Value of early lipid-lowering interventions to prevent later life cardiovascular disease

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Conflicts of Interest

- I have no conflicts of interest to disclose
- All of the information presented in this talk is based on research funded by the National Heart, Lung, and Blood Institute (NHLBI)

Part 1:

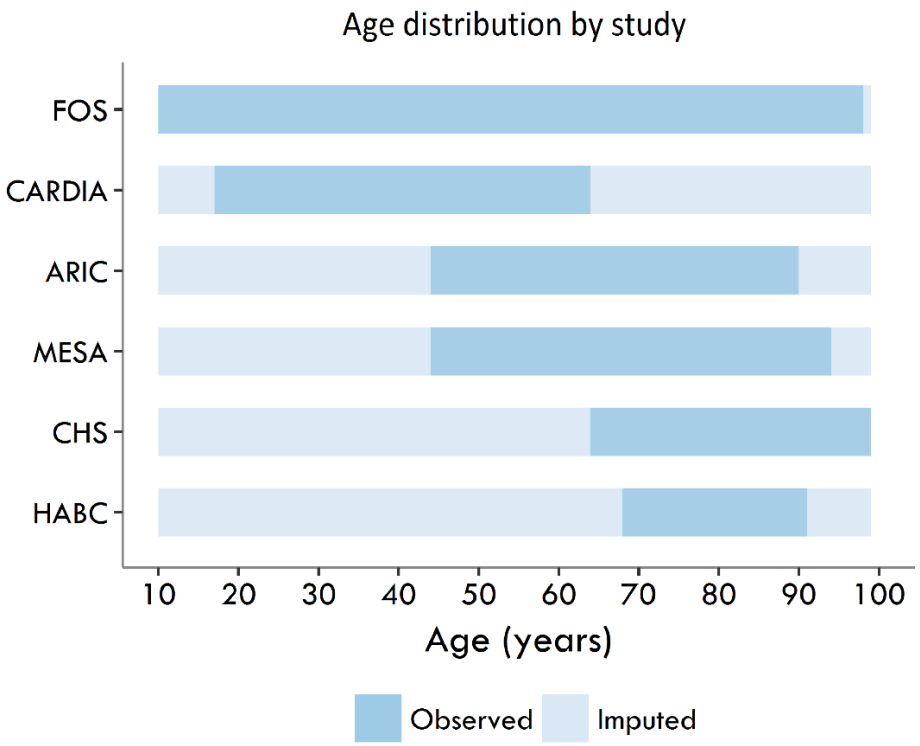
Value of early interventions to lower high cholesterol in young adults

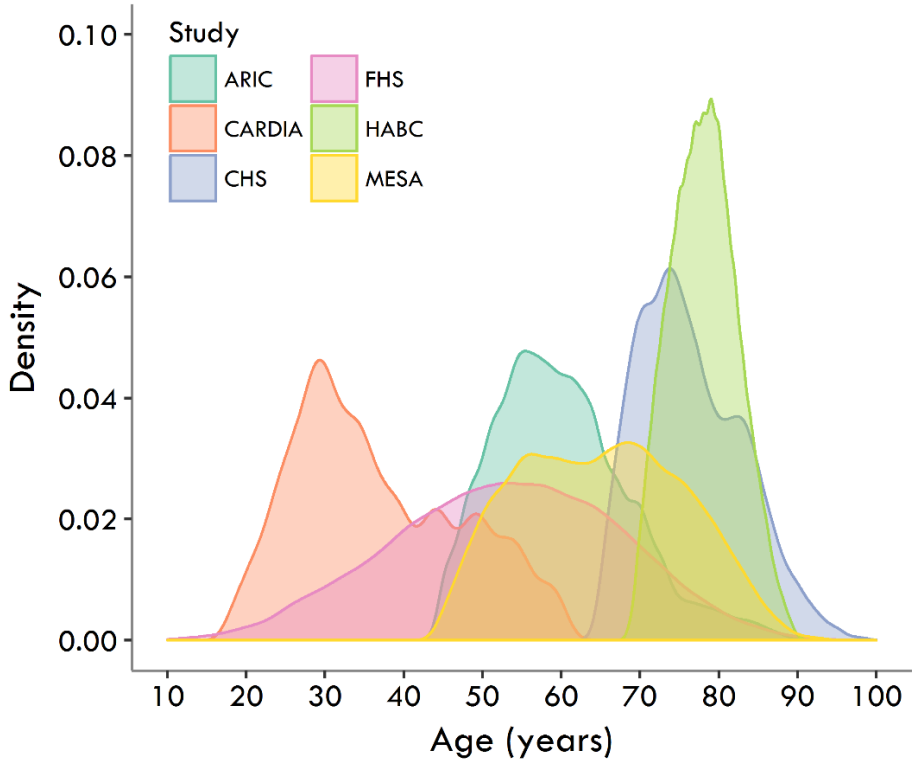
Young Adults Study* Rationale

- **U.S. National Heart, Lung, and Blood Institute Study**
- **Study premise**
  - Strong epidemiologic evidence that cumulative risk factor exposures starting in childhood contribute to the evolution of atherosclerosis and later life atherosclerotic cardiovascular disease
  - Most clinical trials last ~5 years and enroll older, high risk adults
  - Cumulative risk factor exposures not accounted for in treatment guidelines
  - Mathematical models can translate observational evidence into simulated long-term treatment “trials”

