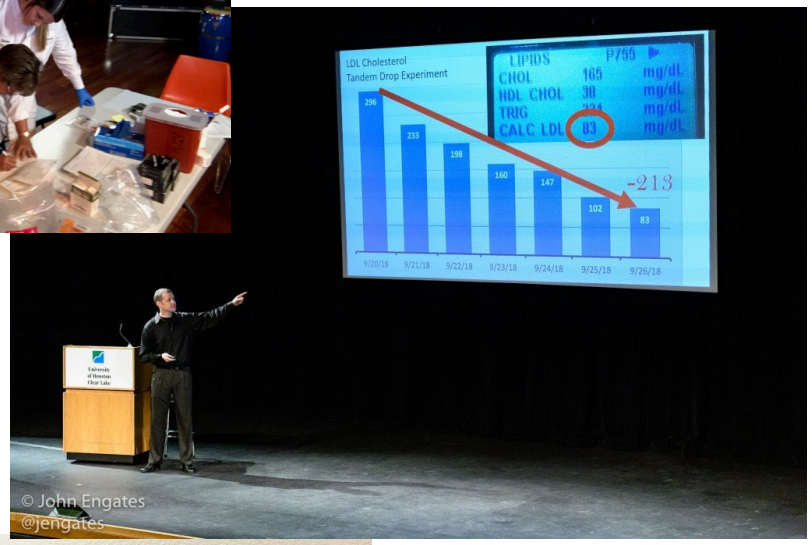
The New Papers, The Coming Study, Where We Go Next, and Why It Matters

Conflicts of Interest:

Membership & Patreon Revenue

Partner & Managing Director

Dave Feldman – Engineer / Citizen Scientist



- Senior Software Engineer / Platform Architect
- Began this journey in 2015 following surprisingly high cholesterol levels on a keto diet
- Became obsessed with Lipidology and lipid metabolism
- Frequent N=1 Experiments / Biohacking / etc

Before we can talk about the new papers…

…We need to go back…

…to 2017

Thank You, American Heart Association (Sincerely) — Doubters, Haters, Colleagues, and Friends

JUL
03

Are you a Lean Mass Hyper-responder?

By Dave in Cholesterol, Guide, Lean Mass Hyper-responder

919

DONATE

My primary costs are the many frequent and expensive blood tests I take for this research and data. Any size donation is appreciated. Thank you for your support!

Donate

DONATE VIA CRYPTOCURRENCY

Bitcoin:
149KGJetUAWqcrfALvhbMNmQYJtj1u7R9K

Bitcoin Cash:
qq384um3ej4znls6spud9k6ec6msns2n3uj3z3uet7

Bitcoin BSV:

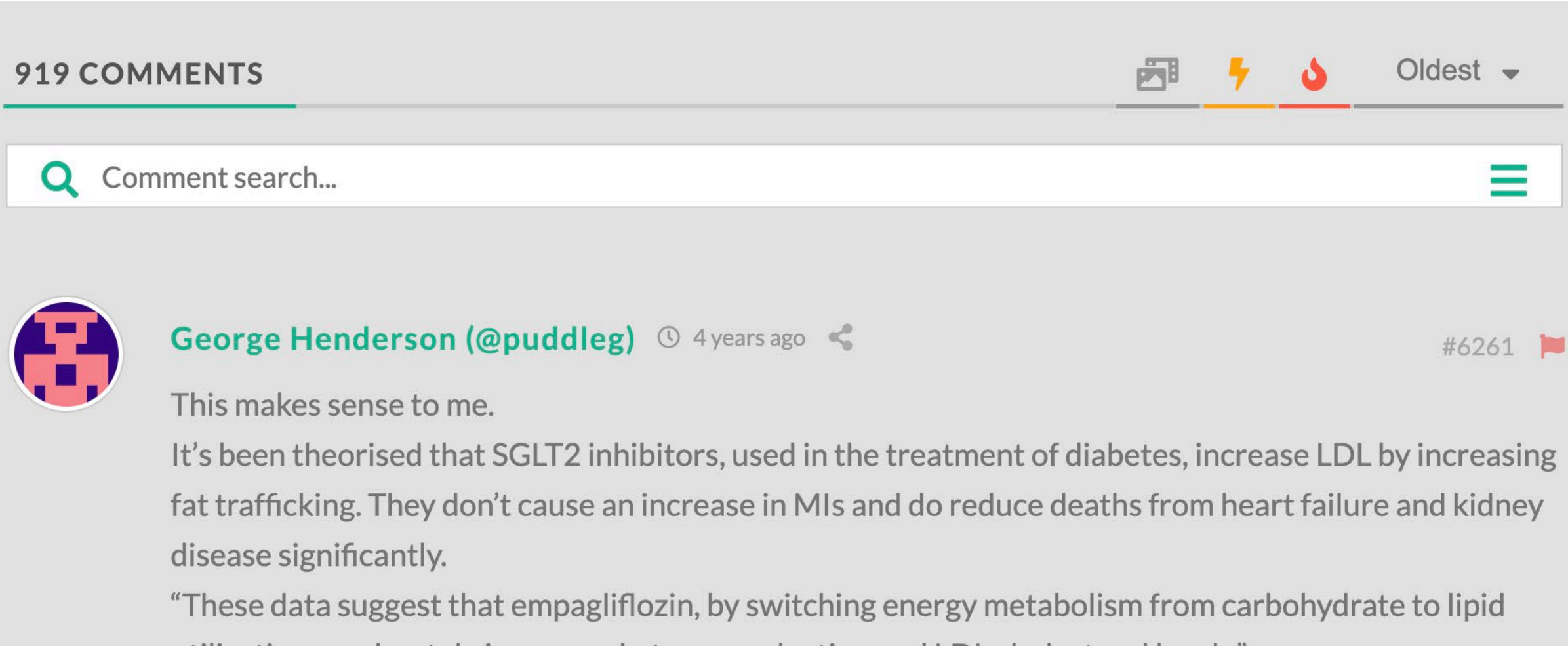
davefeldman@simply.cash

Ethereum:
0x987E72301b8abC7934cfF83330bD10B4D0B874A6

Search


Cholesterol scores can be higher for those who are lean and/or athletic on a low carb diet.
Lean Mass Hyper-responder
Low Carb Diet
= Lower Glycogen Stores
Low Body Fat
= Lower Adipose Stores
Athletic / Active
= Higher Energy Demands
Lipoproteins may be needed to traffic a greater amount of energy from fat, resulting in higher LDL Cholesterol markers
LDL of 200 mg/dL (5.17 mmol/L) or higher
HDL of 80 mg/dL (2.07 mmol/L) or higher
Triglycerides of 70 mg/dL (0.79 mmol/L) or lower
cholesterolcode.com/lmhr

Still the most commented post to date



The New Papers

Entering the Literature

Flash forward to …

… November 2021…

…where we have finally published the LMHR paper!

ORIGINAL RESEARCH

CURRENT DEVELOPMENTS IN NUTRITION

Nutritional Biochemistry and Physiologic Mechanisms

doi.org/10.1093/cdn/nzab144

Elevated LDL Cholesterol with a Carbohydrate-Restricted Diet: Evidence for a "Lean Mass Hyper-Responder" Phenotype

Nicholas G Norwitz,[1] David Feldman,[2] Adrian Soto-Mota,[3] Tro Kalayjian,[4] and David S Ludwig[1,5]

[1]Harvard Medical School, Boston, MA, USA; [2]Citizen Science Foundation, Las Vegas, NV, USA; [3]Metabolic Diseases Research Unit, National Institute for Medical Sciences and Nutrition Salvador Zubiran, Tlalpan, Mexico City, Mexico; [4]Yale New Haven Health System, New Haven, CT, USA; and [5]New Balance Foundation Obesity Prevention Center, Boston Children's Hospital, Boston, MA, USA

ABSTRACT

Background: People commencing a carbohydrate-restricted diet (CRD) experience markedly heterogenous responses in LDL cholesterol, ranging from extreme elevations to reductions.

Objectives: The aim was to elucidate possible sources of heterogeneity in LDL cholesterol response to a CRD and thereby identify individuals who may be at risk for LDL cholesterol elevation.

Methods: Hypothesis-naive analyses were conducted on web survey data from 548 adults consuming a CRD. Univariate and multivariate regression models and regression trees were built to evaluate the interaction between body mass index (BMI) and baseline lipid markers. Data were also collected from a case series of five clinical patients with extremely high LDL cholesterol consuming a CRD.

