

IS ATHEROSCLEROSIS A PEDIATRIC DISEASE?

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Updated October 2, 2025

ABSTRACT

In the US and other developed countries, cardiovascular disease is a major health burden and the leading cause of death. There are at least three lines of evidence that support the concept of atherosclerosis, the principal cause of cardiovascular disease, having its origins in childhood. Although the most direct evidence is in children with genetic dyslipidemia, such as familial hypercholesterolemia, there is evidence that in-utero and acquired effects may play a role as well. The ability to identify genetic mutations and/or acquired factors or conditions early in childhood creates the opportunity to prevent development of risk factors and future CVD-related events by effective and timely intervention.

INTRODUCTION

Since publication of the National Cholesterol Education Program (NCEP) recommendations in 1992 (1), there has been growing interest in early identification and intervention of children at moderate to high risk of premature cardiovascular disease. Since that time, additional pediatric specific guidelines and recommendations have been published (2,3,4). A fundamental question, however, is whether atherosclerosis, the underlying basis for cardiovascular disease, is a pediatric disease.

Arteriosclerosis is characterized by deposits of lipoproteins and calcium in the arterial intima

(plaques), resulting in inflammation and subsequent fibrosis. The buildup of arterial plaques reduces blood flow and often leads to symptoms of cardiovascular disease (CVD), such as angina, and CVD-related events, such as myocardial infarction and stroke. Although the atherosclerotic process rarely leads to CVD-related symptoms or events in children, its origins can be demonstrated at a very young age in those with genetic mutations and acquired risk factors and conditions. In contrast to those with heterozygous familial hypercholesterolemia, children with a homozygous disease have early clinical manifestations (xanthoma) and significant, symptomatic ASCVD that generally results in premature death, often during adolescence or early adulthood.

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FETAL STUDIES

During pregnancy maternal hypercholesterolemia, such as occurs in women with familial hypercholesterolemia, may have an adverse effect on the future health of the fetus. The presence of greatly increased fatty streak formation in human fetal arteries has been reported in over 50% of fetuses of mothers

who were hypercholesterolemic during pregnancy (5). Strong correlations were noted between maternal and fetal plasma cholesterol levels, which in turn were proportional to the extent of lesion formation in the fetus. Despite similar plasma cholesterol levels during childhood, atherosclerosis in children of hypercholesterolemic mothers progressed much more rapidly than did children of mothers who had normal cholesterol levels (6). Use of cholesterol lowering agents or antioxidants in the mother greatly reduced fetal and postnatal atherosclerosis in the offspring (7).

A potential mechanism for this susceptibility to atherosclerosis is suggested by animal models that demonstrate persistence differences in arterial gene expression after birth between offspring of mothers who have normal compared to elevated levels of cholesterol. This evidence supports the assumption that fetal lesion formation is associated with genetic programming, which may in turn affect postnatal atherogenesis (8). Cholesterol lowering and antioxidant treatment during pregnancy appear to positively influence in-utero programming and decrease postnatal susceptibility to atherogenesis (9).

OBSERVATIONAL/EPIDEMIOLOGIC STUDIES

Fatty streaks, the earliest progenitor lesions, are present from early childhood and well established by 20 or 30 years of age. Such lesions, as well as raised plaques, increase rapidly in prevalence and extent during the 15–34-year age span. Relatively advanced levels of atherosclerosis, including fibrous plaques, have been found in adolescents and young adults (10–12). Fatty streaks progress to raised lesions at vulnerable anatomic sites (13). Vascular surfaces subjected to turbulent flow, the preferred sites for fatty streaks, are the same sites as those for advanced lesions, the latter being vulnerable to plaque rupture and thrombosis (10,14,15). Observational studies from autopsies have helped inform us about the timing, extent and severity of atherosclerotic lesions. Thirty percent (30%) of autopsy specimens of black males contained aortic atheroma by age 10 years (16). Autopsy studies of U.S. soldiers killed during the

Korean War showed significant evidence of CVD in 77% of soldiers, with an average age of 22 years (17). Similar findings were reported in Vietnam War casualties (18).