*NHLBI R01HL107475 PI = Moran

Young Adults Study: age distributions of pooled data from 6 NHLBI cohorts (N=36,061)





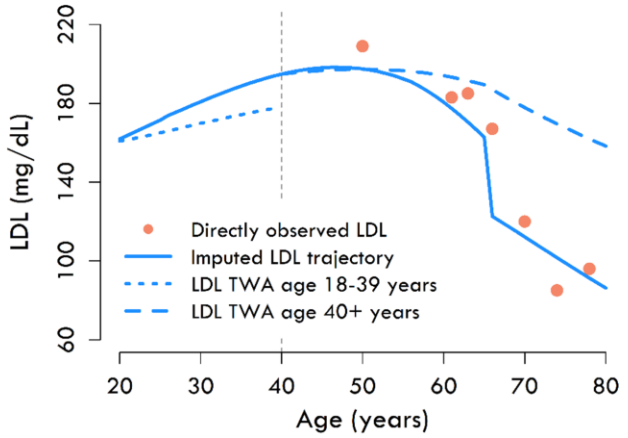
Young Adults Study: summary of epidemiologic research

STUDY DESIGN

36,030 Participants pooled from 6 cohort studies with observations spanning the life course

Incident events:
- **4,570** CHD
- **5,119** Heart failure
- **2,862** Stroke

Impute risk factor trajectories and estimate time-weighted average (TWA) exposures during early and later adulthood. ***Figure below shows example data of a randomly selected study participant.***



KEY FINDINGS

Hazard ratios for CHD and heart failure associated with blood pressure and LDL levels during young adulthood, controlling for later life exposures.

CHD

LDL (TWA 18-39)	
<100	Reference
100-129	1.62 (1.25, 2.10)
130-159	1.89 (1.43, 2.50)
≥160	2.03 (1.47, 2.82)
P-trend	*<0.001*

0.5 1 2 4
HR (95% CI)

CHD

DBP (TWA 18-39)	
<70	Reference
70-79	1.08 (0.94, 1.24)
80-89	1.21 (1.02, 1.43)
≥90	1.21 (0.62, 2.38)
P-trend	*0.04*

0.5 1 2 4
HR (95% CI)

Heart failure

SBP (TWA 18-39)	
<120	Reference
120-129	1.07 (0.96, 1.19)
130-139	1.16 (0.93, 1.45)
≥140	1.51 (1.08, 2.11)
P-trend	*0.08*

0.5 1 2 4
HR (95% CI)

Heart failure

DBP (TWA 18-39)	
<70	Reference
70-79	1.07 (0.97, 1.19)
80-89	1.25 (1.04, 1.50)
≥90	1.84 (1.02, 3.32)
P-trend	*0.01*

0.5 1 2 4
HR (95% CI)

TWA 18-39: Time-weighted average risk factor exposure during age 18-39 years

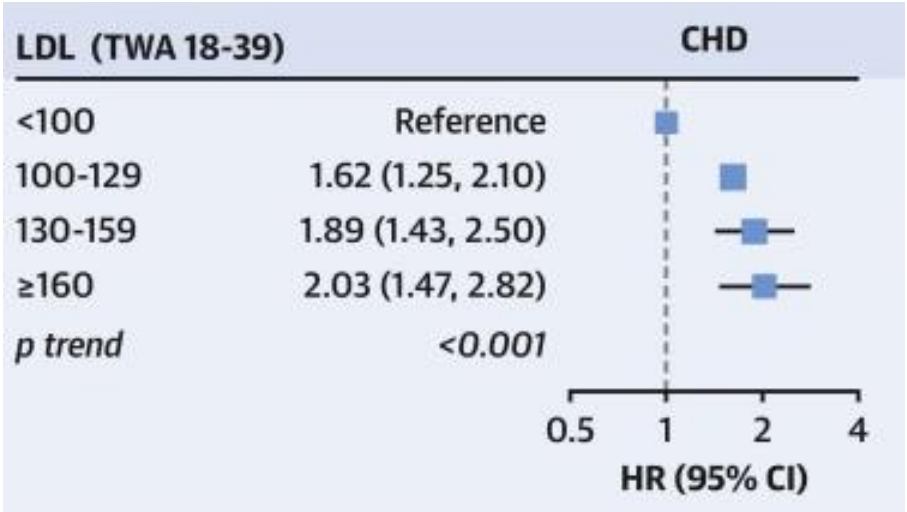
Zhang et al., JACC, 2019 Jul 23;74(3):330-341

Long-term risk factor effects: focus on LDL cholesterol

When young and later adult LDL-C were considered jointly, young adult **LDL ≥100 mg/dl (2.6 mmol/L)** compared with <100 mg/dl (<2.6 mmol/L) was associated with a **64% increased risk for CHD**, *independent of later adult exposures*

CENTRAL ILLUSTRATION: Associations of Blood Pressure and Cholesterol Levels During Young Adulthood With Cardiovascular Events Later in Life