Results: BMI was inversely associated with LDL cholesterol change. Low triglyceride (TG) to HDL cholesterol ratio, a marker of good metabolic health, predicted larger LDL cholesterol increases. A subgroup of respondents with LDL cholesterol ≥200 mg/dL, HDL cholesterol ≥80 mg/dL, and TG ≤70 mg/dL were characterized as "lean mass hyper-responders." Respondents with this phenotype ($n = 100$) had a lower BMI and, remarkably,

Data (1 of 2) – Web survey

The “Cholesterol Super Survey” is a publicly available ongoing questionnaire created by a coauthor (DF) in January 2020 with the aim of describing changes in LDL cholesterol among consumers of a CRD (Carbohydrate Restricted Diet). The survey, advertised through social media, includes questions about height, weight, dietary intake, medications, and current and past lipid test results.

A copy of this survey is available in the Supplemental Survey and responses used in this manuscript were collected between 16 January and 30 November 2020.

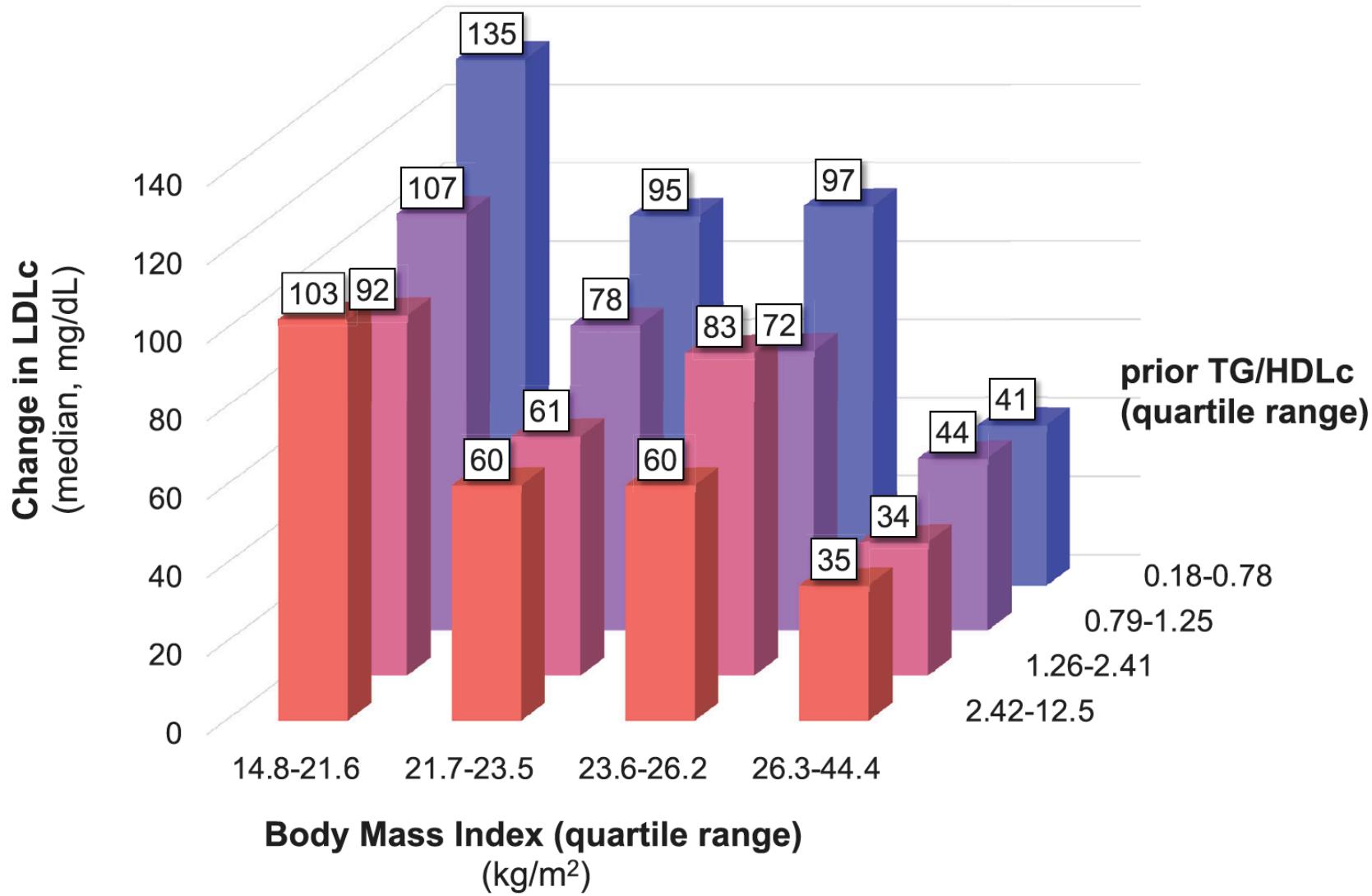


FIGURE 2 BMI and TG/HDL cholesterol ratio predict LDL cholesterol increases on a CRD. Median LDL cholesterol change according to quartiles of TG/HDL cholesterol ratio prior to CRD and of BMI ($n = 34$ per cell) is shown. CRD, carbohydrate-restricted diet; HDLc, HDL cholesterol; LDLc, LDL cholesterol; TG, triglyceride.

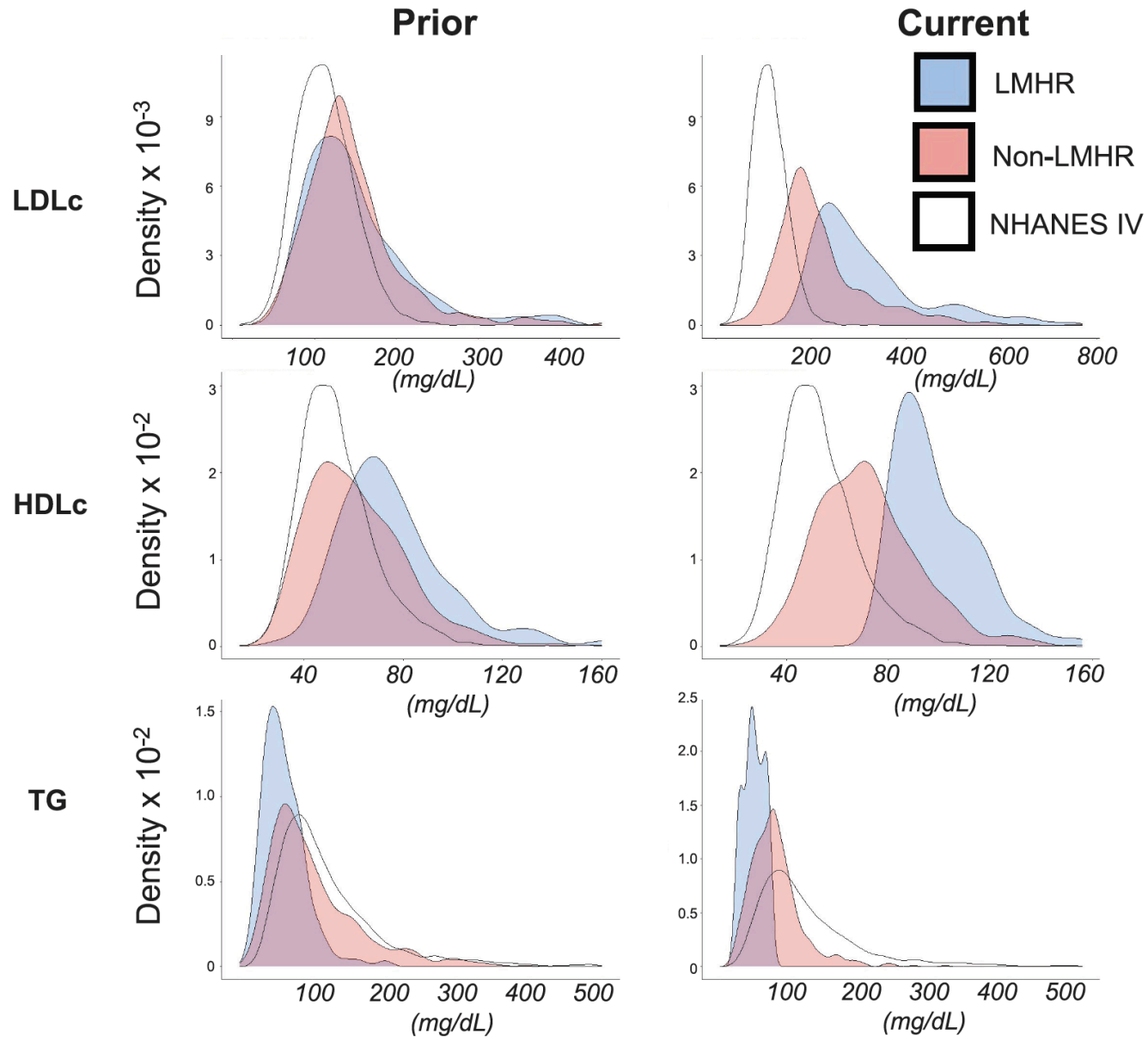
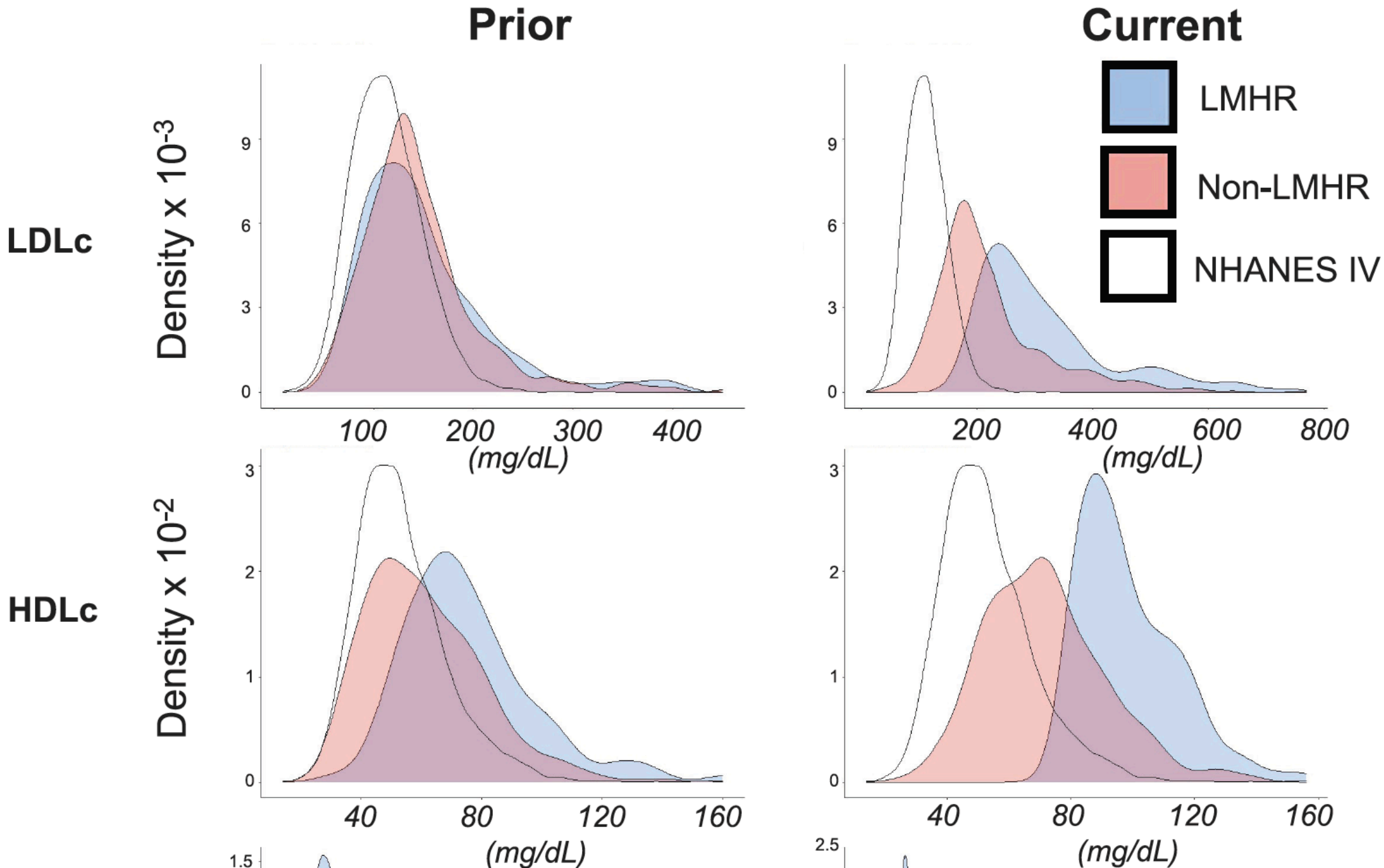