In addition to autopsy findings, studies using noninvasive measures, including carotid intima-medial thickness (cIMT) and arterial distensibility, have shown anatomic and functional changes of atherosclerosis in youth (19–23). Thickness of the far wall of the internal carotid progresses with age and risk factors alone and together predict thickness in young adults (24).

The risk factors associated with early arterial lesions in children and young adults are the same as those associated with the advanced lesions that cause symptomatic coronary artery disease in adulthood (12, 25). Increased body mass index (BMI), elevated systolic and diastolic blood pressures, high low density lipoprotein cholesterol (LDL-C), low levels of high-density lipoprotein cholesterol (HDL-C), and diabetes mellitus are all associated with greater atherosclerotic plaque coverage and more advanced atherosclerotic lesions (12,26–28). Autopsy data show that the severity of asymptomatic CVD increases as the number of risk factors increase from 2 - 39 years of age (13,29).

Based on considerable evidence, we can conclude that observational and epidemiologic studies have documented: 1) the origins of atherosclerosis are present from a very early age; 2) there is a striking increase in both the severity and extent of atherosclerosis as age and the number of risk factors increase; 3) the presence and intensity of risk factors are highly correlated with the extent and severity of atherosclerosis; and 4) the combined impact of multiple risk factors is exponentially greater than individual factors alone.

MENDELIAN RANDOMIZATION STUDIES

Genetic mutations characterized by lifelong elevations of cholesterol are associated with increased

cardiovascular disease and premature events and provide the best evidence relating risk to future probability of ASCVD (30). Conversely, genome wide analysis has demonstrated many alleles that profoundly decrease CVD risk by lifelong lower levels of cholesterol (Table 1) (31, 32). It cannot be assumed, however, that a comparable level of lipid lowering achieved later in life with the use of medication will

offer the same protective effects (33). This, in part, may be due to initiation of lipid-lowering therapy after clinical disease is recognized, which may be insufficient to prevent the progression of established atherosclerosis. Additionally, the duration of the low cholesterol level is lifelong vs. relatively short number of years on lipid lowering therapy.

Table 1. Key Mendelian Randomization Studies				
Mutation	LDL-Cholesterol Reduction			CHD Risk
APOC-III (35)	↓16%	↓23.4 mg/dL	(0.60 mmol/L)	↓40%
NPC1L1 (36)	---	↓12 mg/dL	(0.31 mmol/L)	↓53%
PCSK9 (30)				
Blacks	↓28%	↓40 mg/dL	(1.0 mmol/L)	↓88%
Whites	↓15%	↓20 mg/dL	(0.5 mmol/L)	↓47%
From: Wilson, Don P and Gidding, S. The Journal of Clinical Lipidology. September–October, 2015. Volume 9, Issue 5, Supplement, Pages S1–S4				

In a 20-year follow-up study of statin therapy in children with hypercholesterolemia, 98% of whom had genetically confirmed FH, early treatment was shown to slow the progression of cIMT thickness and reduced the risk of CVD in adulthood (34). In this study 184 subjects with FH were compared to 77 unaffected siblings, as well as the outcomes of their affected parent. The mean LDL-C level in the subjects with FH decreased 32% from the baseline (237.3 to 160.7 mg/L or 6.13 to 4.16 mmol/L); while treatment goals of LDL-C <100 mg/dL (2.59 mmol/L) were achieved in only 20%. Mean progression of cIMT thickness was not significantly different between those with FH and their siblings, indicating a normalization of the rate of cIMT thickening. The cumulative incidence of CVD-related events (1% vs. 26%) and of death from CVD causes at 39 years of age (0% vs. 7%) was lower among the subjects with FH than among their affected parents with FH. Such findings suggest early identification and initiation of effective lipid lowering therapy, although not to LDL-C levels less than 100 mg/dL, significantly reduces the occurrence and progression of atherosclerosis.

Thus, growing trial evidence is consistent with genetic studies that support therapeutic intervention to achieve lower lipid levels, although the long-term safety and efficacy of medications to accomplish this goal in the pediatric population cannot be documented at this time.