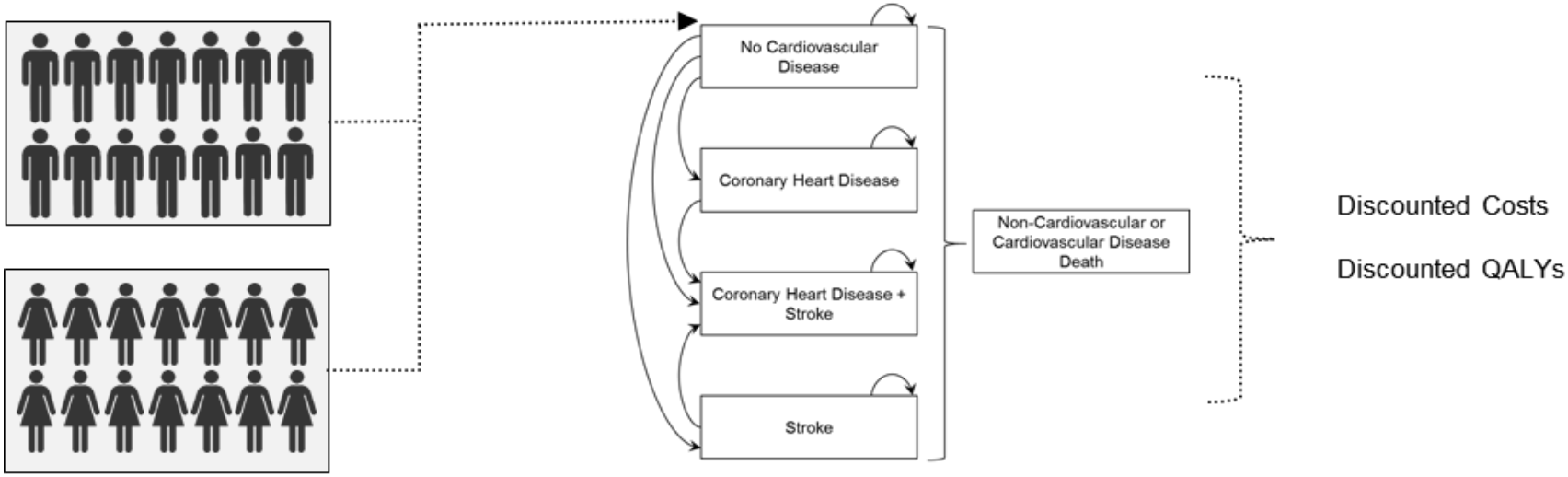
Hazard Ratios for CHD and Heart Failure Associated with Blood Pressure and LDL Levels During Young Adulthood, Controlling for Later Life Exposures



Zhang, Y. et al. J Am Coll Cardiol. 2019;74(3):330–41.

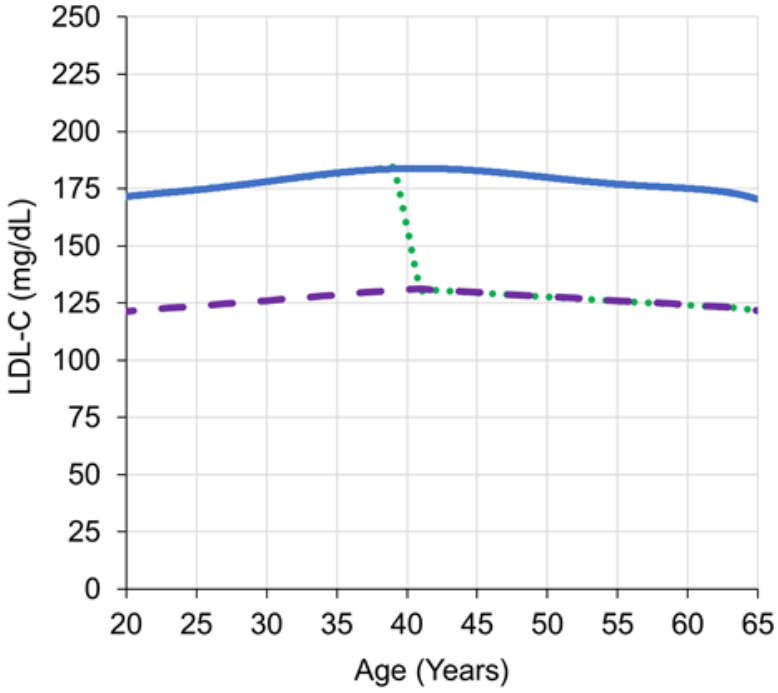
Zhang, Y. et al. J Am Coll Cardiol, 2019