FIGURE 3 Comparison of LMHR and non-LMHR subgroups among respondents with US nationally representative data (NHANES IV). LMHRs and non-LMHRs possess higher LDL cholesterol on a CRD, as well as high HDL cholesterol and lower TG both prior and on a CRD, as compared with adults in the NHANES IV (2011–2012) dataset. Differences from NHANES were more pronounced for LMHRs (see Supplemental Table 3 for details). CRD, carbohydrate-restricted diet; HDLc, HDL cholesterol; LDLc, LDL cholesterol; LMHR, lean mass hyper-responder(s); TG, triglyceride.


Prior
Current
LDLc
HDLc
Density x 10-3
Density x 10-2
LMHR
Non-LMHR
NHANES IV
(mg/dL)
100
200
300
400
600
800
40
80
120
160
0
3
6
9
1
2
1.5
2.5

Data (2 of 2) – Case Series

Patients presenting to the clinic of a coauthor (TK) with a history of elevated LDL cholesterol following initiation of a VLCD containing <25 grams/day carbohydrate and no personal history of myocardial infarction or stroke were initially counselled on standard-of-care pharmacologic options to lower LDL cholesterol, including statins. Patients included in this series refused pharmacotherapy and instead opted to pursue an empiric clinician-supervised dietary therapy, with reintroduction of 50–100 grams carbohydrate/day in the form of fruits or starchy vegetables. Body fat percentage was measured by a Valhalla Scientific BCS Elite 4-point bioimpedance scale.

TABLE 4 Case series summary[1]

Patient initials	Pre-VLCD	VLCD	LCD	LDL cholesterol decrease
IA[2]				
Total cholesterol	214	797	294	–480
LDL cholesterol	116	665	185	
HDL cholesterol	81	122	95	
TG	84	50	72	
TG/HDL cholesterol ratio	1.0	0.4	0.8	
MI[2]				
Total cholesterol	209	698	497	–223
LDL cholesterol	122	583	360	
HDL cholesterol	72	97	122	
TG	54	70	67	
TG/HDL cholesterol ratio	0.8	0.7	0.5	
RO				
Total cholesterol	197	311	180	–124
LDL cholesterol	137	239	115	
HDL cholesterol	45	65	54	
TG	62	56	36	
TG/HDL cholesterol ratio	1.4	0.9	0.7	
NM				
Total cholesterol	179	387	272	–122
LDL cholesterol	113	317	195	
HDL cholesterol	49	59	61	
TG	86	54	56	
TG/HDL cholesterol ratio	1.8	0.9	0.9	
AN				
Total cholesterol	218	423	318	–100
LDL cholesterol	141	336	236	
HDL cholesterol	57	69	66	
TG	98	74	64	
TG/HDL cholesterol ratio	1.7	1.1	1.0	

[1]Lipid values for five patients refusing LDL cholesterol–lowering pharmacotherapy before a VLCD, during consumption of a VLCD, and on an LCD (i.e., after moderate reintroduction of carbohydrate). Results are in mg/dL except for TG/HDL cholesterol ratio. LCD, low-carbohydrate diet; LMHR, lean mass hyper-responder; TG, triglyceride; VLCD, very-low-carbohydrate diet.
[2]Indicates those patients satisfying criteria for LMHR during consumption of VLCD. Patients are ordered according to TG/HDL cholesterol ratio on a VLCD.

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Remember How I Feel About ”Open Science”?

Dave Feldman @realDaveFeldman · Sep 28, 2021

Fascinating new study just dropped via @davidludwigmd et al

Love this study design:
- Very long timeline -> 5 months!
- Very detailed lipid metrics
- Metabolic-centric

And of course, of very special importance to me -- 100% open data and methodology! **#OpenScience** #Transparency

> **Dr. David Ludwig** @davidludwigmd · Sep 28, 2021
>
> New 5-month feeding study, N=164, supported by NuSI, @Arnold_Ventures
>
> Low carb (20%) vs high carb (60%) diet improved:
> 👉Lipoprotein insulin resistance
> 👉Lp(a)
> 👉Adiponectin
>
> And no LDL-chol increase (with high sat fat, 21 vs 7%)
>
> Open access full text 👇 academic.oup.com/ajcn/article-l...

3 18 64

Dave Feldman @realDaveFeldman · Jan 28, 2021

1/ I know there's a lot of spirited diet debate regarding @KevinH_PhD's newly published study -- and I won't be opining on that here...

Rather, I wanted to single out for my strong endorsement is his team making all data publicly accessible. **#OpenScience**

> nature.com
> Effect of a plant-based, low-fat diet versus an ani...
> Nature Medicine - In an inpatient, randomized controlled crossover trial, participants consumed ...

2 1 16

Remember How I Feel About ”Open Science”?