Although limited information is available in youth, there is growing interest in the role of TGs as a CVD risk factor. Mendelian randomization studies of individuals with TG lowering variants in the lipoprotein lipase gene and LDL-C lowering variants in the LDL receptor gene were found to be associated with similar lower risk of coronary heart disease per 10-mg/dL lower level of ApoB-containing lipoproteins (odds ratios of 0.771 and 0.773, respectively). Importantly, the clinical benefit of lower TG levels was similar to that of lower LDL-C levels per 10mg/dl decrease in ApoB. However, a much larger decrease in TG levels (approx. 70mg/dl) was required to decrease Apo B by 10mg compared to LDL cholesterol (approx. 14mg/dl). This finding suggests that the causal effect of all ApoB-containing lipoprotein particles on the risk of CVD appears to be determined by the circulating concentration of those particles rather than by the mass of cholesterol or

triglyceride that they carry (37). This observation, if confirmed, could prove important since 1) significant numbers of youth have elevated non-HDL cholesterol levels, a surrogate marker of apoB, as a result of adverse lifestyles, underlying genetic mutations in TG metabolism, or both; 2) the presence of elevated ApoB during childhood, which often persists into adulthood,

represent a much longer period of exposure than that of adult onset; and 3) several novel therapies that potentially reduce TG levels are currently in development, some of which have been shown to be effective in youth. However, long-term studies addressing risk reduction and outcomes, safety and FDA approval for use in youth are lacking at this time.

Table 2. Effects on the Risk of CV Events per Decrease of 10 mg/dL in the LDL-C* or ApoB containing Lipoproteins** Level				
Polygenic Risk Score	OR	95% CI	P	Reference
*ACLY score	0.823	0.78 to 0.87	4.0×10 ⁻¹⁴	Ference, NEJM 2019
*HMGCR score	0.836	0.81 to 0.87	3.9×10 ⁻¹⁹	Ference, NEJM 2019
**LPL score	0.771	0.741 to 0.802	3.9 × 10 ⁻³⁸	Ference, JAMA 2019
**LDLR score	0.773	0.747 to 0.801	1.1 × 10 ⁻⁴⁶	Ference, JAMA 2019

*Mendelian Randomization Study of ACLY and Cardiovascular Disease. Ference BA, Ray KK, Catapano AL, Ference TB, Burgess S, Neff DR, Oliver-Williams C, Wood AM, Butterworth AS, Di Angelantonio E, Danesh J, Kastelein JJP, Nicholls SJ. N Engl J Med. 2019 Mar 14;380(11):1033-1042. **Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants With Risk of Coronary Heart Disease. Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, Laufs U, Oliver-Williams C, Wood AM, Butterworth AS, Di Angelantonio E, Danesh J, Nicholls SJ, Bhatt DL, Sabatine MS, Catapano ALJAMA. 2019 Jan 29;321(4):364-373.

As an alternative to statins, the utility of newer therapies such as ATP citrate lyase inhibitors (ACLY), an enzyme in the cholesterol-biosynthesis pathway upstream of 3hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), are being explored. Studies of genetic variants that mimic the effect of ATP citrate lyase inhibitors showed that, compared to statins, ACLY inhibitors appear to lower plasma LDL-C levels by the same mechanism of action. Both were associated with similar effects on the risk of CVD per unit decrease in the LDL-C level (38). These findings, if found to be safe and effective, offer new opportunities for future drug development.

ACQUIRED RISK FACTORS AND RISK CONDITIONS

Risk factors and risk conditions (Table 3) are often

acquired during childhood and may accelerate development of ASCVD. In clinical practice dyslipidemia is most commonly encountered in children and adolescents who are obese (BMI > 95th percentile) and insulin resistant, the latter clinically manifest by the presence of acanthosis nigricans, impaired or elevated fasting glucose, hypertension, and in girls, polycystic ovarian syndrome (PCOS). There is a striking increase in both severity and extent of atherosclerosis as age and the number of risk factors increases. The presence and intensity of risk factors are highly correlated with the extent and severity of atherosclerosis. Furthermore, risk factors measured in childhood and adolescence have been shown to be better predictors of the severity of atherosclerosis than risk factors measured in young adults (13).