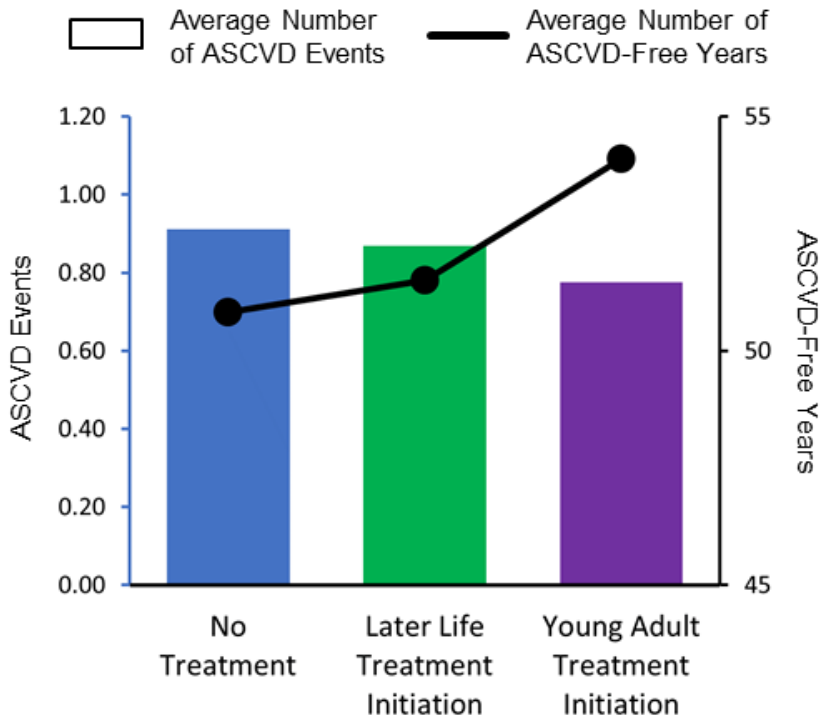
Young Adults Study Methods Overview: Simulated long-term treatment "trials" using the CVD Policy Model



Individuals enter the CVD Policy Model disease-free at age 18 years and are simulated until age 89. Incidence of CHD, stroke, and non-CVD mortality is determined by risk functions developed with NHLBI-PCS data which condition on multiple variables including time-weighted average (TWA) LDL-C and SBP from age 18 to present age.

Young Adults Study methods: Conceptual model





Left Panel: three LDL-C trajectories for an individual with raised LDL-C: no treatment, later life treatment (29% LDL-C reduction at age 40), and early treatment starting at age 20.
Right Panel: results from 250,000 lifetime simulations of these three scenarios using the CVD Policy Model with all other risk factors held constant.

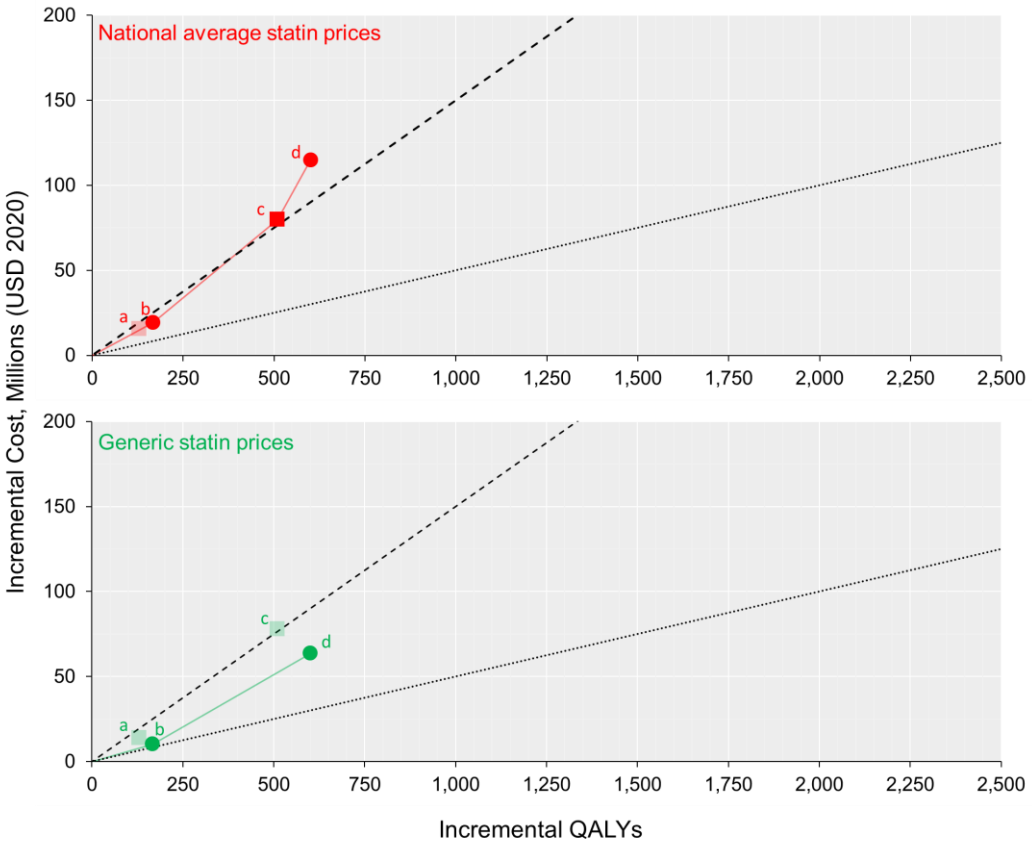
Young Adult Study Methods: lipid-lowering strategies

- **Standard care**, per U.S. ACC/AHA 2018 lipid guideline: statin treatment for adults aged ≥40 years based on LDL-C, ASCVD risk, or diabetes plus young adults with LDL-C ≥190 mg/dL *(4.9 mmol/L)*
- **Statin Strategies:** moderate-intensity statins in young adults with
  - LDL-C ≥160 mg/dL *(4.1 mmol/L)*
  - LDL-C ≥130 mg/dL *(3.4 mmol/L)*
  - Evaluated national mean and low-cost "generic" statin prices
- **US Preventive Services-endorsed lifestyle modification strategies*** for young adults starting with
  - LDL-C ≥160 mg/dL *(4.1 mmol/L)*
  - LDL-C ≥130 mg/dL. *(3.4 mmol/L)*
- All individuals were treated according to ACC/AHA 2018 guidelines after age 40 years

