Dr. Paul Mason lecture on 'The truth about high cholesterol'

Version 1.0

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<https://youtu.be/rdgS3PuSuyg>



I'm Dr Paul Mason, this lecture is about the science which contradicts nearly everything I learned about LDL in medical school.

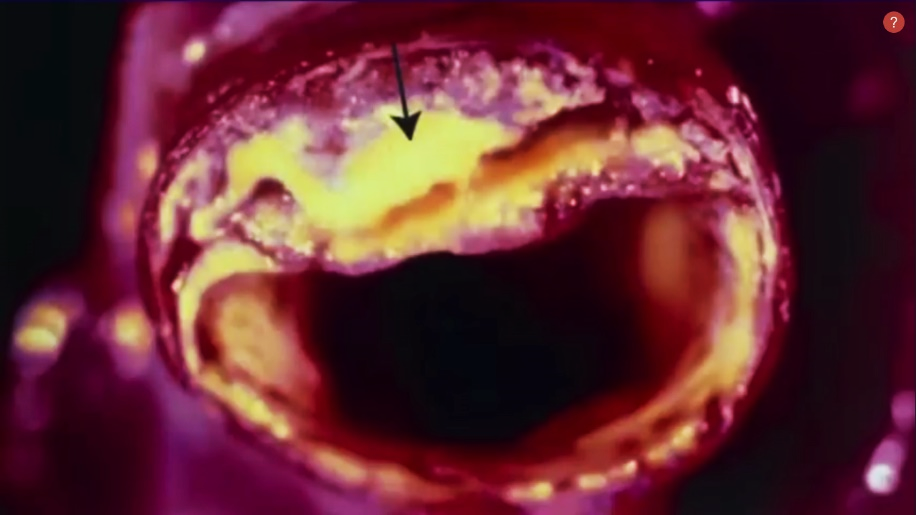
You may have seen this anti-smoking ad:



This is part of an aorta main artery from the heart. Smoking makes artery wall sticky and collect dangerous fatty deposits. This much was found stuck to the aorta wall of a smoker age 32.



Until recently we tended to blame this disease on the fat and cholesterol within our diet.



This is known as the *lipid hypothesis* simplistically eating fat causes our LDL level to rise which then blocks our arteries and unfortunately when President Eisenhower had his heart attack in 1955, this was the reasoning wheeled out by the most vocal and influential scientists of the time.



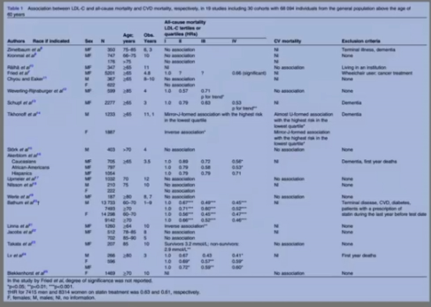
This put the lipid hypothesis on track to haunt us for generations to come.

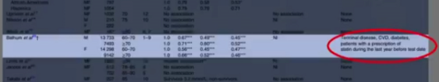
The question is: what is the evidence that high LDL will kill you?

This systematic review[[1]](#footnote-1) answered that question 19 prospective cohort studies with over 68,000 participants were reviewed and the overwhelming finding was that individuals with the highest LDL levels lived *the longest*.



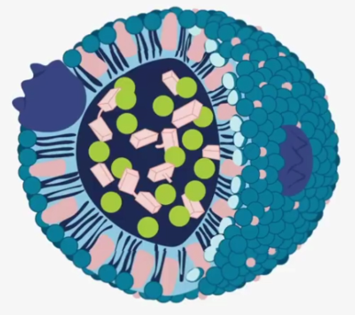
In fact, 16 of the 19 studies found this relationship the higher the LDL level the lower the chance of death and it didn't matter how your sliced it or diced it.





Comparing the very highest LDL group with the lowest or just the second lowest high LDL levels came out on top even when study subjects with terminal diseases heart disease diabetes were excluded the results stayed the same this study found about a 50% reduction in the chance of death in the highest LDL group compared to the lowest. In a nutshell the findings of this systematic review are robust and dismissing or ignoring them is *scientific fraud*.

Let's take a look at exactly what LDL is. You may be surprised to see that it doesn't have horns.



It might also surprise you to see how complex it is, in fact the body devotes a lot of resources to producing it. It's a complex structure called a *lipoprotein*.

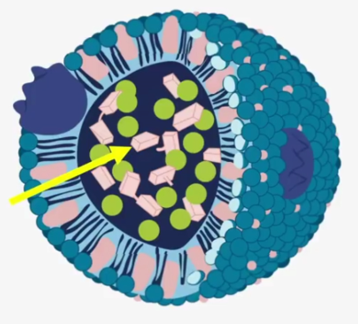
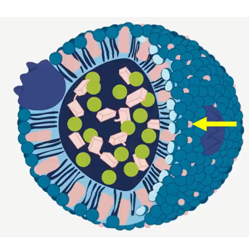
It's made a fat cholesterol and protein and remember the term lipoprotein.

You've probably come to associate LDL with cholesterol though maybe even mistake one for the other in fact many doctors do.

They often talk about LDL and cholesterol like they're the same thing.

The thing is LDL is so much more than just cholesterol.

Here you can see that LDL carries cholesterol bound to fatty acids as cargo while also containing cholesterol penetrating its surrounding membrane.

Clearly LDL is more than just cholesterol still both cholesterol and LDL particles can be found in atherosclerotic plaques so does it have a *causative role* scientifically speaking. This is what guilt by association looks like:

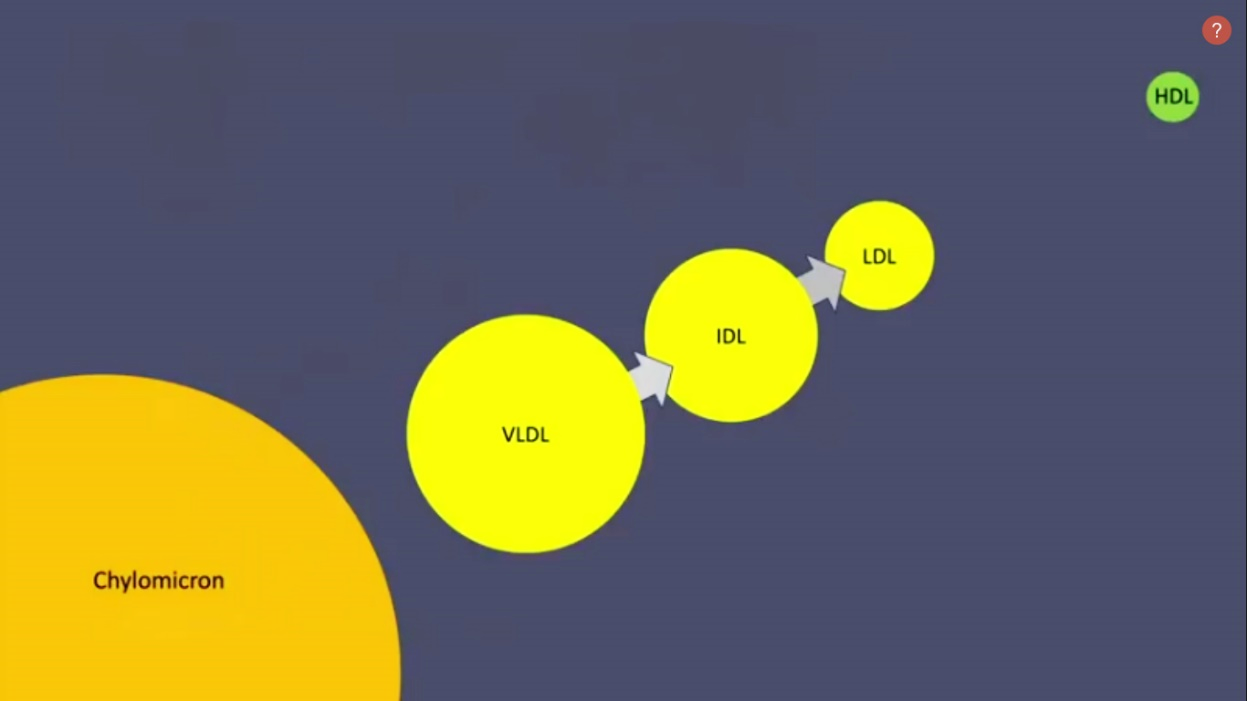


nonsense

it's confusing *correlation* with *causation*. Just because two things exist together at the same time doesn't mean one caused the other.

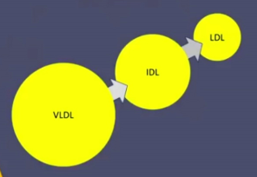
So, let's now take a closer look at all the lipoproteins.