Table 3. Acquired Risk Factors and Risk Conditions	
Risk Factors	
Non-Modifiable <ul style="list-style-type: none"> • Family History • Age • Gender • Perinatal Factors 	Modifiable <ul style="list-style-type: none"> Nutrition/Diet Physical Inactivity Tobacco Exposure Blood Pressure Lipid Levels Overweight/Obesity Diabetes Mellitus Metabolic Syndrome Inflammation
Risk Conditions	
Moderate Risk <ul style="list-style-type: none"> • Kawasaki disease with regressed coronary aneurysms • Chronic inflammatory diseases • HIV infection 	High Risk <ul style="list-style-type: none"> Kawasaki disease with current coronary aneurysms Type 1 and 2 Diabetes Mellitus Post-orthotopic heart transplant

The ability to identify genetic mutations and/or acquired factors or conditions early in this vulnerable population creates the opportunity to prevent development of risk factors and future CVD-related events by effective and timely intervention. All children, including those with genetic dyslipidemia, should be encouraged to follow a heart healthy lifestyle. If begun early, such efforts have the potential of preventing behaviors and risk factors that increase future CVD risk. To assist clinicians in this task, the American Heart Association (AHA) has defined four health behaviors and four health factors that are strongly correlated with ideal cardiovascular health (39). Observational studies of individuals who were able to achieve and maintain one or more ideal cardiovascular health behaviors into middle age had greater longevity, longer morbidity-free survival, compression of morbidity to the end of the lifespan, greater health-related quality of life in older age, and substantially lower healthcare costs later in life (Table 4) (40, 41). This evaluation of cardiovascular wellness can be applied to evaluation of adolescents and targeted as part of primordial prevention (42).

Table 4. Correlation of Health Behaviors and Factors with Ideal Cardiovascular Health						
		Number of Health Behaviors* (% lower risk for incidence CHD)				
Study	N	1	2	3	4	5
Males (40)	42,847	(54%)	(63%)	(71%)	(78%)	(87%)
Females (41)	84,129	---	---	(57%)	(66%)	(83%)

Cardiovascular disease risk factors are associated with both the early and advanced stages of atherosclerosis. Individuals at increased risk should be encouraged to achieve a low lifetime risk by preventing development of risk factors starting in youth. Recognizing that this process begins during

childhood is key to facilitating implementation of measures that will prevent atherosclerosis and thereby reduce or eliminate future CVD-related events.

Using the seven AHA cardiovascular health metrics, scoring of adolescents using NHANES data showed low scores, especially deficient in points for diet and exercise (42). Retrospective analysis revealed that the seven metrics score in adolescents is inversely associated with cIMT and directly associated with arterial elasticity, suggesting that this evaluation of cardiovascular wellness can be applied to evaluation of adolescents and targeted as part of primordial prevention (43).

Cardiovascular disease risk factors are associated with both the early and advanced stages of atherosclerosis. Individuals at increased risk should be encouraged to achieve a low lifetime risk by preventing development of risk factors starting in youth. Recognizing that this process begins during childhood is key to facilitating implementation of measures that will prevent atherosclerosis and thereby reduce or eliminate future CVD-related events.

