Mapping Hyperlipidemia in Young Adulthood to Coronary Risk:
Importance of Cumulative Exposure and How to Stay Young

Running title: Martin et al.; Cumulative lipid exposure and how to stay young

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The atherogenic cholesterol content of blood, commonly clinically assessed as low-density lipoprotein cholesterol (LDL-C) or non-high-density lipoprotein cholesterol (non-HDL-C), is the central causal factor in atherosclerosis. Given within-person variability, a one-time assessment of cholesterol tends to underestimate the strength of relationship to coronary heart disease (CHD) risk.\(^1\) An etiologically relevant time window for examination of lipids in association with atherosclerotic cardiovascular disease (CVD) risk is multiple decades of life. That is the timeline by which atherosclerosis tends to develop. Therefore, epidemiologic studies with successive lipid assessments and extended time horizons provide especially valuable information.

A classic example is the Johns Hopkins Precursor Study involving 1,017 white male medical students with a mean age of 22 years.\(^2\) They had a median of 3 total cholesterol (TC) measurements, then were followed for a median of 3 decades (range 27-42 years). Serum TC concentrations showed a strong, independent association with incident CVD. After adjustment for other risk factors, a 0.9 mmol/L (35 mg/dL) higher baseline TC was associated with 1.7-fold higher risk of CVD events and 2-fold higher risk of CVD mortality.

**Cumulative Hypercholesterolemia Exposure & CHD Risk in Framingham**

Extending the Hopkins Precursor Study in multiple ways, this issue of *Circulation* contains a superb analysis by Dr. Navar-Boggan et al. The investigators map cumulative hypercholesterolemia exposure in early adulthood to future CHD risk.\(^3\) The paper deserves a close look from those in preventive cardiology, clinical lipidology, internal medicine, pediatrics, and endocrinology.

The analysis included 1,478 Framingham Offspring Cohort participants who were free of CVD at age 53-57. The primary study exposure was duration of hyperlipidemia, defined by Adult Treatment Panel III criteria as a non-HDL-C \(\geq160\) mg/dL. Non-HDL-C levels were
assessed multiple times in the two decades before age 55 and follow-up continued for a median of 15 years.

In addition to the 35 year timespan, a unique strength of this Framingham Heart Study analysis is its natural history context. Data were collected in an era largely free of statin use, which allowed the investigators to assess the CHD risk consequences of long-term exposure to untreated hyperlipidemia. Doing so in some more modern National Heart Lung and Blood Institute cohorts is undeniably more challenging due to widespread statin use.

The proportions of participants who developed CHD by non-HDL-C exposure were as follows: 4.4% for those with no exposure, 8.1% with 1-10 years of exposure, and 16.5% for those with 11-20 years of exposure. Each decade of hyperlipidemia was associated with a ~40% higher adjusted proportional hazard of incident CHD. One of the adjustors was baseline non-HDL-C, thus a one-time assessment was not sufficient to characterize cumulative exposure to atherogenic cholesterol.

**Blood Lipids Change Throughout Life**

A single assessment cannot be expected to adequately reflect blood cholesterol since levels change throughout life. Biological and seasonal variations occur within individuals. Moreover, development of certain medical conditions, such as hypothyroidism or post-menopausal state, can increase atherogenic lipids as can a change in lifestyle habits, like a decrease in physical activity or increase in red meat consumption.

It follows that a cholesterol profile in childhood or youth does necessarily predict what the lipid profile will look like in adulthood. There is tracking from youth to adulthood generally speaking. In the Bogalusa Heart Study, about two-thirds of individuals who ranked in the top quintile for non-HDL-C or LDL-C in childhood later rank in the fourth or fifth highest quintiles.
in adulthood. Only 26% of the explained variance in non-HDL-C after 27 years of follow-up, however, was explained by the baseline non-HDL-C at age 5-14 plus body mass index change over time, race, sex, and age.

Current Guidelines Use One-Time Assessments in Risk Estimation Models

Cardiovascular guidelines currently base risk estimation equations on one-time measurements of risk factors. For example, per the 2013 ACC/AHA risk assessment guideline, an individual who is 40-79 years of age, without diabetes or established atherosclerotic CVD, and with an LDL-C 70-189 mg/dL, should undergo 10-year risk estimation for CHD/stroke. The estimation equations use one-time TC and HDL-C levels, along with sex, race, blood pressure, smoking, and diabetes, but are dominated by chronologic age, a gross marker of the cumulative exposure to risk factors.

In the current era of digital medicine, electronic health records, big data, and overall advances in computing and informatics, it may be feasible to more fully leverage time-varying information about cholesterol and other risk factors. Akin to smoking pack-years, we could multiply the cholesterol level by the duration of exposure (e.g., “LDL-C years” or “non-HDL-C years” or if available, “apoB years”) to compute cardiovascular risk. If automated estimation tools were handled by the computer, then estimation would require no more time investment for clinicians.

Many individuals without a history of CHD who are living in the U.S. may already have repeated lipid measures. The Adult Treatment Panel recommended lipid testing at least once every 5 years from age 20 onward. Testing was to include major blood lipid fractions: TC, LDL-C, HDL-C, and triglycerides. Therefore, non-HDL-C could be calculated even though it is not routinely reported by all labs. The 2013 ACC/AHA guidelines also support assessment of TC
and HDL-C every 4-6 years in individuals aged 20-79 years. Based on 2010 data, the Centers for Disease Control and Prevention reported that about two-thirds of Americans ≥20 years old had their cholesterol checked within the preceding 5 years.⁷

Cumulative exposure is also relevant to non-lipid risk factors and the ideal expression of cardiovascular risk in theory would be an integration of cumulative exposure to all risk determinants.⁸ Although it’s likely to become increasingly feasible to integrate cholesterol-years, tobacco pack-years, diabetes-years, and hypertension-years, and potentially even environmental and genetic factors, we’re not there yet. Moreover, inaccuracies in measurements, significant time gaps between measurements, and missed information from unmeasured exposures represent serious potential limitations. Nevertheless, a cumulative exposure risk model warrants consideration, and would require rigorous derivation and validation as has been done for current risk estimation tools.