The first thing to understand is that LDL is only one of five major classes of lipoprotein the most obvious difference between them being *by size* the lipoprotein on the bottom left is called a Chylomicron and it's formed after we eat.



By the time we do a fasting blood test though mostly this is disappeared so we don't need to worry about that anymore up in the top right you can see HDL which is colloquially known as *good HDL.*

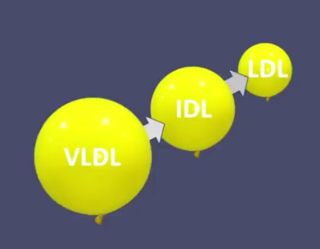
For the moment though I just want to focus on the three lipoproteins in the middle. The LDL, IDL and VLDL.



This stands for very low-density, intermediate density and\* very-low-density lipoprotein the smaller the lipoprotein the density is and you'll observe that rather than show them separately. I've linked the more with arrows and that's because in essence they are all the same particle given these lipoproteins defined by size as it shrinks.

Think of LDL as a balloon with a slow leak. given these lipoproteins are

defined by size as it shrinks it arbitrarily becomes another type of

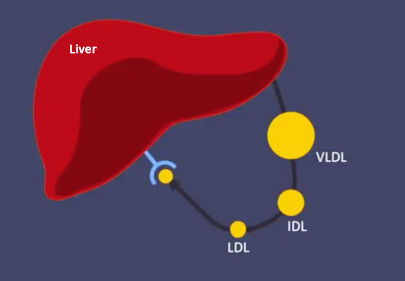


lipoprotein eventually becoming LDL. So, in essence LDL is just a shrunken form

of VLDL and VLD shrinks as it delivers its lipid cargo to various tissues around the body because well that's its job. So where does VLDL come from in the first place?

It's made by the liver.

It then circulates around the blood delivering its liquid cargo first becoming an intermediate density lipoprotein and finally a low-density lipoprotein LDL is then taken back up by the liver for recycling.



I'd like to take a detour for a moment and address the longstanding myth that *dietary cholesterol* and *dietary saturated fat* increase LDL levels.

Examine this diagram and ask yourself what factors could increase LDL levels.

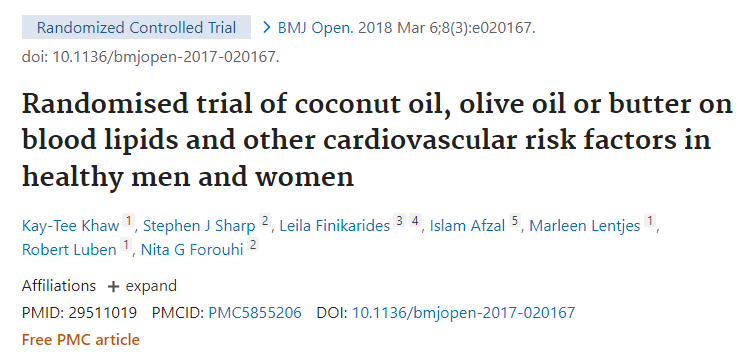
Increase production of the LDL precursor of the LDL could be one.

Another is by reducing the reuptake back into the Liver.

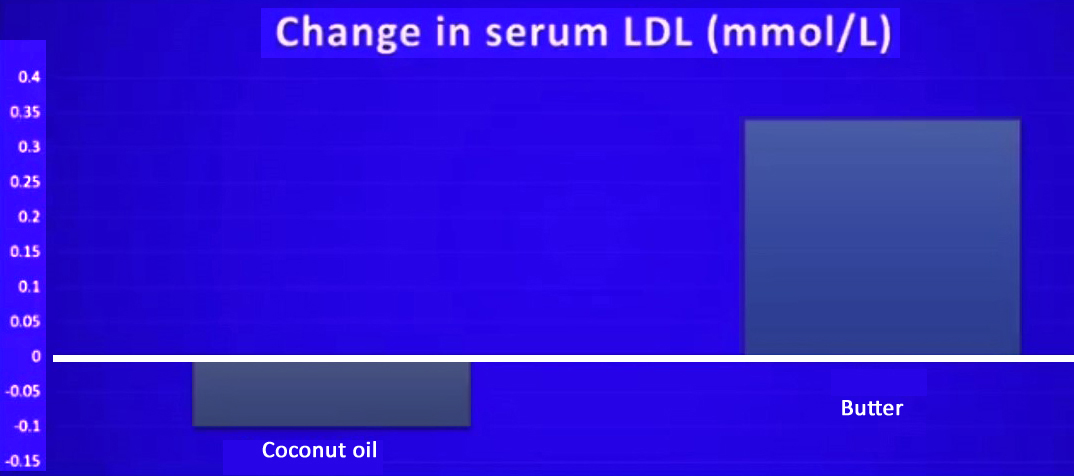
Here's the thing though: cholesterol and saturated fat do neither. If dietary cholesterol increased LDL, then one would presume that by consuming 7,000 milligrams daily of cholesterol would lead to high LDL levels.

And in this quite fabulous study they fed patients 35 eggs daily for a month[[2]](#footnote-2) their cholesterol levels remained normal nor does saturated-fat increased LDL.

Consider this randomized controlled trial[[3]](#footnote-3) which case subjects 50 grams of either coconut oil, olive oil or butter before weeks compare what happened in these subjects who consume the coconut oil which contained 94% saturated fat to those consuming butter containing 66% saturated fat this is what happened:

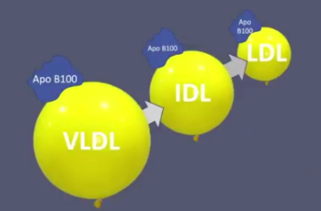
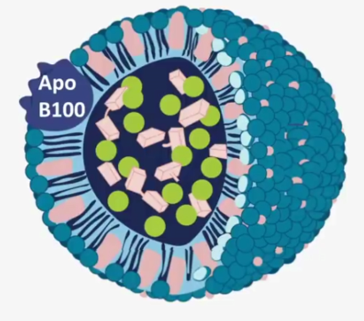


In the coconut oil group, their LDL level dropped.

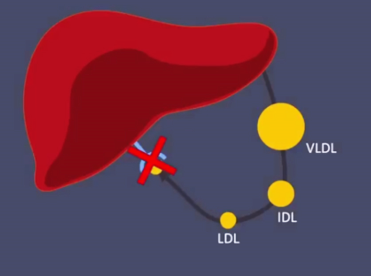
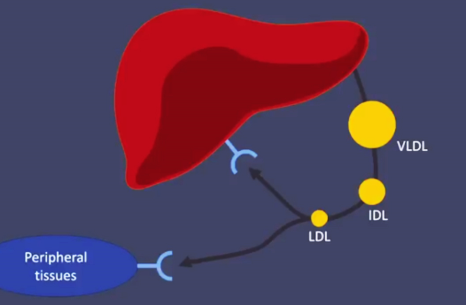