REFERENCES

1. American Academy of Pediatrics. National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 1992 Mar;89(3 Pt 2):525-84.
2. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. *Pediatrics*. 2011 Dec;128 Suppl 5:S213-56.
3. Jacobson TA, Maki KC, Orringer CE, Jones PH, Kris-Etherton P, Sikand G, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 2. *J Clin Lipidol*. 2015 Nov-Dec;9(6 Suppl):S1,122.e1.
4. Grundy, S. M., Stone, N. J., Bailey, A. L., Beam, C., Birtcher, K. K., Blumenthal, R. S., . . . Yeboah, J. (2019). 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/AASPC/NLA/PCNA guideline on the management of blood cholesterol: A report of the American college of Cardiology/American heart association task force on clinical practice guidelines. *Circulation*, 139(25), e1082-e1143.
5. Napoli C, D'Armiento FP, Mancini FP, Postiglione A, Witztum JL, Palumbo G, et al. Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. *J Clin Invest*. 1997 Dec 1;100(11):2680-90.
6. Napoli C, Glass CK, Witztum JL, Deutsch R, D'Armiento FP, Palinski W. Influence of maternal hypercholesterolemia during pregnancy on progression of early atherosclerotic lesions in childhood: Fate of Early Lesions in Children (FELIC) study. *Lancet*. 1999 Oct 9;354(9186):1234-41.
7. Napoli C, Witztum JL, Calara F, de Nigris F, Palinski W. Maternal hypercholesterolemia enhances atherogenesis in normocholesterolemic rabbits, which is inhibited by antioxidant or lipid-lowering intervention during pregnancy: An experimental model of atherogenic mechanisms in human fetuses. *Circ Res*. 2000 Nov 10;87(10):946-52.
8. Palinski W. Effect of maternal cardiovascular conditions and risk factors on offspring cardiovascular disease. *Circulation*. 2014 May 20;129(20):2066-77.
9. Palinski W, Napoli C. The fetal origins of atherosclerosis: Maternal hypercholesterolemia, and cholesterol-lowering or antioxidant treatment during pregnancy influence in utero programming and postnatal susceptibility to atherogenesis. *FASEB J*. 2002 Sep;16(11):1348-60.
10. McGill HC, Jr, McMahan CA. Determinants of atherosclerosis in the young. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Am J Cardiol*. 1998 Nov 26;82(10B):30T-6T.
11. Strong JP. Natural history and risk factors for early human atherogenesis. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Clin Chem*. 1995 Jan;41(1):134-8.
12. Berenson GS, Srinivasan SR, Bao W, Newman WP, 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. 1998 Jun 4;338(23):1650-6.
13. McGill HC, Jr, McMahan CA, Gidding SS. Preventing heart disease in the 21st century: Implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study. *Circulation*. 2008 Mar 4;117(9):1216-27.
14. Constantinides P. Experimental atherosclerosis. Amsterdam: Elsevier; 1965:1
15. Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W, Jr, Rosenfeld ME, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on