At present, coronary artery calcium scoring can do much of the extra work for us.⁸ By directly visualizing the arteries, we are evaluating the result of integrated risk exposure up until a given point in time. Moreover, we learn whether or not the patient has the disease atherosclerosis – that we propose to treat. And we learn the burden of atherosclerosis, which may be conceptualized as “arterial age”.⁹ The additional information could be important in some patients when lifelong treatment decisions are being made. Indeed, the 2013 ACC/AHA guidelines endorse the use of coronary artery calcium scoring in selected patients.

How to Stay Young

While we can’t change the inevitable reality that we find ourselves further each day from the date of our birth certificate, we can do something about our vascular age. To understand how to maintain a younger vascular age for more individuals in our population, perhaps it helps to place
the typical trajectory of lipids in context. Healthy neonates have an LDL-C of 30-70 mg/dL,\textsuperscript{10} corresponding on a population percentile basis to a non-HDL-C of ~50-90 mg/dL.\textsuperscript{11} Although hunter-gatherers following indigenous lifestyles may maintain atherogenic cholesterol levels in similarly favorable ranges,\textsuperscript{11} modern adults living in Western agricultural societies typically carry levels at least two-fold higher. We’re not genetically adapted to handle the excess atherogenic cholesterol, and in response, atherosclerosis is virtually synonymous with age, although it doesn’t have to be.

By the second decade of life in the U.S., an average person’s LDL-C rises to ~90 mg/dL\textsuperscript{12} and non-HDL-C to ~110 mg/dL.\textsuperscript{4} During the third and fourth decades, LDL-C and non-HDL-C continue to rise, particularly in men.\textsuperscript{4} An average man in his 30s has a non-HDL-C of ~150 mg/dL and woman in her 30s ~130 mg/dL.\textsuperscript{4} Overall, about one-third of adults aged ≥20 years have an LDL-C >130 mg/dL\textsuperscript{12} and a similar proportion are estimated to have a non-HDL-C >160 mg/dL. Given such a sheer abundance of hyperlipidemia, we’ve redefined “normal” by averages in our population, rather than biological or evolutionary norms.

We’re then faced in an enormous burden of atherosclerotic CVD in the second half of life, which is when we currently focus treatment. It’s more of a reactionary approach. In many individuals atherosclerosis is already at an advanced stage or a CVD event has occurred by the time that a major lipid-lowering is made. Fortunately, we have statins as an option, which reduce the relative risk of CVD by about one-fifth for each 1 mmol/L (39 mg/dL) lowering of LDL-C. However, substantial residual risk remains. Moreover, as Navar-Boggan and colleagues note, under current guidelines, only 1 in 6 adults in their study with prolonged duration of exposure to hyperlipidemia would have been directly recommended for statin therapy at age 40, and one in three at age 50.
Some have proposed starting primary prevention earlier with statins. Atherosclerosis regression can occur with aggressive LDL-C lowering to on-treatment levels of <70 mg/dL. If implemented early enough, treatment might be essentially curative. One concept map is to give initial regression therapy followed by periodic retreatment to suppress atherosclerosis development.\textsuperscript{13} Proof-of-concept studies and outcome trials were proposed, and it will be many years before such data becomes available.

Current best evidence on the impact of earlier and long-term exposure to lower atherogenic cholesterol comes from genetic studies. For example, carrier status for mutations in the Niemann-Pick C1-like protein and PCSK-9 is associated with reduced LDL-C from birth and a very large reduction in CHD risk.\textsuperscript{14, 15} Overall, individuals with LDL-lowering polymorphisms have a relative reduction in CHD of 55% per mmol/L lower LDL-C, which is a nearly 3-fold greater reduction per LDL-C lowering than observed with statin therapy later in life.\textsuperscript{16} The greater reduction could be explained by the prolonged duration of lowering and may also represent a benefit of starting earlier in life.

Questions remain about whether starting a statin earlier could produce similarly greater benefits. Regardless, widespread statin use is already controversial enough for older people, let alone for younger patients. The sheer cholesterol burden in our society speaks to the need for societal level changes in the way we live and age.

While some are lucky to have favorable genes, if we want to keep our arteries young as a society, we need to start much earlier in life. The time period of young adulthood highlighted in Navar-Boggan’s study need to be given the respect they deserve. The first answer of course is to improve lifestyle habits. This is easy to evoke, but more challenging to implement. Possible suggestions include taking advantage of the widespread use of mobile technology to utilize smart
text prompts of fitness reminders and/or diet/fitness apps to help motivate and prompt lifestyle changes. Patients should be encouraged to track their own lipid values over time, “know their numbers” to help promote partnership with their clinicians.

This study and the related literature reinforce the importance of AHA initiatives such as Life’s Simple 7, Jump Rope for Heart, Hoops for Heart, Teaching Gardens for Children, and Simple Cooking with Heart. We, not only as researchers and clinicians, but as a society, need to come together and make it a top priority to eat better, be more physical active, and maintain healthy weights. The sooner the better. We need to shift population lipid levels close to those of healthy babies and redefine the norm closer to what is biologically normal. As Theodore Roosevelt said, "Old age is like everything else. To make a success of it, you've got to start young."

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