*O'Connor EA JAMA 2020;324(20):2076

Young Adult Study Results: U.S. young adult women

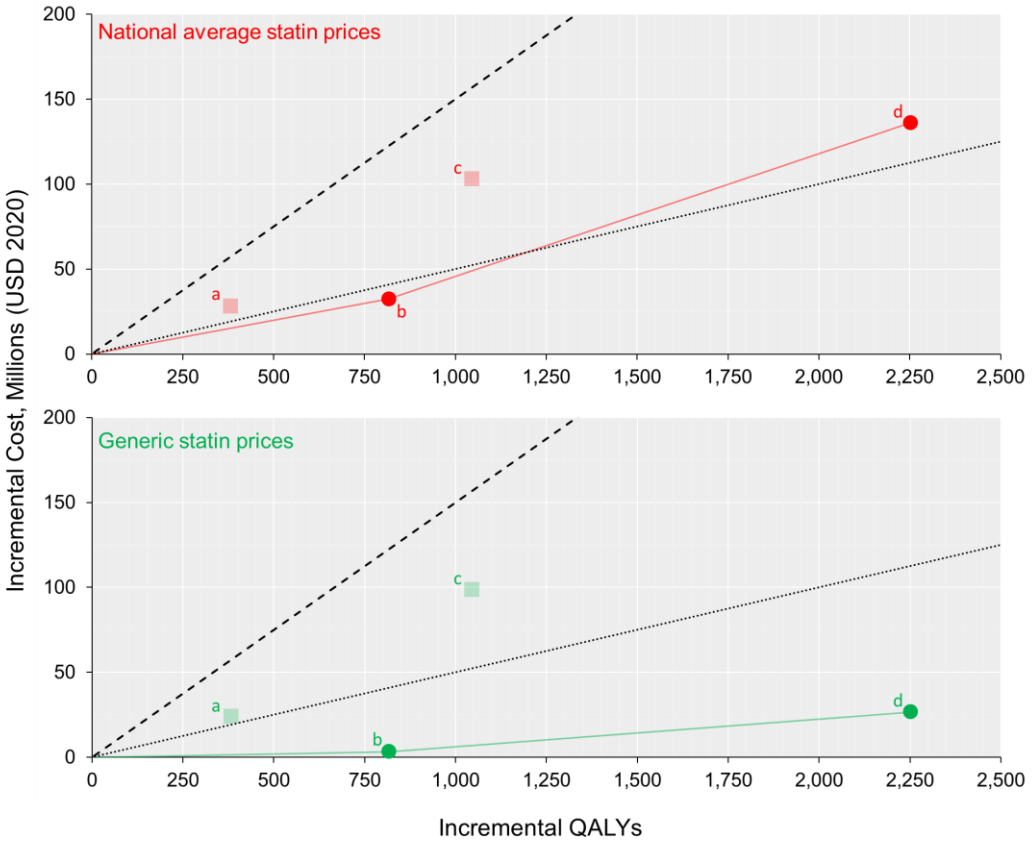
- **LDL-C ≥160 mg/dL** *(≥ 4.1 mmol/L)*
  - Statins intermediately cost-effective at national mean prices (ICER: $115,000/QALY)
  - Statins intermediately cost-effective at lower generic statin prices (ICER: $61,000/QALY)
- **LDL-C ≥130 mg/dL** *(≥ 3.4 mmol/L)*
  - Statins not cost-effective at national mean prices (ICER: $384,000/QALY)
  - Statins intermediately cost-effective at lower generic statin prices (ICER: $123,000/QALY)
- **Lifestyle treatment strategies** were either extendedly dominated by statin strategies or not cost-effective



a. Standard care + young adult LDL-C ≥160 mg/dL, lifestyle
b. Standard care + young adult LDL-C ≥160 mg/dL, statins
c. Standard care + young adult LDL-C ≥130 mg/dL, lifestyle
d. Standard care + young adult LDL-C ≥130 mg/dL, statins
- - - - - cost-effectiveness threshold: $150,000/QALY
..... cost-effectiveness threshold: $50,000/QALY

Young Adult Study Results: U.S. young adult men

- **LDL-C ≥160 mg/dL.** *(≥ 4.1 mmol/L)*
  - Statins **highly** cost-effective at national mean prices (ICER: $40,000/QALY)
  - Statins **highly** cost-effective at lower generic statin prices (ICER: $4,000/QALY)
- **LDL-C ≥130 mg/dL** *(≥ 3.4 mmol/L)*
  - Statins intermediately cost-effective at national mean prices (ICER: $72,000/QALY)
  - Statins **highly** cost-effective at lower generic statin prices (ICER: $16,000/QALY)
- **Lifestyle treatment strategies** were either extendedly dominated by statin strategies or not cost-effective



a. Standard care + young adult LDL-C ≥160 mg/dL, lifestyle
b. Standard care + young adult LDL-C ≥160 mg/dL, statins
c. Standard care + young adult LDL-C ≥130 mg/dL, lifestyle
d. Standard care + young adult LDL-C ≥130 mg/dL, statins
– – – – – cost-effectiveness threshold: $150,000/QALY
..... cost-effectiveness threshold: $50,000/QALY