Open Science for the LMHR Paper

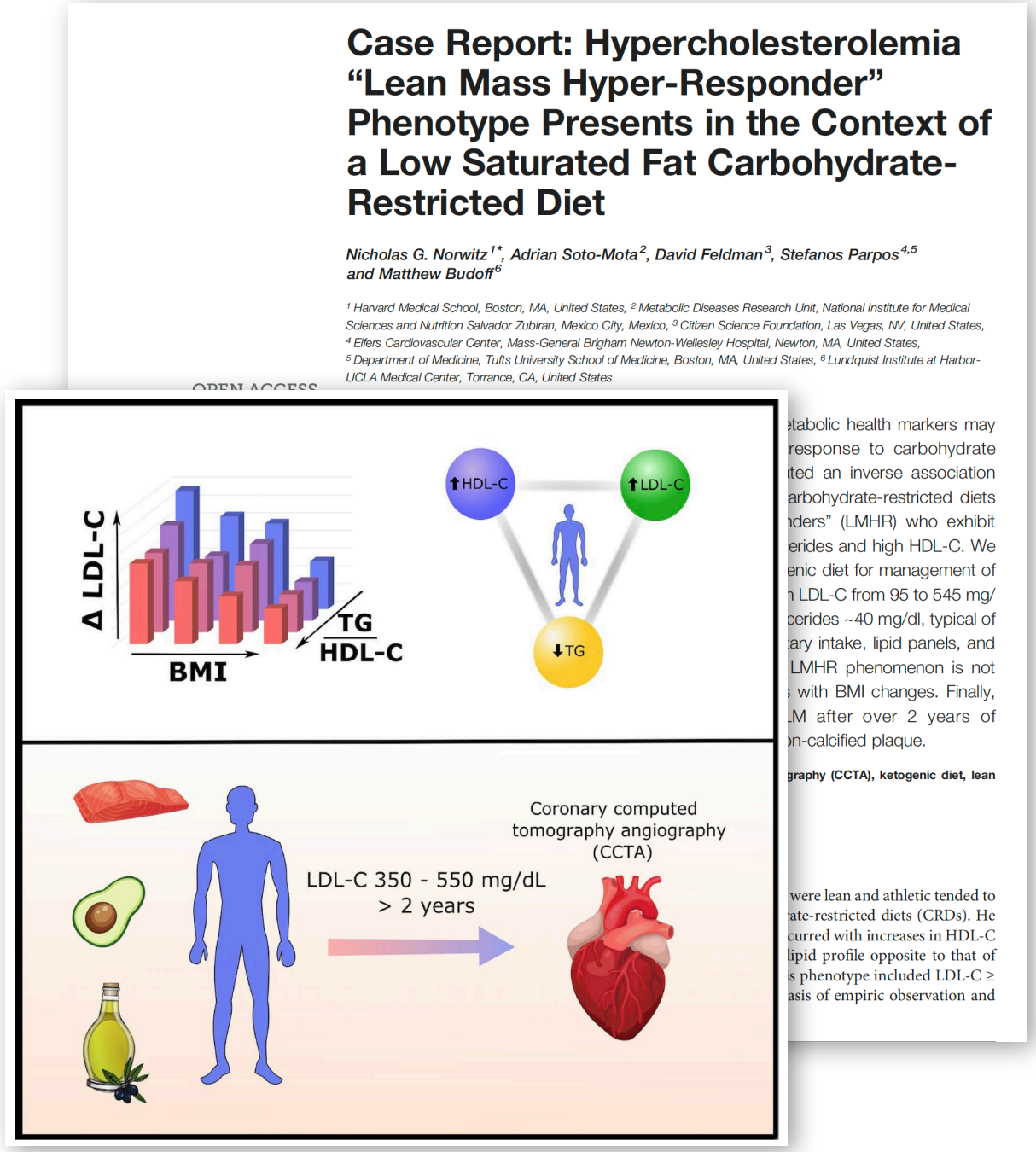
- When we published the uncorrected proof of the LMHR paper, we immediately released all the code and anonymized data at the exact same time. Our paper wasn't just for the eyes of a few reviewers in private, it was available without precondition to our biggest critics as well. Everybody could review our work, find anything we overlooked or could do better, and provide feedback in real time.
- Don't get me wrong, not every research team I'm working with may hold to this standard in exactly the same way. And I don't want to tie my own hands from working with them. But I will say, you can absolutely count on me to work toward maximum transparency on these crucial questions.

New LMHR Case Study has just dropped!

- Let’s cue the video abstract…

Highlights:

- LDL-C increased from 95 to 545 mg/dL on a keto diet with >4:1 unsaturated/sat fat ratio
- Increased BMI correlated with decreased LDL cholesterol, even with higher sat fat
- No genetic abnormalities found to explain phenotype
- CTA at 2.5 years = no plaque



Case Report: Hypercholesterolemia "Lean Mass Hyper-Responder" Phenotype Presents in the Context of a Low Saturated Fat Carbohydrate-Restricted Diet

Nicholas G. Norwitz[1*], Adrian Soto-Mota[2], David Feldman[3], Stefanos Parpos[4,5] and Matthew Budoff[6]

[1] Harvard Medical School, Boston, MA, United States, [2] Metabolic Diseases Research Unit, National Institute for Medical Sciences and Nutrition Salvador Zubiran, Mexico City, Mexico, [3] Citizen Science Foundation, Las Vegas, NV, United States, [4] Elfers Cardiovascular Center, Mass-General Brigham Newton-Wellesley Hospital, Newton, MA, United States, [5] Department of Medicine, Tufts University School of Medicine, Boston, MA, United States, [6] Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA, United States

OPEN ACCESS

...tabolic health markers may ...response to carbohydrate ...ted an inverse association ...arbohydrate-restricted diets ...nders" (LMHR) who exhibit ...erides and high HDL-C. We ...enic diet for management of ...n LDL-C from 95 to 545 mg/ ...cerides ~40 mg/dl, typical of ...ary intake, lipid panels, and ...LMHR phenomenon is not ...s with BMI changes. Finally, ...LM after over 2 years of ...on-calcified plaque.

...graphy (CCTA), ketogenic diet, lean

...were lean and athletic tended to ...ate-restricted diets (CRDs). He ...curred with increases in HDL-C ...lipid profile opposite to that of ...s phenotype included LDL-C ≥ ...asis of empiric observation and

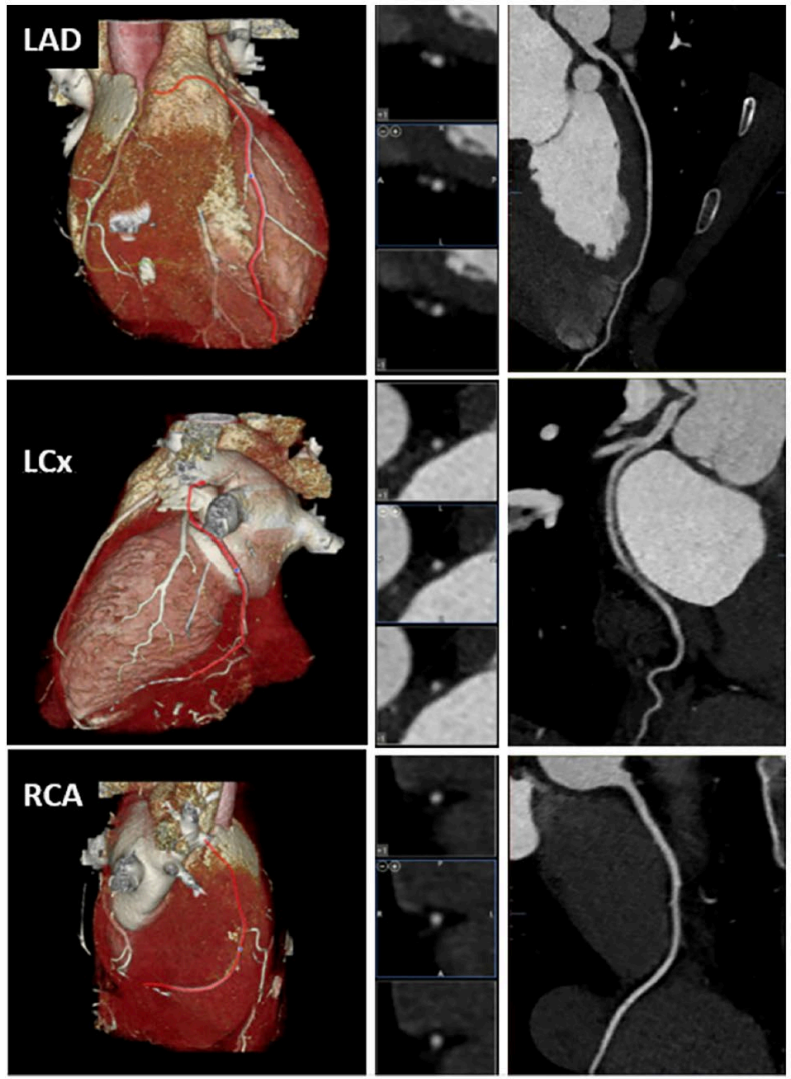


FIGURE 2 | Computed tomographic angiogram demonstrating no coronary artery disease. Left column: Volume-rendered reformations. Middle column: Multiplanar reformation cross-sectional views. Right column: Curved multiplanar reformations. LAD, Left anterior descending artery; LCx, Left circumflex artery; RCA, Right coronary artery.

