iron overload without unnecessary testing of unaffected individuals, and using this level identifies 98 percent of people who are homozygous for HFE mutations and 22 percent of heterozygotes.

There is less data to support a functional range for serum iron, TIBC, UIBC, transferrin saturation, and soluble transferrin receptor, so I've simply narrowed the range in some cases here, and that should be interpreted in the context of ferritin and iron saturation.