Young Adults Study: Conclusions

- Lacking clinical trial evidence, simulating decades-long “trials” is a feasible approach to estimating the effectiveness and cost-effectiveness of long-term statin treatment in young adults with raised LDL-C.
- **Based on our results, we have the most confidence in recommending early statin treatment for young adult men with LDL-C ≥160 mg/dL (≥ 4.1 mmol/L)**
- In the U.S., initiating statin treatment in young adult men with raised LDL-C is **highly cost-effective at generic prices.**

Part 2: Value of early cholesterol-lowering in childhood:

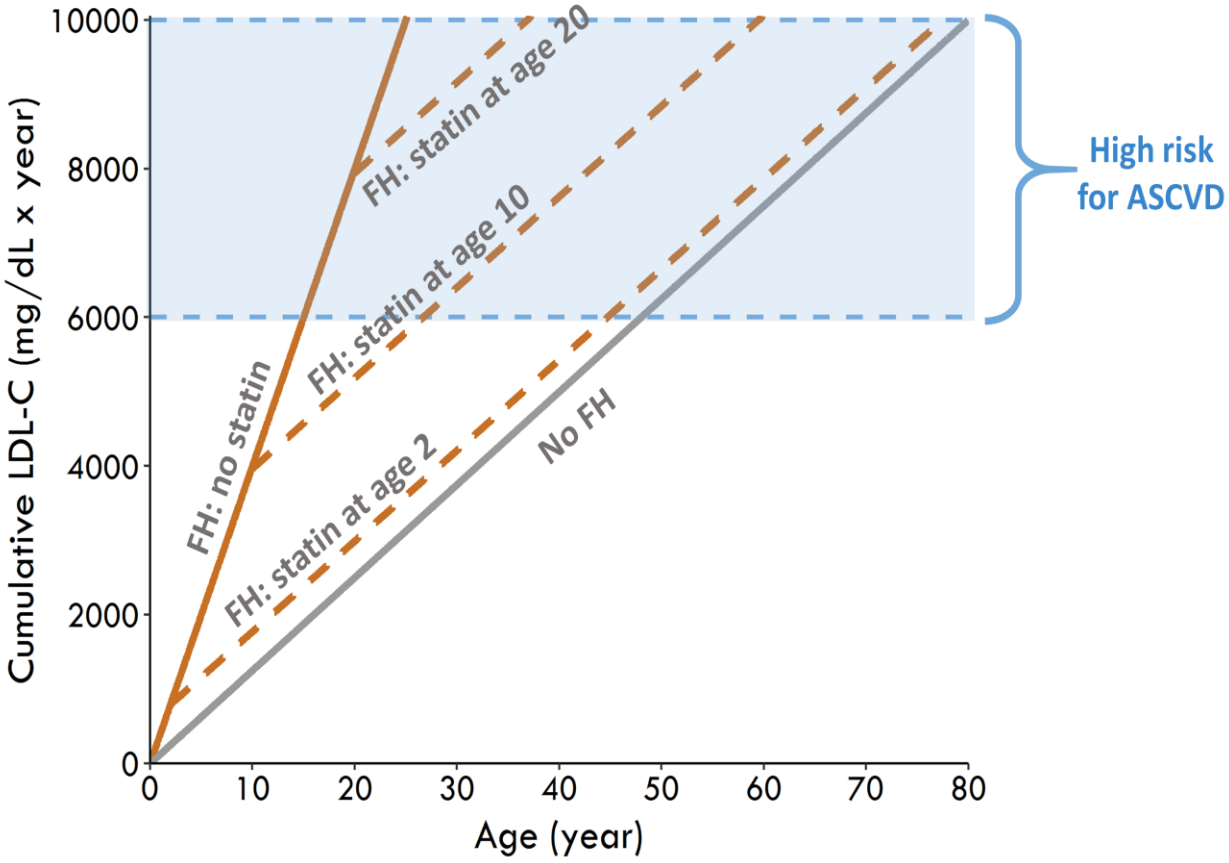
The Familial Hypercholesterolemia screening study

What is Familial Hypercholesterolemia?