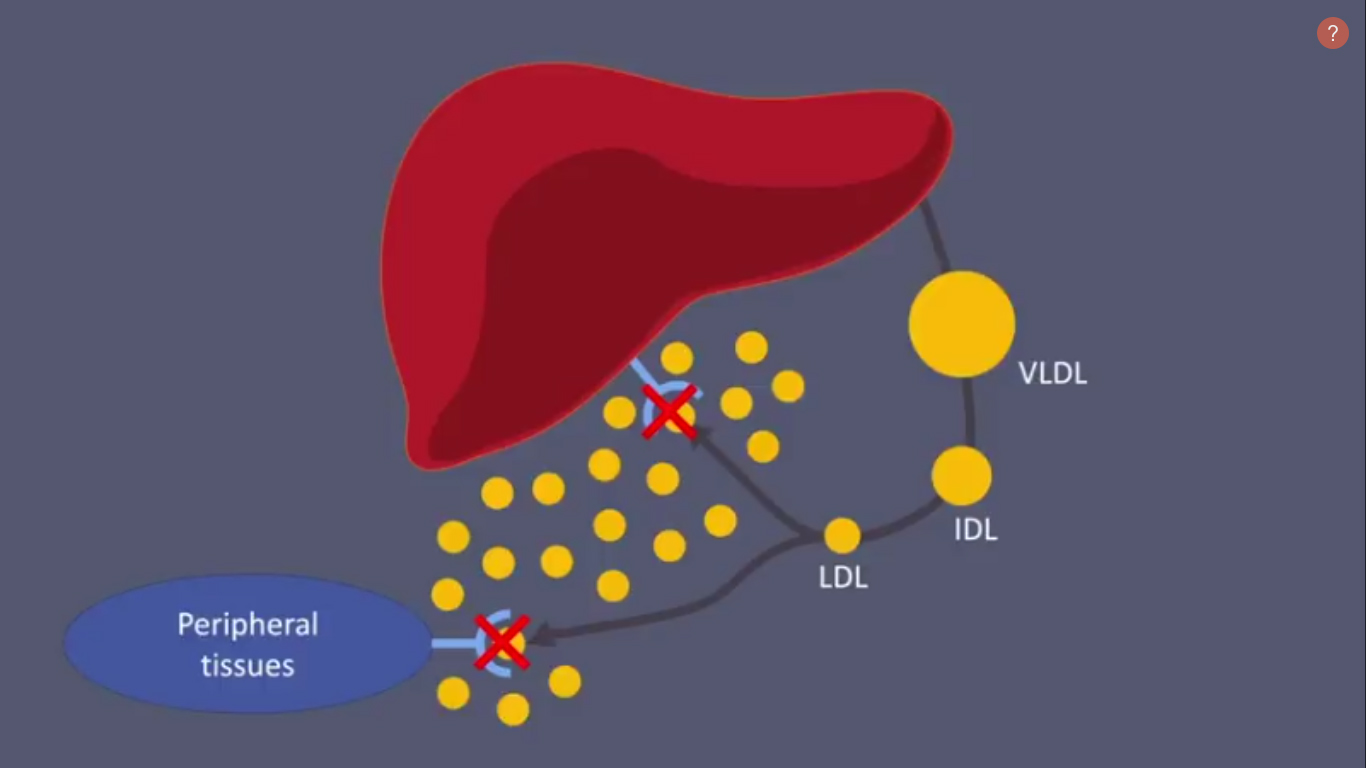
This saturated fat causes LDL to rice. *Theory isn't looking so good anymore* and despite containing far less saturated fat, the butter led to a significant *increase* in LDL!

So let's now get back to our lipoproteins the LDL ideal and LDL now each of these particles being essentially the same they carry the same unique identifying protein in their membrane is called APO B100

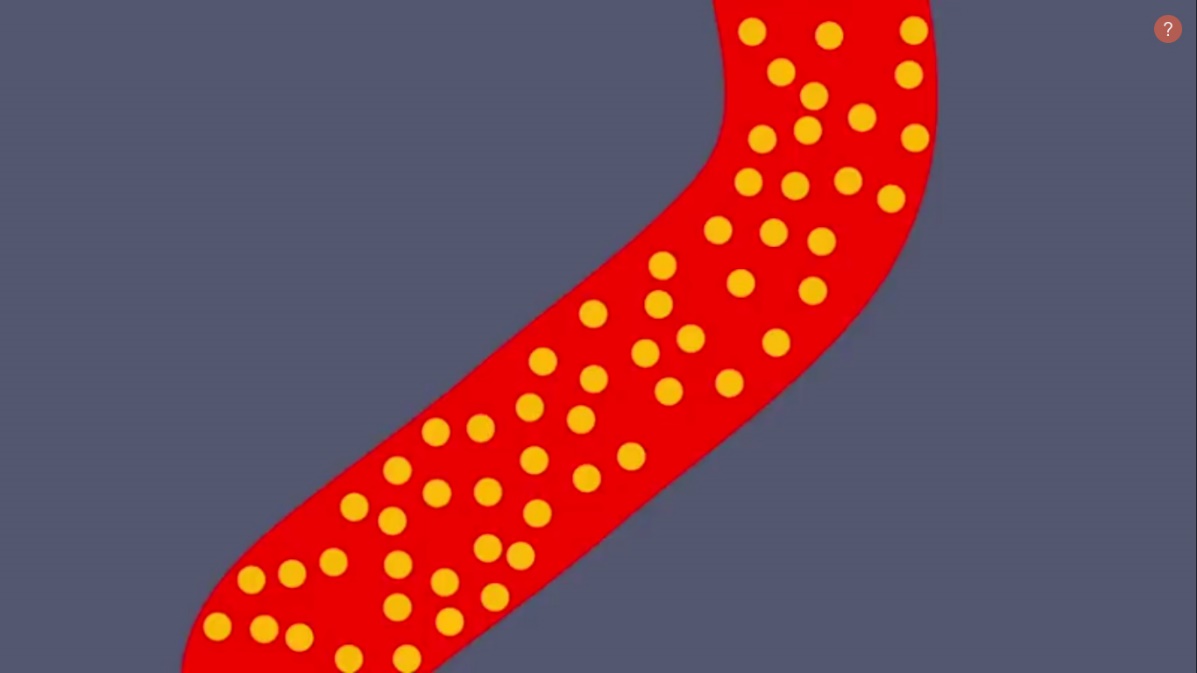
APO B 100 serves the Essential function of acting like a swipe card that allows these particles to be recognized by receptors on the liver and souls around the body if they can't be identified because the APO B100 is damaged they can't deliver their essential cholesterol cargo.



Here you can see for example LDL is unable to enter the Liver these APO B100 damaged proteins can still reach the receptors they just aren't led in and this leads to their accumulation in the circulation.

This leads to what is known as an *increase LDL particle count.*



Now because they're small the *absolute volume* of these accumulated particles is actually not that much when it's compared relative to *their number count* so in essence you end up with lots of particles but not much volume, not much what we call LDL cholesterol level which is what's normally measured and this explains while *particle number is actually a much better predictor of vascular disease than total LDL volume*.



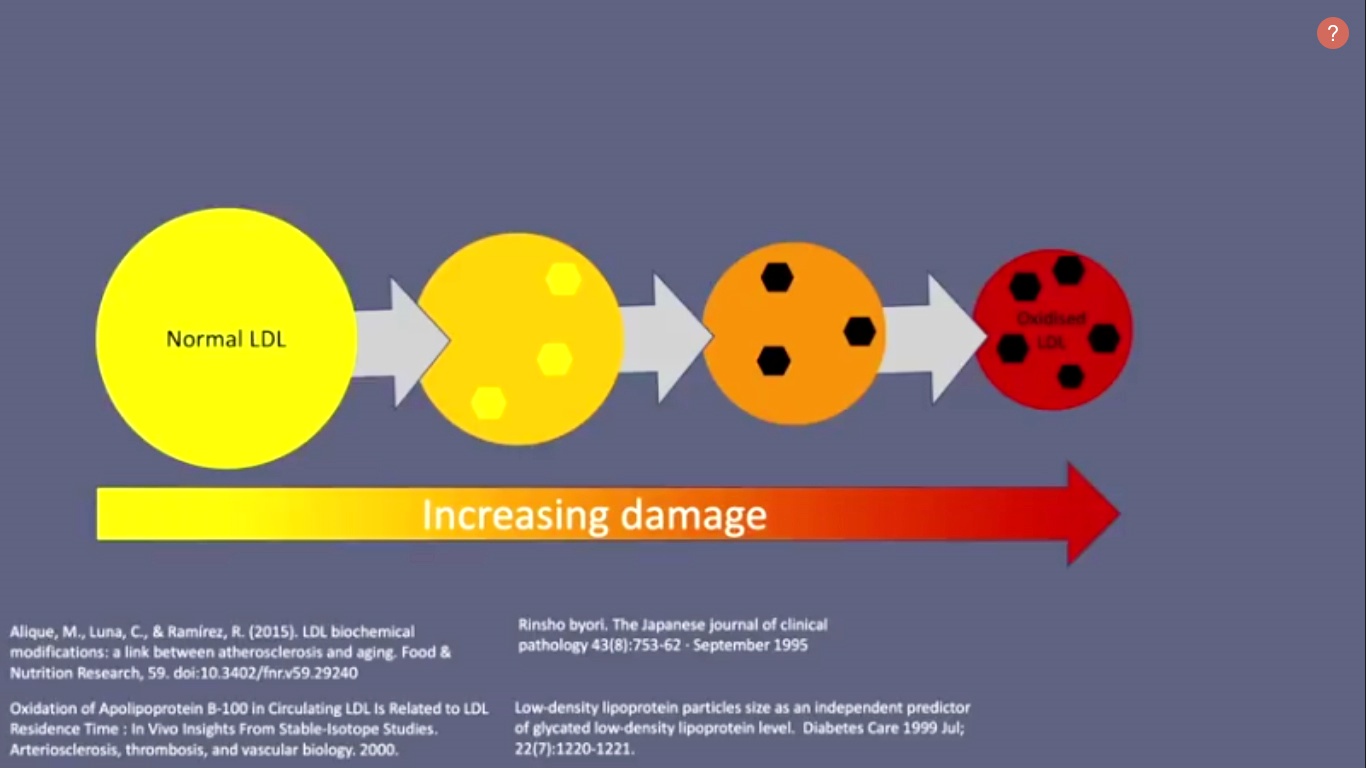
This 2018 study[[4]](#footnote-4) based on 15 years of follow-up of nearly 28,000 females

supports this it found that *while the volume of LDL cholesterol didn't predict heart disease at all the particle count did* those with a high particle count had a normally *two and a half times increased risk* of heart disease so then the question is



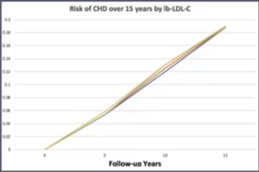
if damage to LDL lipoproteins increases the risk of cardiovascular disease can we tell if we have normal or damaged LDL?

and the answer is yes!