Computed Tomography Angiography (CTA) Shows No Evidence of Atherosclerotic Plaque in LM

LM's CCTA data are difficult to interpret given his young age and the relative paucity of comparator data. At the time the scan was ordered (for the purposes of directing pharmacotherapy), it was reasonable to assume that he might exhibit plaque development based on the available data. This includes a study on young adults with type II diabetes, mean HbA1c 7.9%, in which 80% of those above 25 years exhibited measurable plaque burden (6), and, of course, that children with homozygous familial hypercholesterolemia and LDL-C levels comparable to LM can present with xanthoma and suffer from myocardial infarctions by age 8 (8). In retrospect, however, it can also reasonably be argued that, despite the magnitude of his exposure, two and half years is insuf!cient for any measurable atherosclerotic plaque to precipitate. The absence of comparator data itself highlights the need for further study on the LMHR population.

The Coming Study

Entering the Literature

Two organizations, two sets of responsibilities

Citizen Science Foundation

Funding, Recruitment,
Travel Arrangement



The Lundquist Institute

Participant Examination,
Bloodwork, CT Scanning

If you saw your cholesterol skyrocket from your diet…

I WANT YOU for the LMHR Study

CitizenScienceFoundation.org/study

1/We're still recruiting for the #LMHRstudy – Please RT!

If you (or someone you know):
✅Had #LDL #Cholesterol ↗️ go from 160 and under to 190 and over
✅Has #HDL of 60 or higher
✅Triglycerides of 80 or lower
✅US based

...You may qualify for our study!
citizensciencefoundation.org/study/

Dave Feldman
@realDaveFeldman

Hello!

👉Did your #LDL #Cholesterol skyrocket on #keto?

Would you like...
✅ Free low dose CT angiogram,
-✅ Free genetic testing, and
--✅ Free wide spectrum bloodwork
... to assess risk?

Just qualify for our study! For more details, visit:
👉👉LMHRstudy.com 👈👈

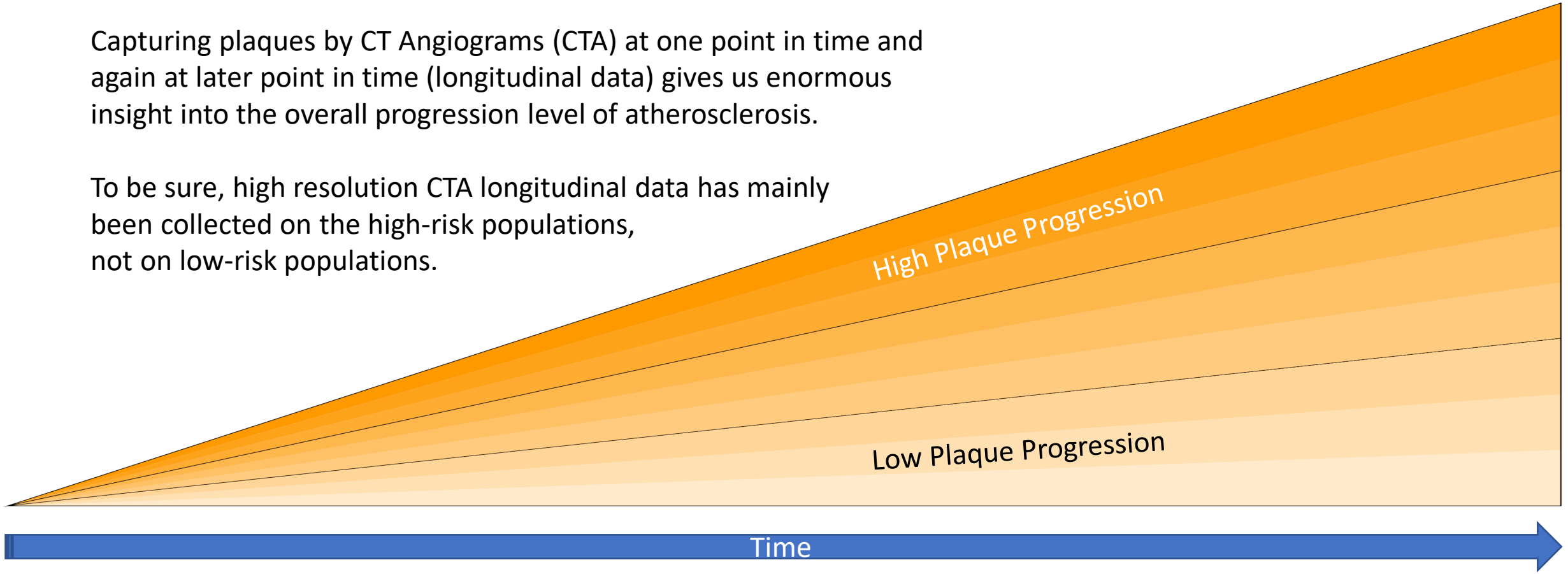
The crucial data we’re collecting and why it matters

Tracking Plaque Progression (1/2)

It’s assumed the vast majority of people have some degree of overall plaque progression (atherosclerosis) over time.

Capturing plaques by CT Angiograms (CTA) at one point in time and again at later point in time (longitudinal data) gives us enormous insight into the overall progression level of atherosclerosis.

To be sure, high resolution CTA longitudinal data has mainly been collected on the high-risk populations, not on low-risk populations.

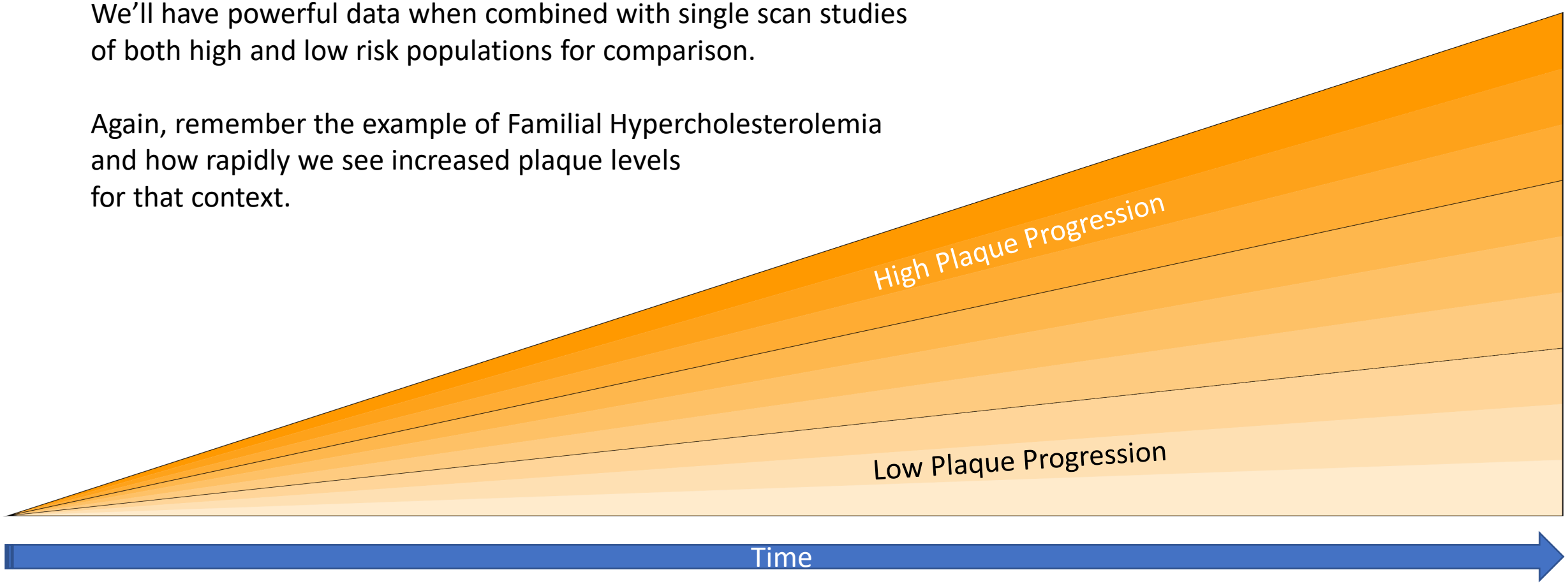


Tracking Plaque Progression (2/2)