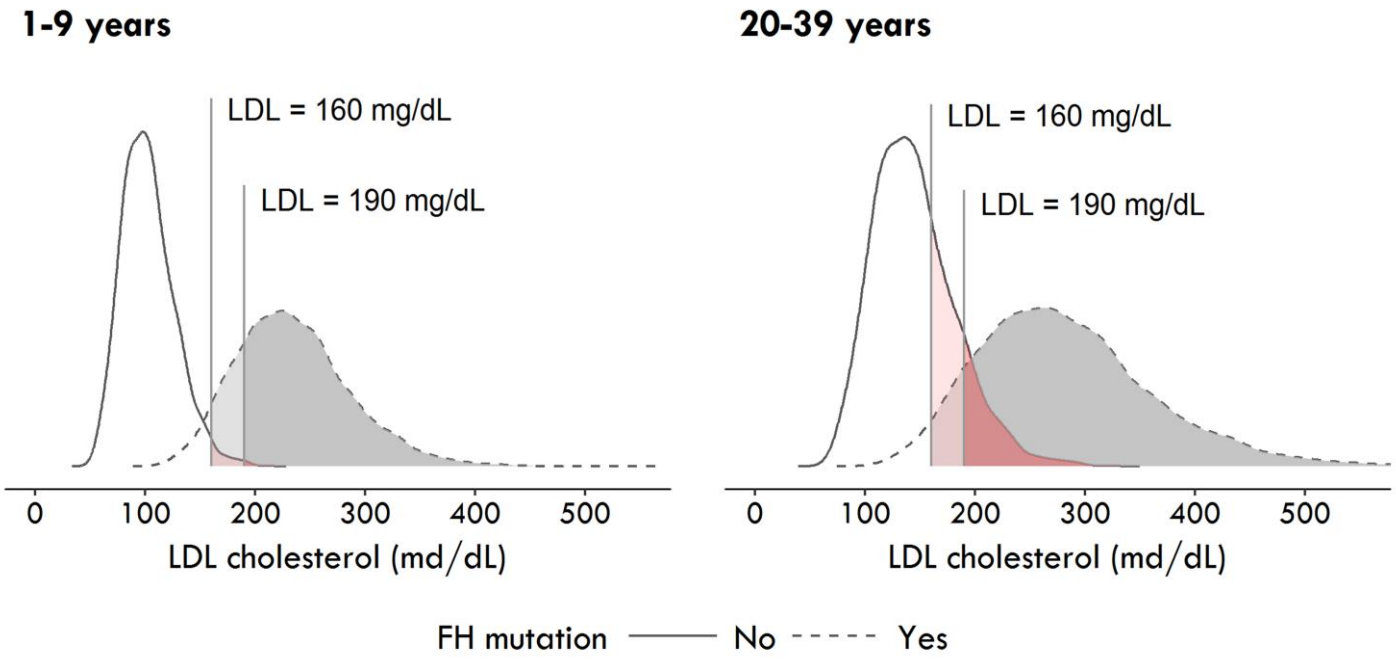
- Familial hypercholesterolemia (FH) is a common genetic disease caused by mutation of one or more of the genes critical for low-density lipoprotein cholesterol (LDL-C) catabolism (see 'Genetic considerations' below). [1] The clinical syndrome (phenotype) is characterized by extremely elevated levels of LDL-C and a propensity to early onset atherosclerotic cardiovascular disease.

- An individual may be labeled as having FH in one of two ways:
- ●DNA-based evidence of mutation in the *LDLR, PCSK9,* or *APOB* gene. Each of these genes influence LDL-C levels.
- ●Clinical characteristics that usually include a high LDL-C

Rationale for familial cholesterol screening in children: **earlier treatment is better**

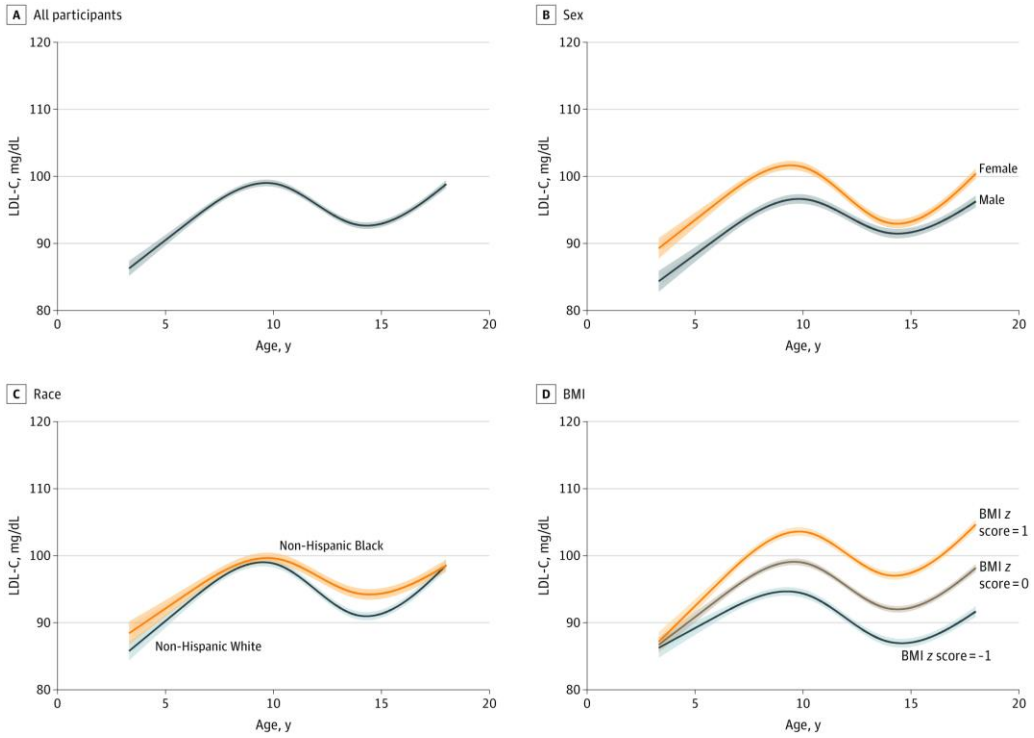


Rationale for familial cholesterol screening in children: **improved accuracy of detection**