- Arteriosclerosis, American Heart Association. *Arterioscler Thromb*. 1994 May;14(5):840-56.
16. Strong JP, Malcom GT, Oalman MC. Environmental and genetic risk factors in early human atherogenesis: Lessons from the PDAY study. *Pathobiological Determinants of Atherosclerosis in Youth*. *Pathol Int*. 1995 Jun;45(6):403-8.
17. Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in action in Korea; preliminary report. *J Am Med Assoc*. 1953 Jul 18;152(12):1090-3.
18. McNamara JJ, Molot MA, Strempel JF, Cutting RT. Coronary artery disease in combat casualties in Vietnam. *JAMA*. 1971 May 17;216(7):1185-7.
19. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimalmedial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine study. *Circulation*. 2001 Dec 4;104(23):2815-9.
20. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: The Cardiovascular Risk in Young Finns study. *JAMA*. 2003 Nov 5;290(17):2277-83.
21. Urbina EM, Kietky L, Tsai J, Srinivasan SR, Berenson GS. Impact of multiple cardiovascular risk factors on brachial artery distensibility in young adults: The Bogalusa Heart Study. *Am J Hypertens*. 2005 Jun;18(6):767-71.
22. Juonala M, Magnussen CG, Venn A, Dwyer T, Burns TL, Davis PH, et al. Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: The Cardiovascular Risk in Young Finns study, the Childhood Determinants of Adult Health study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. *Circulation*. 2010 Dec 14;122(24):2514-20.
23. Tuzcu EM, Kapadia SR, Tutar E, Ziada KM, Hobbs RE, McCarthy PM, et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: Evidence from intravascular ultrasound. *Circulation*. 2001 Jun 5;103(22):2705-10.
24. Magnussen CG, Venn A, Thomson R, Juonala M, Srinivasan SR, Viikari JS, et al. The association of pediatric low- and high-density lipoprotein cholesterol dyslipidemia classifications and change in dyslipidemia status with carotid intima-media thickness in adulthood: Evidence from the Cardiovascular Risk in Young Finns study, the Bogalusa Heart study, and the CDAH (Childhood Determinants of Adult Health) study. *J Am Coll Cardiol*. 2009 Mar 10;53(10):860-9.
25. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006 Feb 14;113(6):791-8.
26. Newman WP, 3rd, Freedman DS, Voors AW, Gard PD, Srinivasan SR, Cresanta JL, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. The Bogalusa Heart Study. *N Engl J Med*. 1986 Jan 16;314(3):138-44.
27. McGill HC, Jr, McMahan CA, Zieske AW, Malcom GT, Tracy RE, Strong JP. Effects of nonlipid risk factors on atherosclerosis in youth with a favorable lipoprotein profile. *Circulation*. 2001 Mar 20;103(11):1546-50.
28. McGill HC, Jr, McMahan CA, Malcom GT, Oalman MC, Strong JP. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. The PDAY research group. *Pathobiological Determinants of Atherosclerosis in Youth*. *Arterioscler Thromb Vasc Biol*. 1997 Jan;17(1):95-106.
29. McMahan CA, McGill HC, Gidding SS, Malcom GT, Newman WP, Tracy RE, et al. PDAY risk score predicts advanced coronary artery atherosclerosis in middle-aged persons as well as youth. *Atherosclerosis*. 2007 Feb;190(2):370-7.
30. Mortality in treated heterozygous familial hypercholesterolaemia: Implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group. *Atherosclerosis*. 1999 Jan;142(1):105-12.
31. Cohen JC, Boerwinkle E, Mosley TH, Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006 Mar 23;354(12):1264-72.
32. Kathiresan S, Melander O, Guiducci C, Surti A, Burt NP, Rieder MJ, et al. Six new loci associated with blood lowdensity lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. *Nat Genet*. 2008 Feb;40(2):189-97.
33. Cohen JC, Stender S, Hobbs HH. APOC3, coronary disease, and complexities of Mendelian randomization. *Cell Metab*. 2014 Sep 2;20(3):387-9.
34. Lurink, Wiegman, Kusters, et al. 20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia. *N Engl J Med* 2019;381:1547-56.
35. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute, Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitzel NO, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med*. 2014 Jul 3;371(1):22-31.
36. Myocardial Infarction Genetics Consortium Investigators. Inactivating mutations in NPC1L1 and protection from coronary heart disease. *N Engl J Med*. 2014 Nov 27;371(22):2072-82.
37. Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, Laufs U, Oliver-Williams C, Wood AM, Butterworth AS, Di Angelantonio E, Danesh J, Nicholls SJ, Bhatt DL, Sabatine MS, Catapano AL. Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants With Risk of Coronary Heart Disease. *JAMA*. 2019 Jan 29;321(4):364-373.
38. Ference BA, Ray KK, Catapano AL, Ference TB, Burgess S, Neff DR, Oliver-Williams C, Wood AM, Butterworth AS,

-
- Di Angelantonio E, Danesh J, Kastelein JJP, Nicholls SJ. Mendelian Randomization Study of ACLY and Cardiovascular Disease. *N Engl J Med*. 2019 Mar 14;380(11):1033-1042)
39. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association's strategic impact goal through 2020 and beyond. *Circulation*. 2010 Feb 2;121(4):586-613.
40. Chiuve SE, McCullough ML, Sacks FM, Rimm EB. Healthy lifestyle factors in the primary prevention of coronary heart disease among men: Benefits among users and nonusers of lipid-lowering and antihypertensive medications. *Circulation*. 2006 Jul 11;114(2):160-7.
41. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med*. 2000 Jul 6;343(1):1622.
42. Shay CM, Ning H, Daniels SR, Rooks CR, Gidding SS, Lloyd-Jones DM. Status of cardiovascular health in US adolescents: Prevalence estimates from the National Health and Nutrition Examination Surveys (NHANES) 2005-2010. *Circulation*. 2013 Apr 2;127(13):1369-76.
43. Pahkala K, Hietalampi H, Laitinen TT, Viikari JS, Ronnema T, Niinikoski H, et al. Ideal cardiovascular health in adolescence: Effect of lifestyle intervention and association with vascular intima-media thickness and elasticity (the Special Turku Coronary Risk Factor Intervention Project for Children [STRIP] study). *Circulation*. 2013 May 127(21):2088-96.