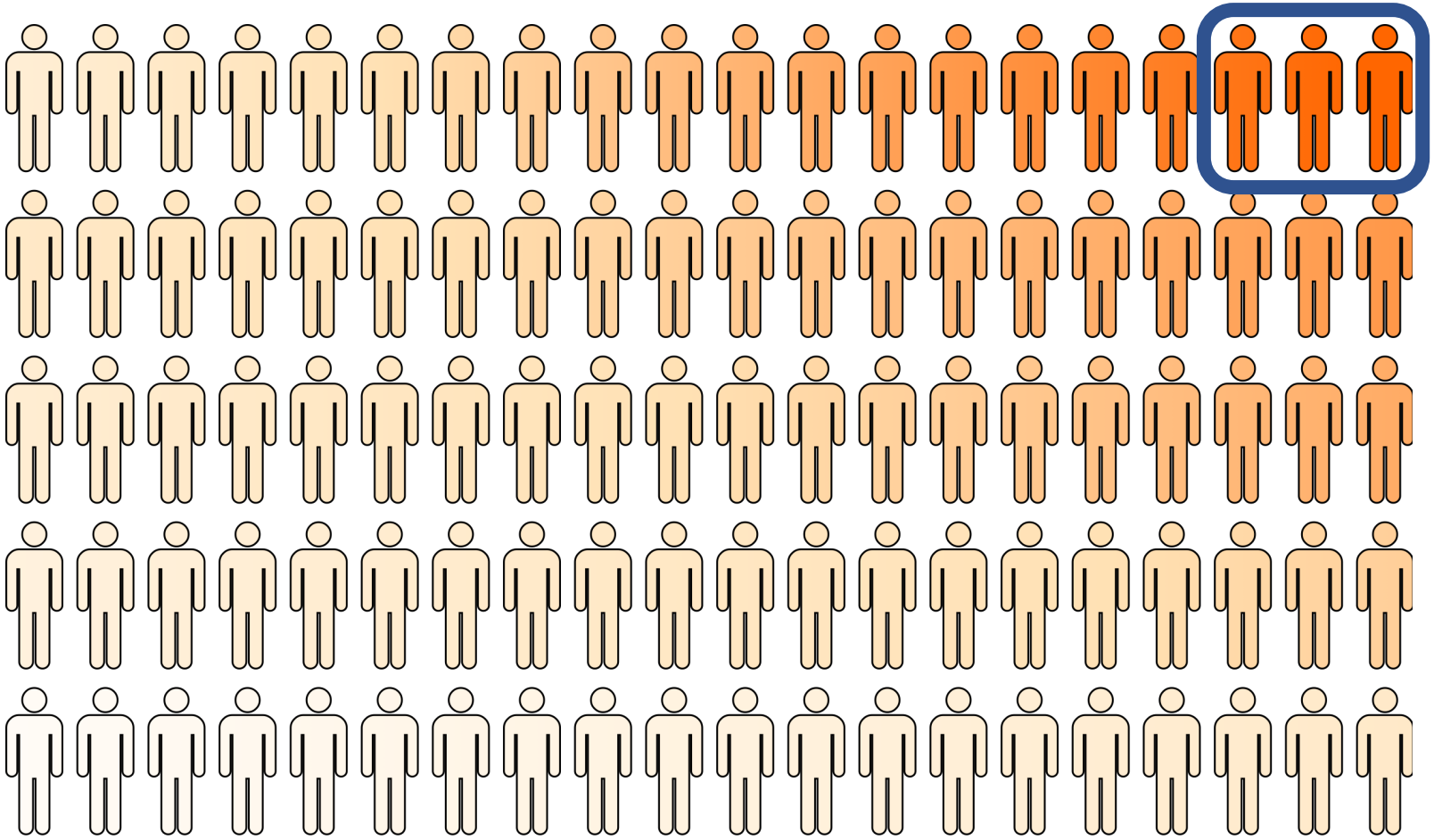
However, this gives us plenty to work with.

We'll have powerful data when combined with single scan studies of both high and low risk populations for comparison.

Again, remember the example of Familial Hypercholesterolemia and how rapidly we see increased plaque levels for that context.



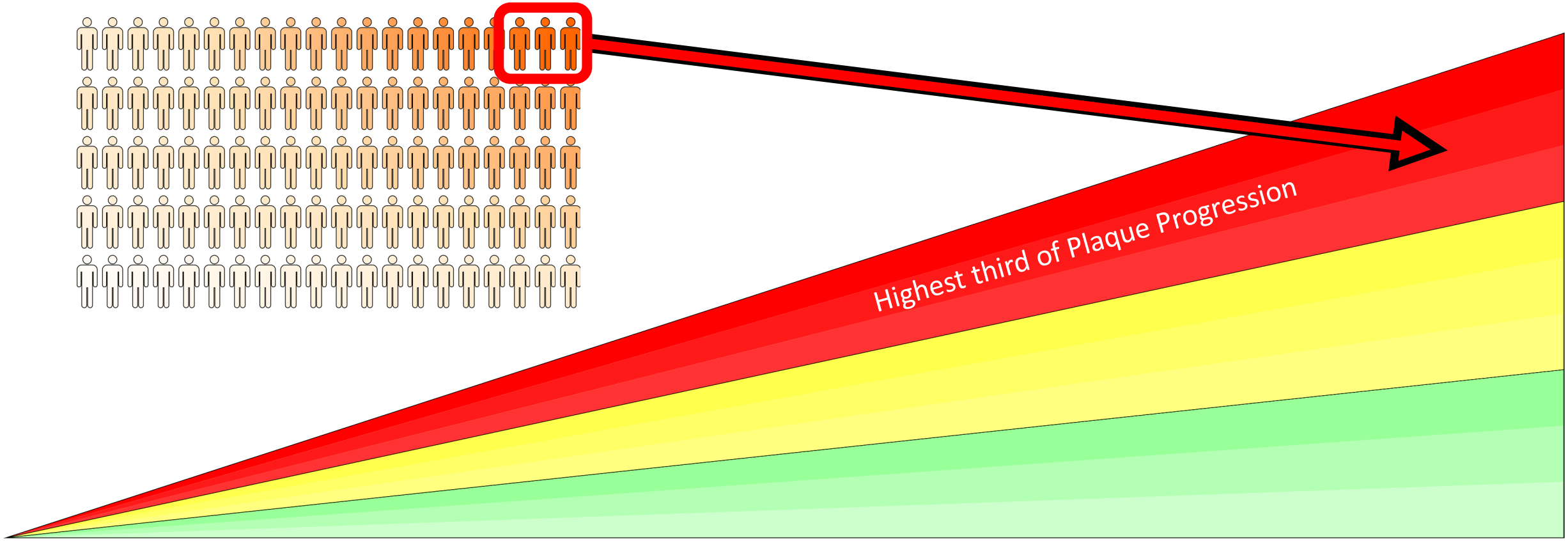
LDL Cholesterol in the General Population



Less than 3% of the US population has an LDL Cholesterol of 190 mg/dL or higher
(Est. via NHANES)

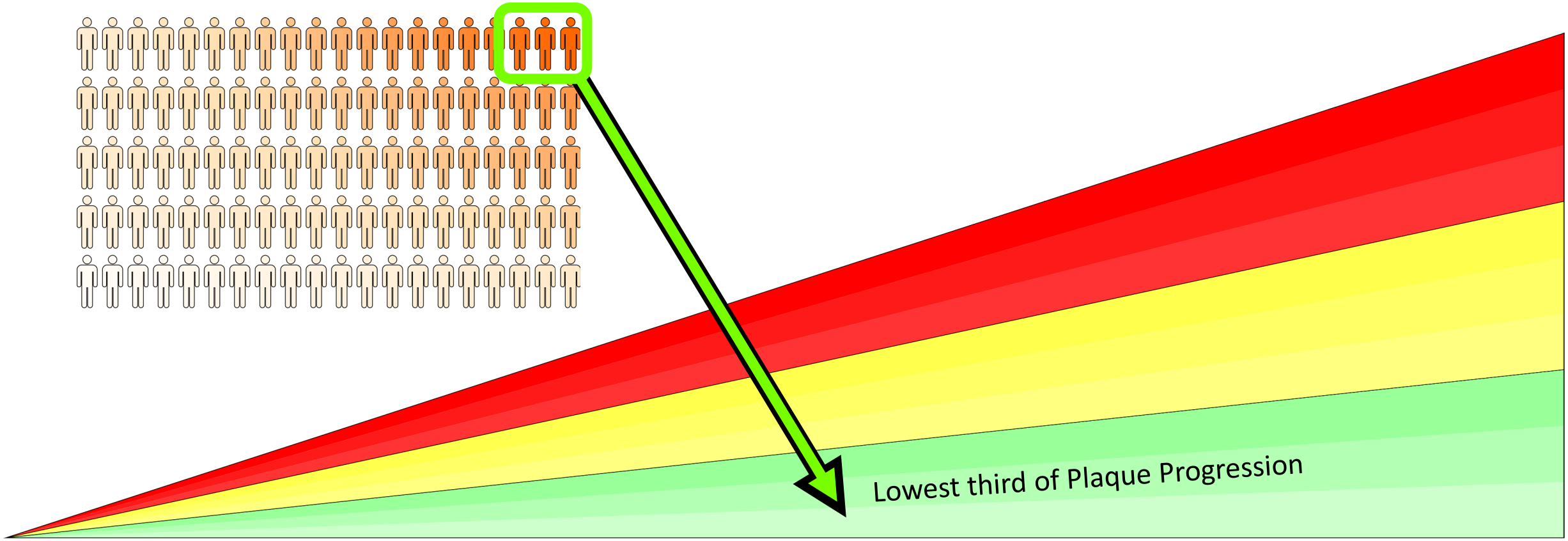
High Plaque Volume Progression?