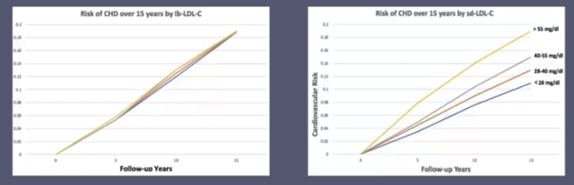


you see when an LDL lipoprotein gets damaged it functionally shrinks the more

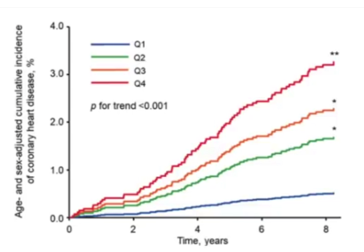
damage the greater the shrinkage and the damage tends to happen in stages which means that damaged LDL tends to have distinct populations.



Evidence of the importance of this in considering risk of heart disease comes from this study[[5]](#footnote-5) more than 11 000 subjects and you can see four different lines each representing varying levels of undamaged LDL and this is often called large buoyant LDL and this is graphed against cardiovascular risk and you can see that increasing levels of undamaged LDL represented by the different colored lines does not increase cardiac Risk essentially the four lines are on top of each other



compare this into an analysis of small dense LDL but damaged version of LDL you can clearly see that the elevated levels are small dense LDL are associated with a much greater risk of heart disease even when total LDL levels are low the presence of small dents LDL predicts cardiac Risk



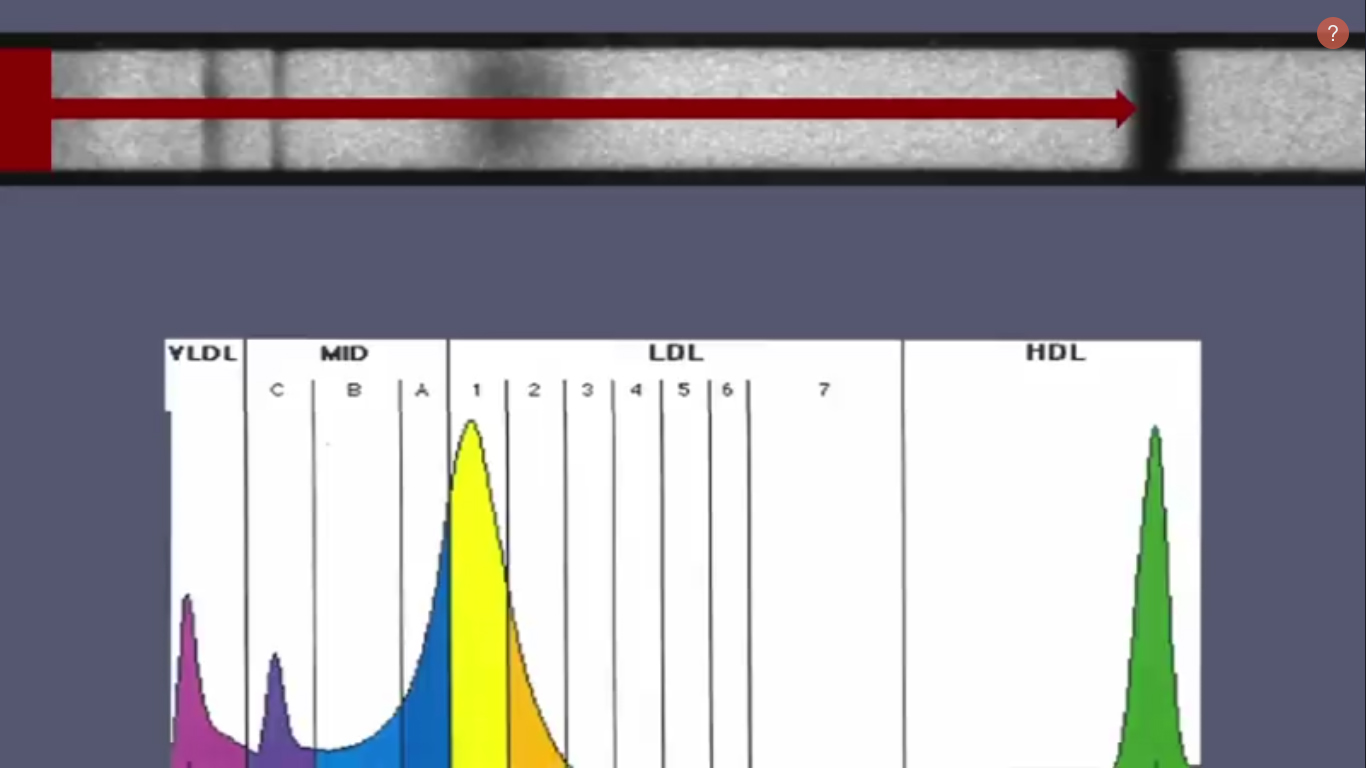
and this is far from an isolated finding take this 8-year study from Japan[[6]](#footnote-6) which found those with the highest small dense LDL levels were five times more likely to suffered from heart disease and we can test for the presence of small dense LDL using a centrifuge to separate LDL particles based on size and density



This is an example of a healthy LDL sample first of all it gets placed in a gel and then spun down so that the different lipoproteins move through the gel

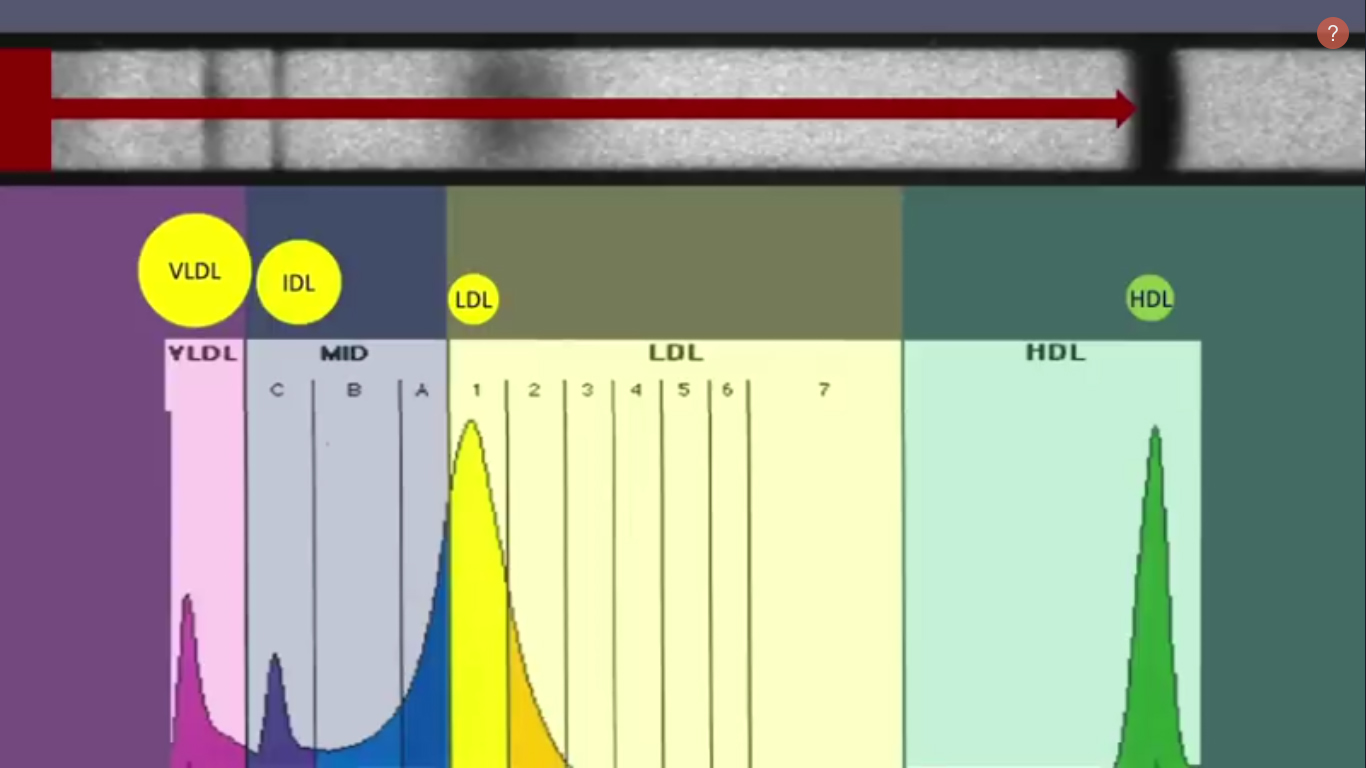


based on their size and density the dark lines at the top represent different lipoprotein populations which have moved different distances and the results are presented like this:

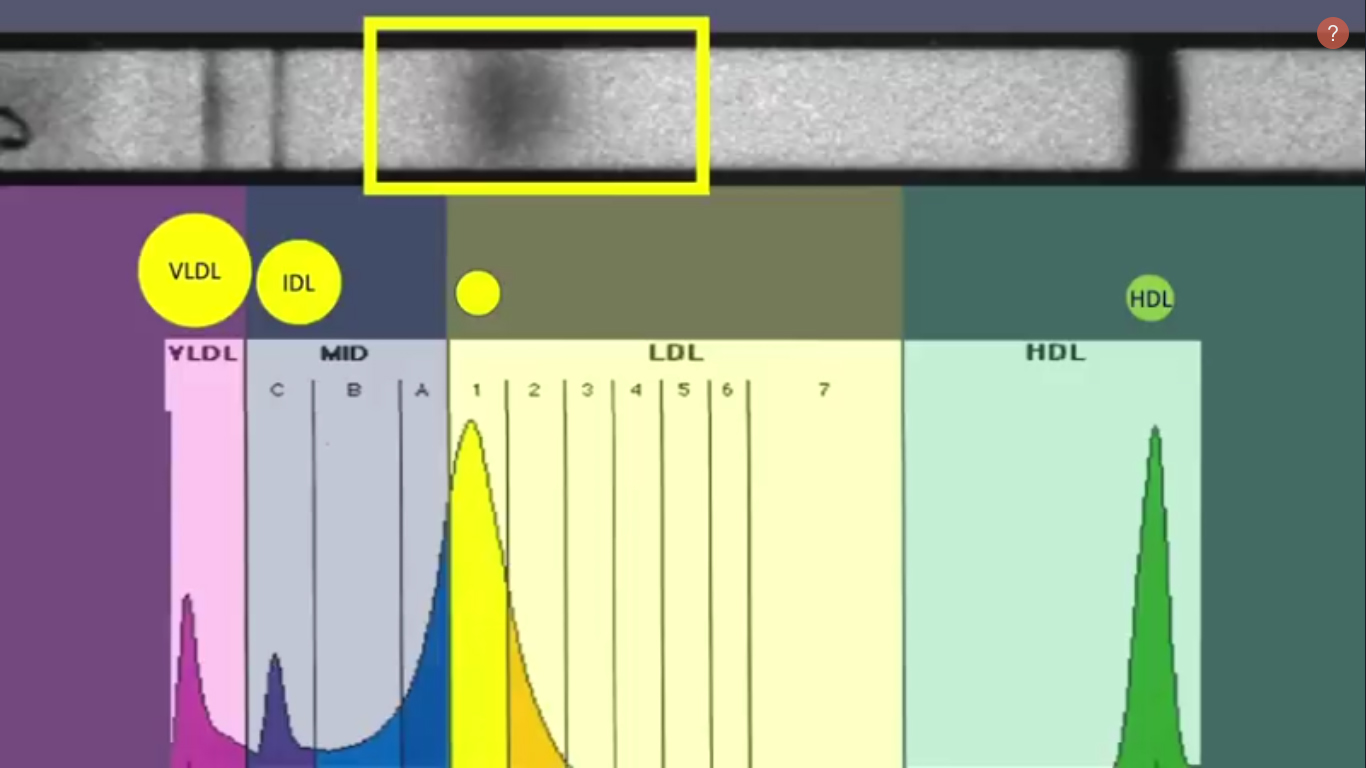


you can see the Peaks matching the dark lines in the gel.

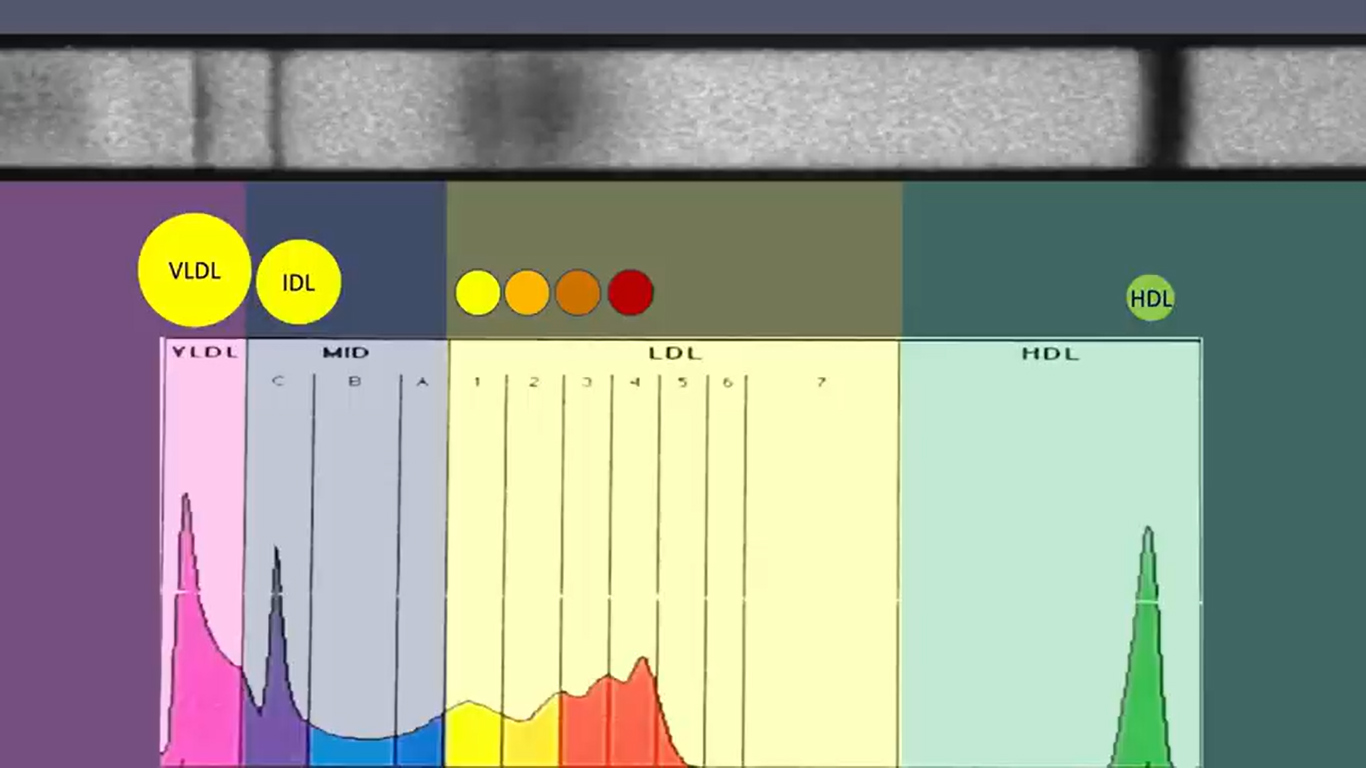
The height of the peaks represents the overall volume of each life a protein you'll note in the LDL section in the middle



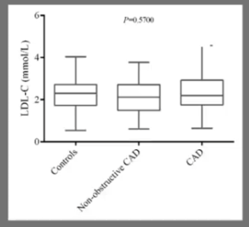
that there is only one clear peak evidence of a single healthy LDL population let's see what an unhealthy LDL sample looks like:



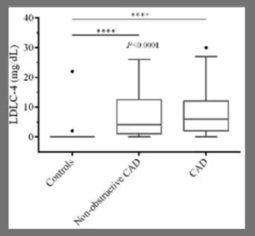
Focus here on the LDL section within the gel within the yellow box now you can see that there's two distinct populations which on a graph would look like this:



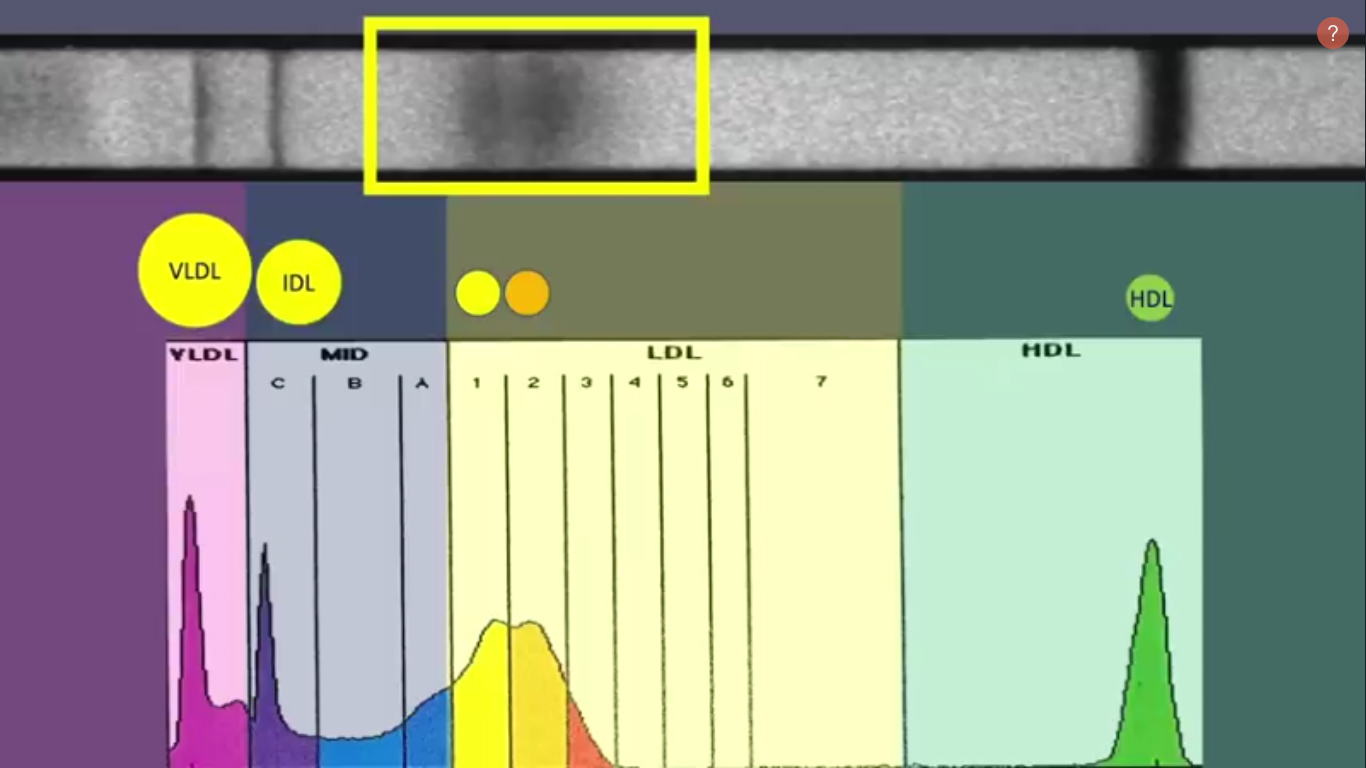
you can now see two distinct Peaks of LDL and further damage to LDL could lead to a third or even a fourth pick in this example you can see that the damaged LDL population is significant much more than the healthy one and you can also see a large amount of Life protein in the fourth and fifth bands those vertical columns and the fourth and is where things really start to hit up



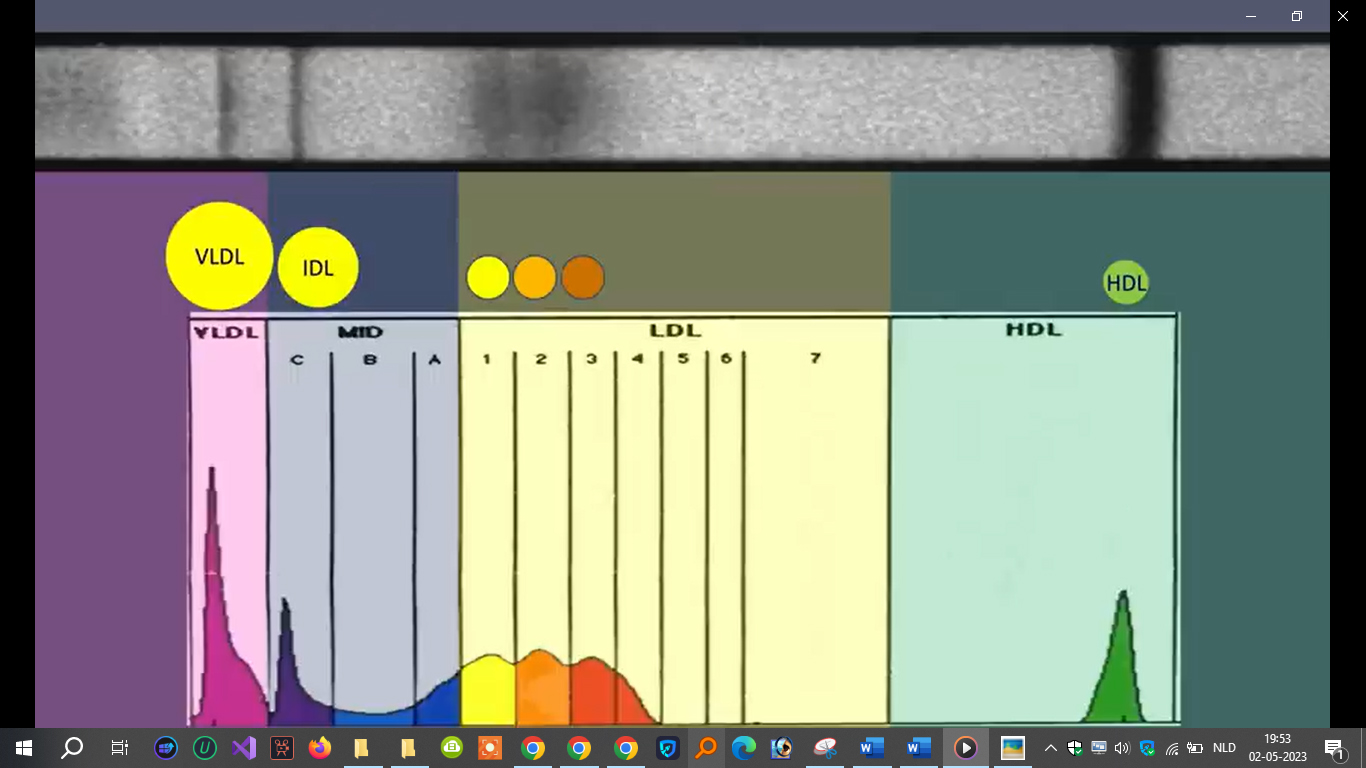
This 2021 study[[7]](#footnote-7) found predictably there was no difference in LDL levels between those with and without coronary artery disease that was just total LDL



when they looked at LDL subfractions though they found the presence of LDL in banned for or above was almost always associated with coronary heart disease

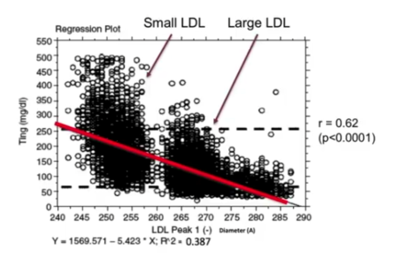


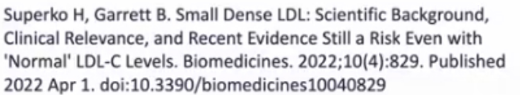
that means this twin peak LDL pattern with LDL extending out to band 3 might well be okay



while this three peaker, where you can see LDL going out to band 4 almost certainly indicates a problem and while informative, this testing is expensive.