Given LMHRs have LDL cholesterol in the top 3% of the US population, it would commonly be expected they would likewise have high progression of atherosclerosis, such as in the highest third for the general population.



… or Low Plaque Volume Progression?

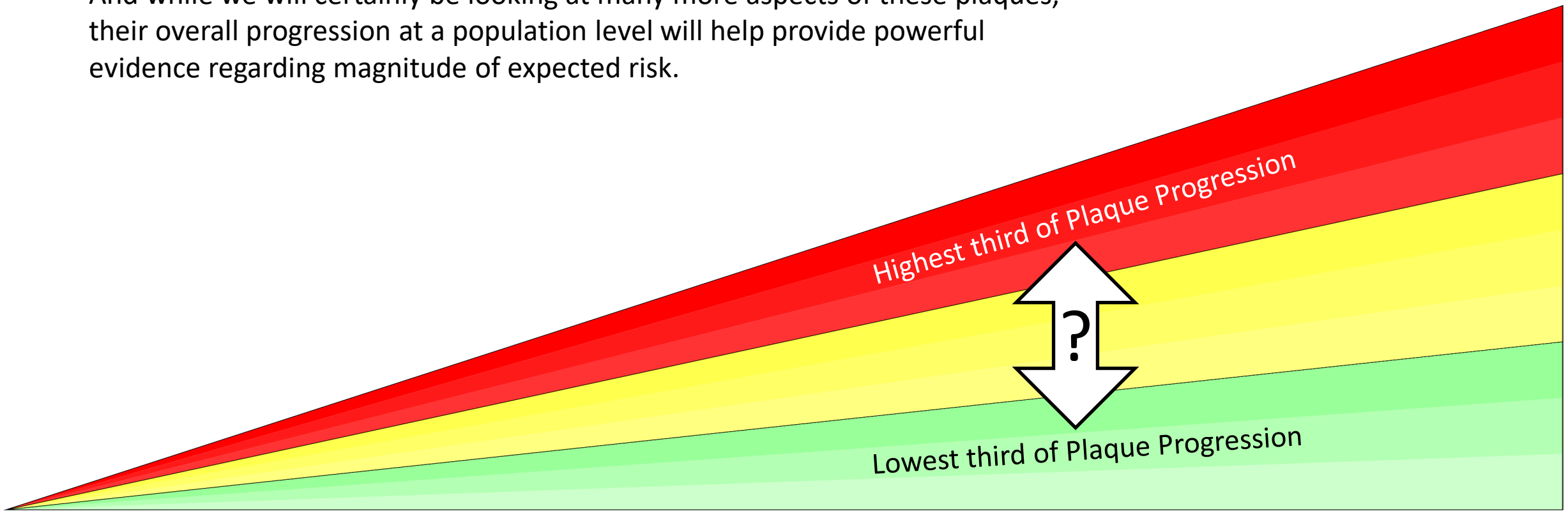
Conversely, where LMHRs have LDL cholesterol in the top 3%, ***it would run counter to conventional expectations to observe a low progression of atherosclerosis, such as in the lowest third of the population.***



Big vs Small Magnitude of Plaque Progression

Plainly stated, a high magnitude of plaque progression is easy to detect with CTA image comparison in a very short span of time; many existing studies have demonstrated this.

And while we will certainly be looking at many more aspects of these plaques, their overall progression at a population level will help provide powerful evidence regarding magnitude of expected risk.

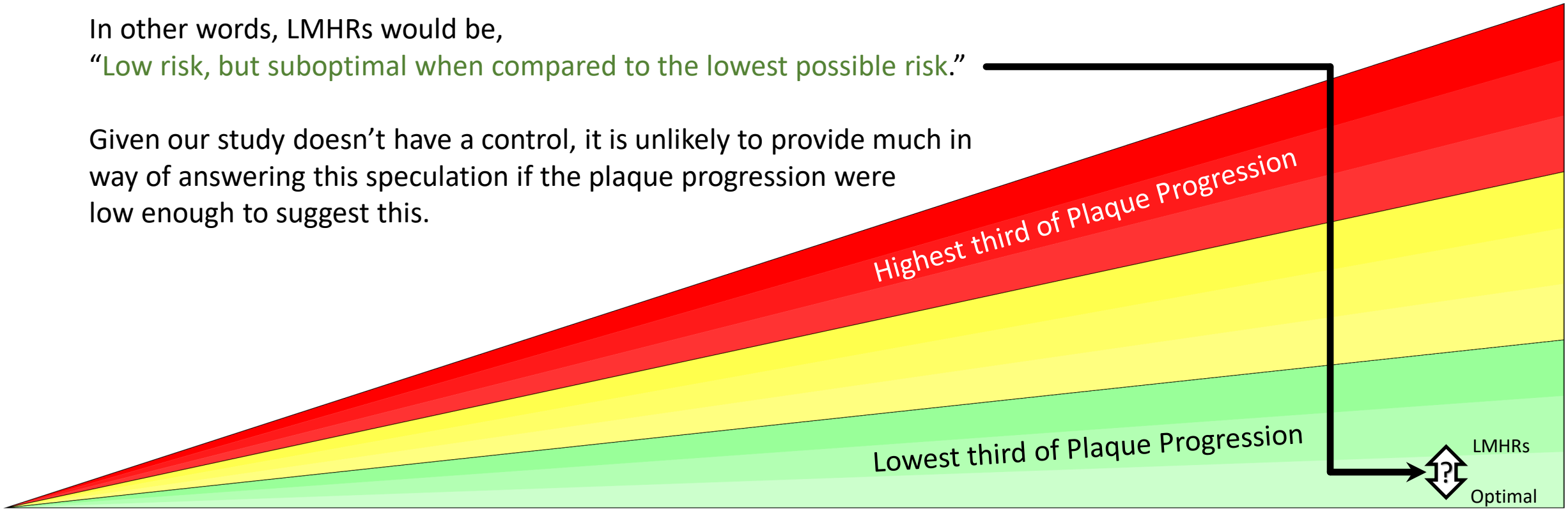


Big vs Small Magnitude of Plaque Progression

Interestingly, as we get closer to the study, there have been many who predict LMHRs will demonstrate a low progression of atherosclerosis, but speculate their progression would be even lower were every risk factor the same save a low LDL cholesterol rather than a high.

In other words, LMHRs would be,
"Low risk, but suboptimal when compared to the lowest possible risk."

Given our study doesn't have a control, it is unlikely to provide much in way of answering this speculation if the plaque progression were low enough to suggest this.



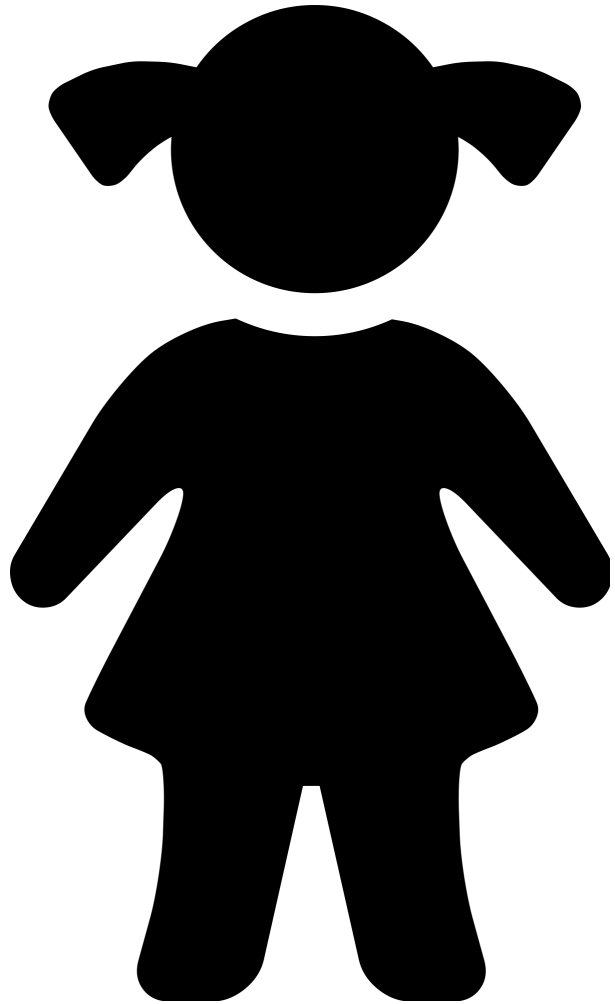
In the early 1970s Drs Brown and Goldstein saw a pivotal patient that, in their words, "…actually determined the scientific course of the rest of our lives."