Fortunately, we can get some assessment of the likelihood of the pattern B LDL subtraction that is one without damaged LDL based on measures from a standard blood lipid panel the most important marker is triglycerides





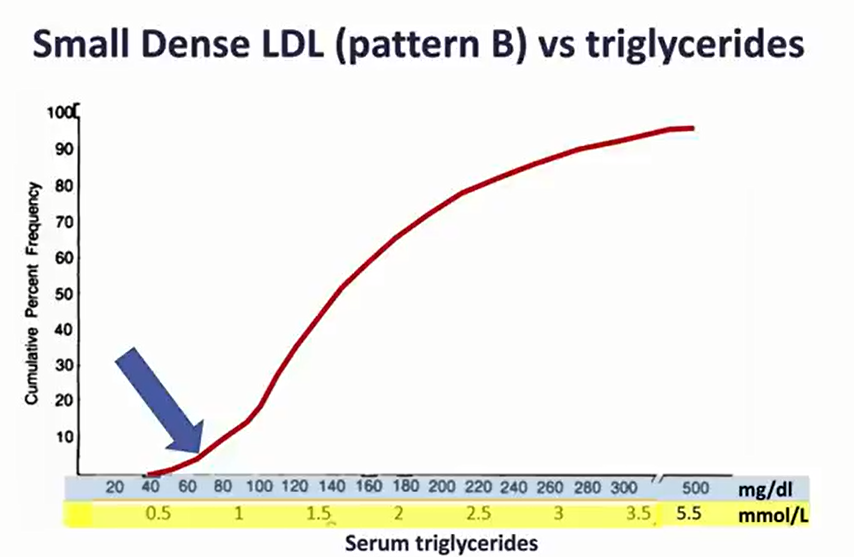
and analysis of more than 5,000 patients with heart disease found to clear correlation between triglyceride levels and the presence of small dense LDL particles

The grouping on the left that represents those patients with small dense LDL and the cluster on the right that sort of L-shaped cluster that represents patients with the large buoyant LDL and the y-axis is the level of triglycerides and you can see that the cluster on the left representing the small dense LDL the damage LDL they had on average much higher triglyceride levels.

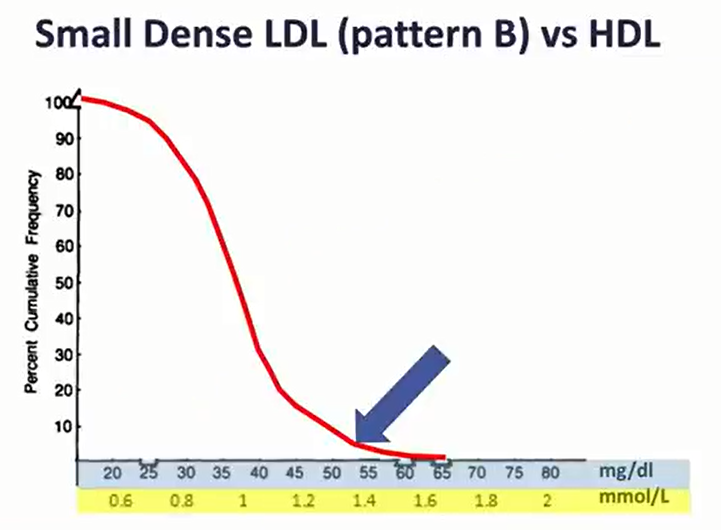
Furthermore, you can see as you move towards the right in the graph where the LDL was larger or more buoyant high triglyceride levels become quite rare in fact a triglyceride level of less than 0.8 millimoles or 70 milligrams a deciliter is



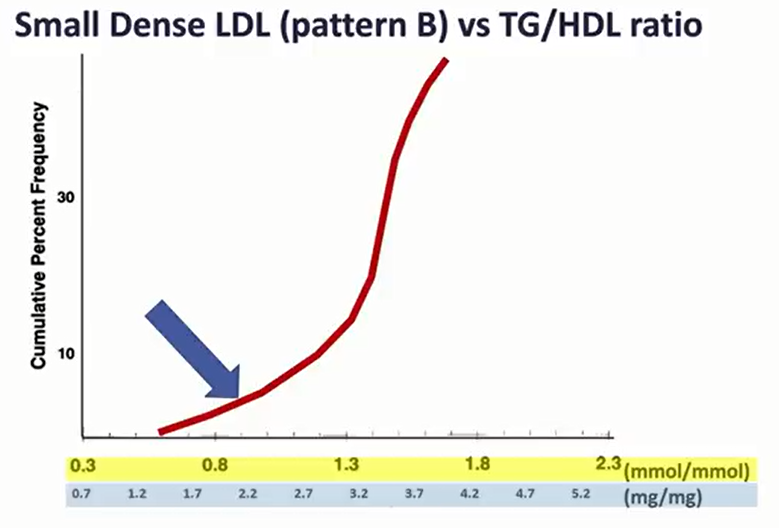
study predictive of a low risk of having small dense LDL conversely a trigoside \* level of over 2.8 millimoles a liter or 250 milligrams of deciliter is bad news bare and this data correlates very well with previous research this study was from



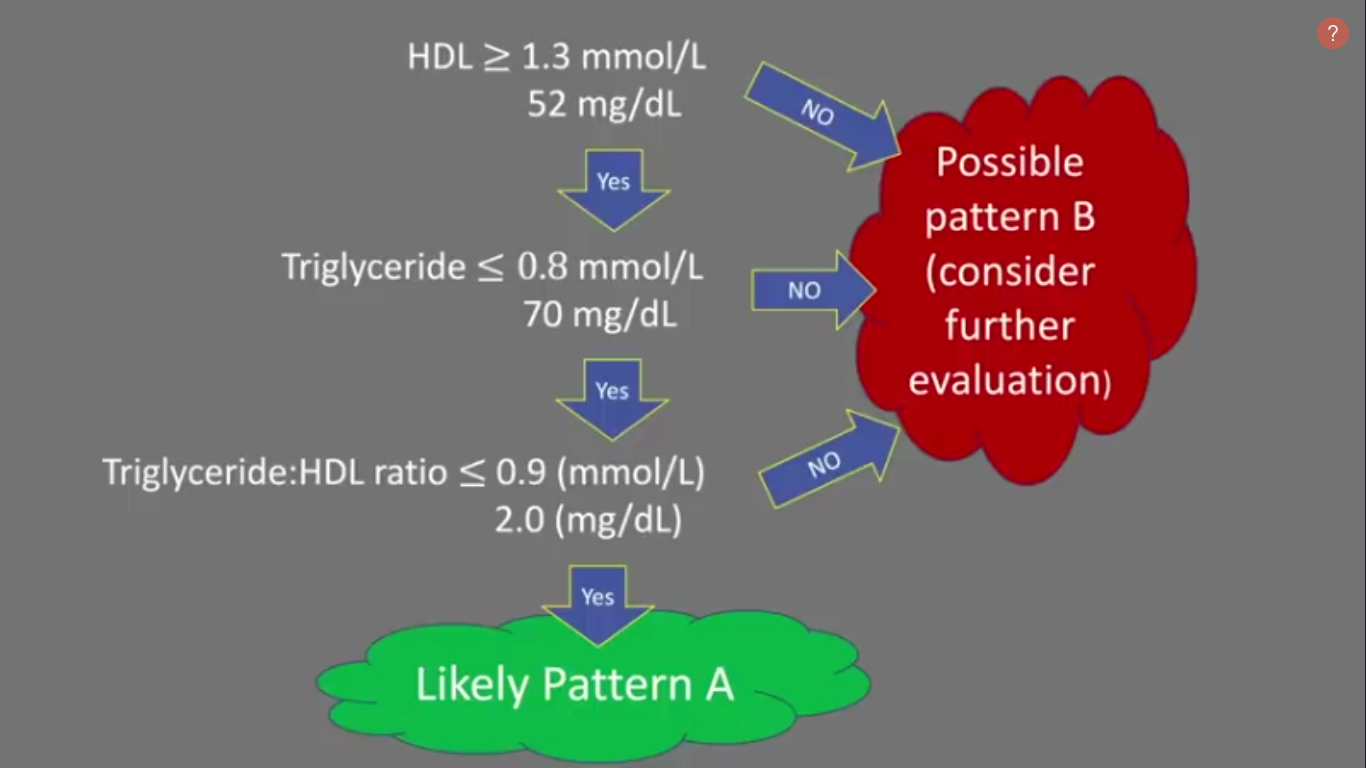
1990[[8]](#footnote-8) \* and you can see that only about five percent of subjects had small dense LDL when their triglyceride was less than 0.8 millimoles a liter or about 70 milligrams a deciliter and I'd also like to point out that at less than 0.5 millimoles a liter or 40 micrograms a deciliter the incidence of small dense LDL approaches zero.



We now come to HDL we're a higher level is desirable here it is clear that the rate a small dense LDL is increased substantially with HDL levels below about 1.3 millimoles a liter or 52 micrograms of deciliter even better than triglycerides are HDL in isolation when predicting for small dense LDL is the ratio between the two.



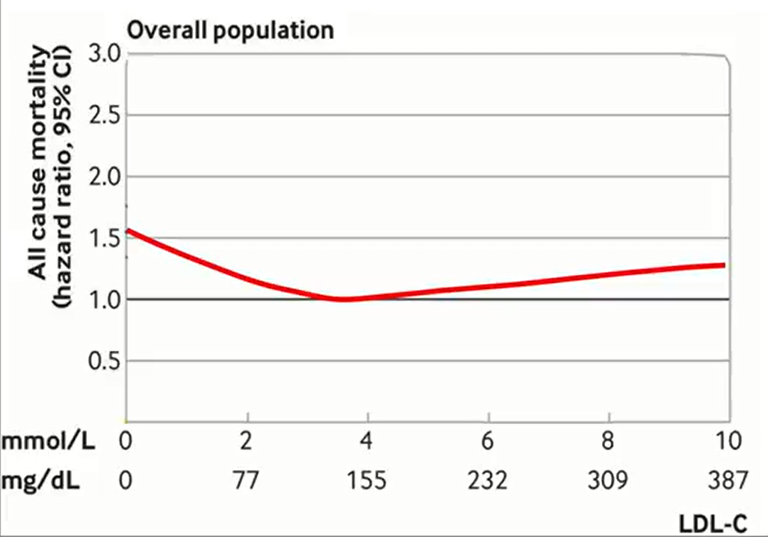
You can see here that a ratio of over about 0.9 in millimoles a liter units or over 2.0 in milligram of deciliter units is associated with a greater probability of small dense LDL.



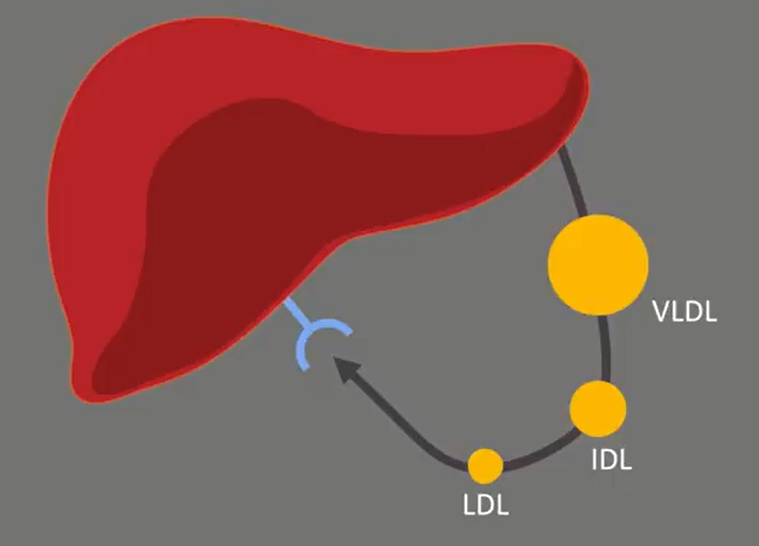
I therefore think that this is a reasonable algorithm to assess the probability that a lipid profile is either atherogenic or non-atherogenic that is artery clotting or not artery clod.

I'm now going to muddy the waters a little bit.

I've demonstrated that higher LDL levels are on average associated with longevity that doesn't mean that every case of LDL elevation is a good thing, however, take this graph[[9]](#footnote-9) of LDL versus mortality



you can clearly see on the left that the greatest risk of death is with the lowest level of LDL



you can also see that risk increases although less so with the highest levels of LDL and this is not surprising because several factors can increase VLDL production ultimately increasing the number of LDL particles



Red meat, dairy, and insulin sensitivity: a randomized crossover intervention study[[10]](#footnote-10)

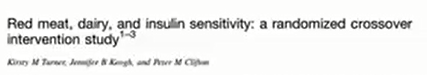
the most obvious of these is *insulin resistance* and something that may surprise you is that *insulin resistance can increase on the low carbohydrate diets* often in association with increased LDL and usually in the context of a high dairy consumption



you see dairy can contribute to insulin resistance. This study



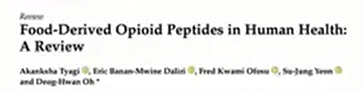
found[[11]](#footnote-11) a high dairy intake predicted insulin resistance in middle age females a finding supported by this experimental study [[12]](#footnote-12)



Red meat, dairy, and insulin sensitivity: a randomized crossover

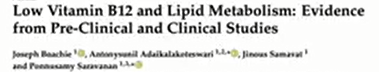
intervention study

which compared diets rich and dairy to a diet rich in red meat while maintaining a constant weight over four weeks the subjects consuming the high dairy diet were found to experiencing increase in their fasting insulin levels consistent with insulin resistance despite having a normal glucose tolerance at the start of the study and one caveat is that while dairy can worse an insulin resistance it's still not as bad as most of the foods on a standard Western diet. And this is why population studies can indicate that dairy is associated with improved insulin resistance because dairy is taking the place of some pretty bad food.



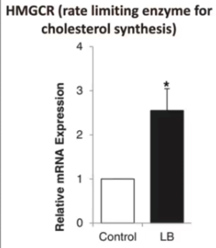
Food-Derived Opioid Peptides in Human Health: A Review[[13]](#footnote-13)

it's also easy to over consume dairy and I believe one of the reasons for this is that it naturally contains *a version of morphine* for many who was struggling to give up the warm hug that you get from sugary foods provided by that dopamine rush dairy can simply become a replacement, becomes the go-to and incidentally this is one of the reasons while dairy can be constipating. The constipating effects being well known.



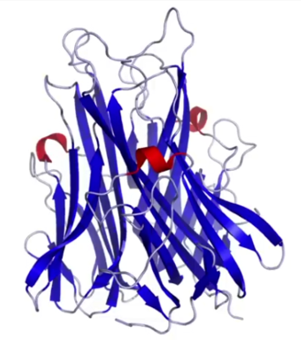
Low Vitamin B12 and Lipid Metabolism: Evidence from Pre-Clinical and Clinical Studies[[14]](#footnote-14)

There's also good evidence that B12 deficiency is causally associated with increased LDL here you can see a significant increase in cholesterol synthesis

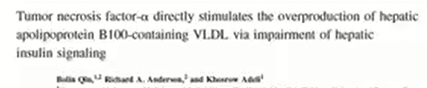


due to low vitamin B12 and don't for a second think that the standard B12 reference interval reliably identifies B12 deficiency.

It's a reflection of population averages and given that B12 deficiency is increasingly common many cases go missed.



Another potential cause of elevated LDL relates to *inflammation* in particular a signaling protein that often circulates in the blood in inflammatory States this is called *tumor necrosis factor alpha* this study



Tumor necrosis factor- directly stimulates the overproduction of hepatic apolipoprotein B100-containing VLDL via impairment of hepatic insulin signaling[[15]](#footnote-15)

Used golden hamsters whose lipid system closely resembles that of humans and demonstrated that human tumor necrosis Factor Alpha caused over production of the LDL.

The LDL precursor up *to eight times* normally in fact so when I observe an unexpectedly high LDL level, I'm always on the lookout for sources of inflammation and along a similar vein I'd just like to point out that there are numerous potential causes for elevated triglyceride levels *besides sugary carbs*

*and alcohol* some of the most common ones I come across include an underactive thyroid kidney disease, diabetes, hemochromatosis and numerous drugs including beta blockers and corticosteroids so as with LDL if you see an

unexpectedly elevated triglyceride level be sure to consider more than just diet

in closing the story we've been fed about LDL is the major cause of heart disease is clearly nonsense when LDL becomes oxidized however it can

become a problem and *the triglyceride to HDL ratio* is a reliable way of

predicting this, even if LDL is not oxidized a very elevated LDL level may be

symptomatic of another issue that ought not be overlooked.

Thank you



1. <https://pubmed.ncbi.nlm.nih.gov/27292972/> [↑](#footnote-ref-1)
2. <https://pubmed.ncbi.nlm.nih.gov/1191862/> [↑](#footnote-ref-2)
3. <https://pubmed.ncbi.nlm.nih.gov/29511019/> [↑](#footnote-ref-3)
4. <https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.118.035432> [↑](#footnote-ref-4)
5. <https://www.ahajournals.org/doi/epub/10.1161/ATVBAHA.114.303284> [↑](#footnote-ref-5)
6. <https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC7406411&blobtype=pdf> [↑](#footnote-ref-6)
7. <https://www.frontiersin.org/articles/10.3389/fcvm.2021.619386/full> [↑](#footnote-ref-7)
8. <https://www.ahajournals.org/doi/pdf/10.1161/01.CIR.82.2.495> [↑](#footnote-ref-8)
9. <https://www.researchgate.net/publication/347428043_Association_between_low_density_lipoprotein_and_all_cause_and_cause_specific_mortality_in_Denmark_Prospective_cohort_study> [↑](#footnote-ref-9)
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