Patient was a little girl with Homozygous **Familial Hypercholesterolemia** (FH)

- Total Cholesterol: ~850 mg/dL
- LDL Cholesterol: ~783 mg/dL
- Angina and Xanthomas at age 3
- Heart attack at age 6

The odds of getting FH at these levels are

one in a million.

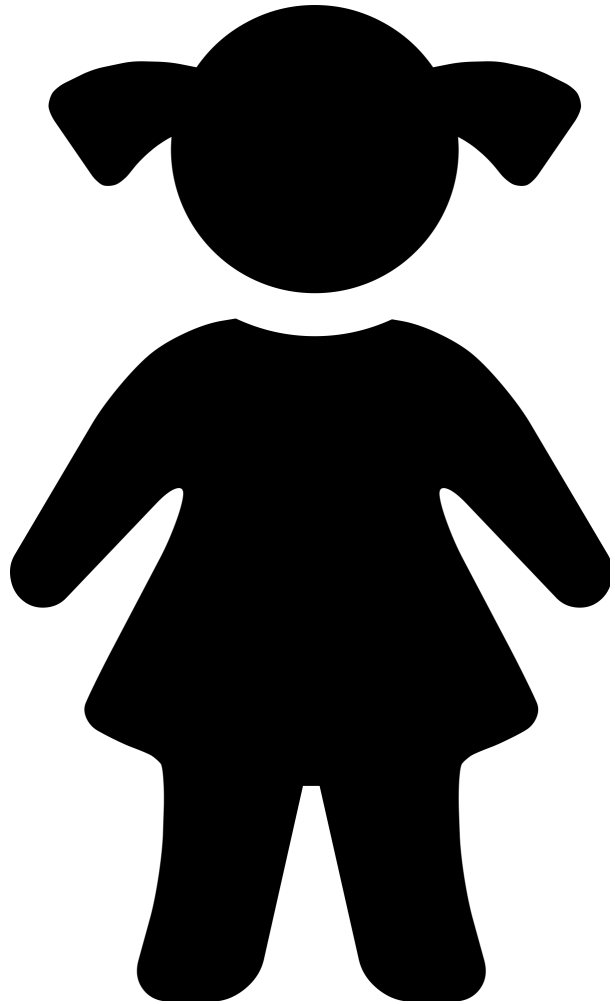


Dr. Goldstein:

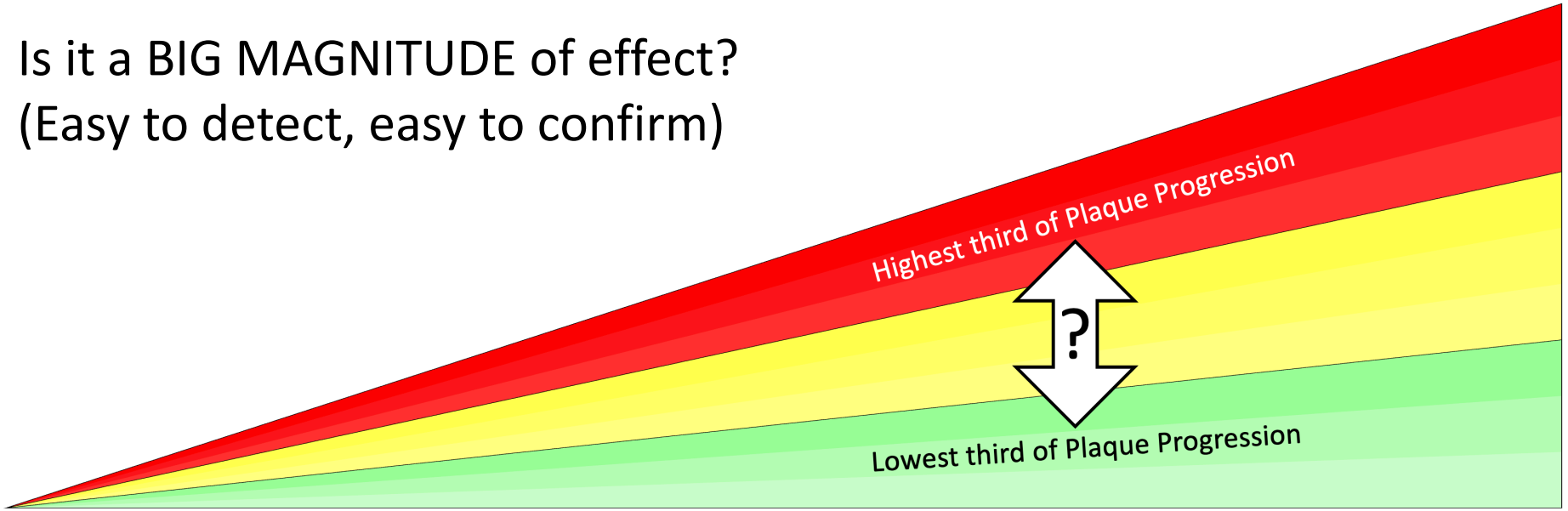
"This little girl had only an elevated LDL.

She had no high blood pressure, she had no diabetes, she didn't smoke, she didn't have a Type A personality.

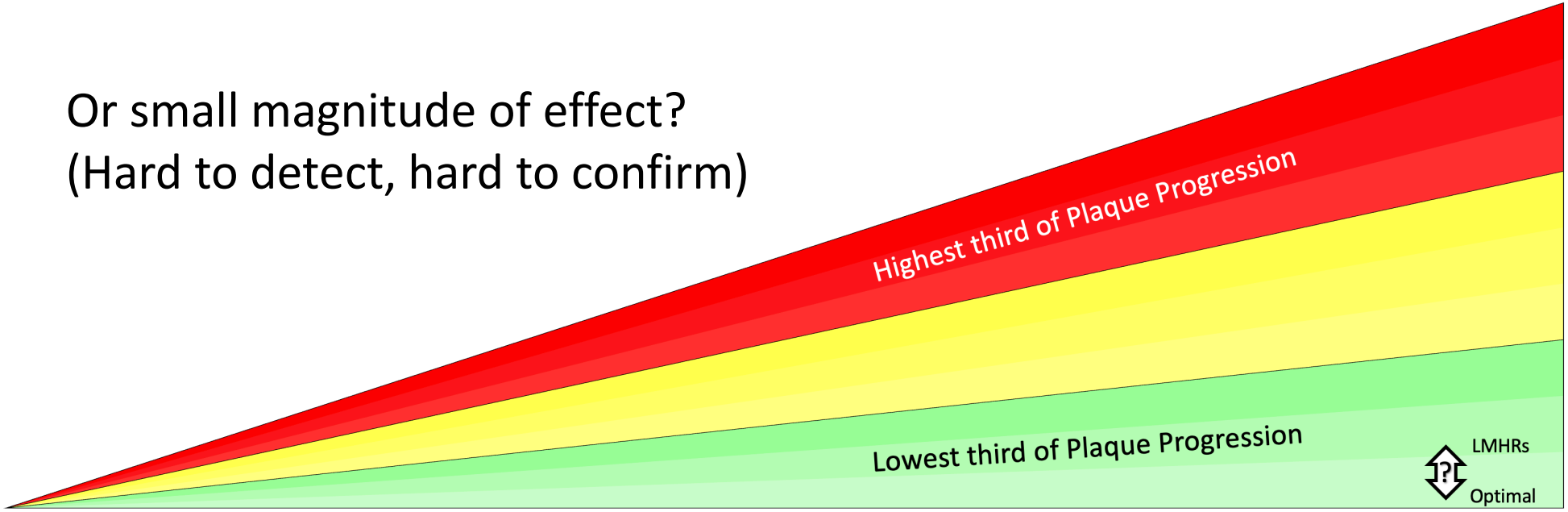
Her only risk factor for having a heart attack at age 6 was this high level of LDL, so it's one of the best examples of a disease where we really know the cause, the cause of the disease in this little girl is an increased level of her LDL."



Is it a BIG MAGNITUDE of effect?
(Easy to detect, easy to confirm)



Or small magnitude of effect?
(Hard to detect, hard to confirm)



Remembering Sarah

Very special thanks to

All members and patrons to Cholesterol Code

All contributors the Citizen Science Foundation

All my amazing coauthors for these and coming papers

Siobhan Huggins for her tireless work in helping us get here

And to my very good friend and collaborator, Nick Norwitz

Thanks for watching

If you or anyone you know may be eligible
for the study, please visit:

CitizenScienceFoundation.org/study

For social media, please use #LMHRstudy