From: **Low-Density Lipoprotein Cholesterol Trajectories and Prevalence of High Low-Density Lipoprotein Cholesterol Consistent With Heterozygous Familial Hypercholesterolemia in US Children**

JAMA Pediatr. 2021;175(10):1071-1074. doi:10.1001/jamapediatrics.2021.2046



Trajectories of Low-Density Lipoprotein Cholesterol (LDL-C) Between Ages 3 and 17 years in the US cohorts of the i3C consortium

- The observation that childhood LDL-C peaked around age 9 years with levels similar to those at age 18 years supports **current recommendations for childhood lipid screening at ages 9 to 11 years**
- Prevalence of **persistent high LDL-C levels consistent with FH was 1.0% to 0.3%**, depending on the definition used.

FH screening simulation

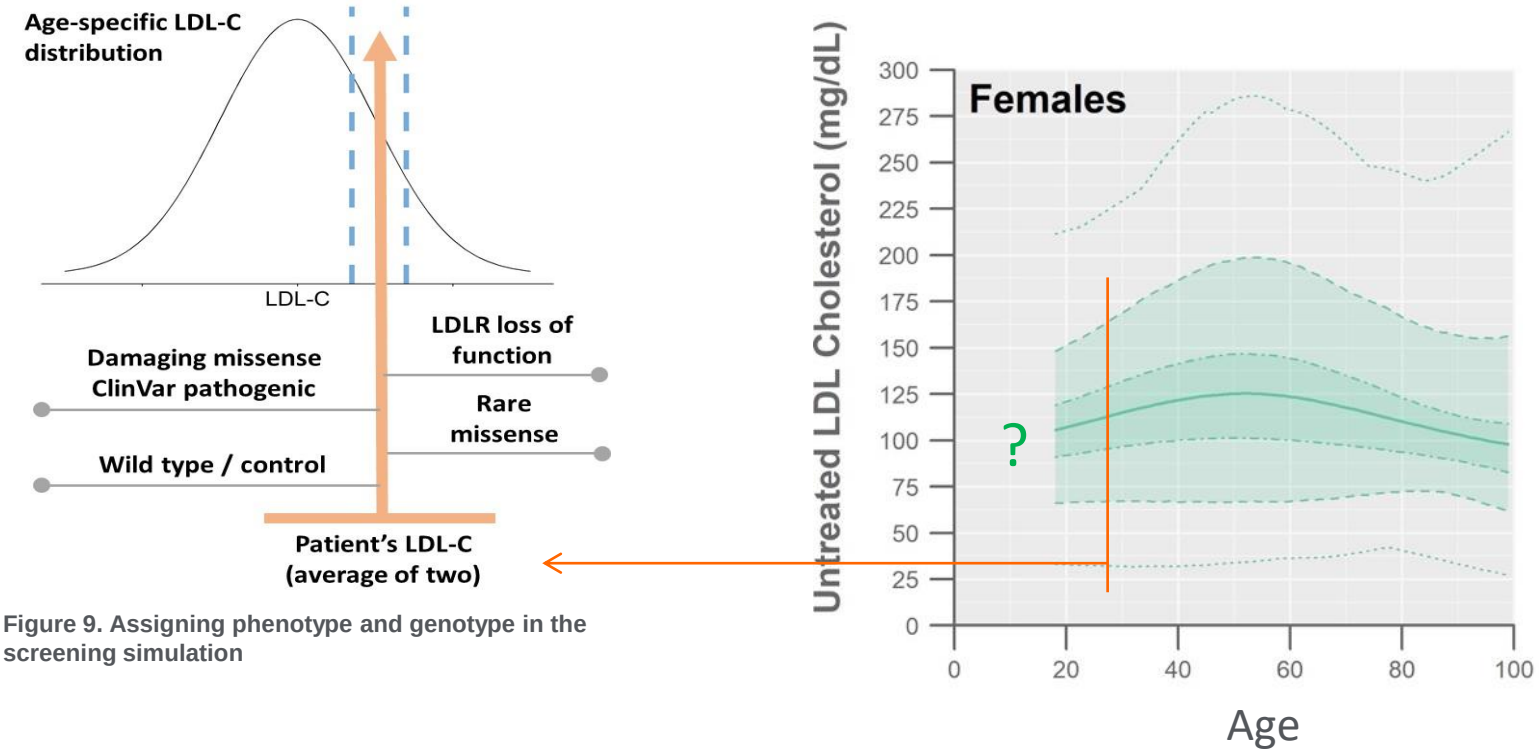


Figure 9. Assigning phenotype and genotype in the screening simulation

1. Lifetime LDL-C and CVD risk simulation without intervention
2. Lifetime LDL-C and CVD risk simulation with intervention

Familial Hypercholesterolemia Screening Project* Specific Aims Overview

Computer simulation model to assess societal value of different **FH screening** approaches

Aim 1
Universal Screening

- Quantify the health and economic value of universal FH screening at different ages (2, 10, 20, or 35 years) and LDL-C levels
- Assess the incremental value of adding confirmatory genetic screening

Aim 2
Targeted Screening

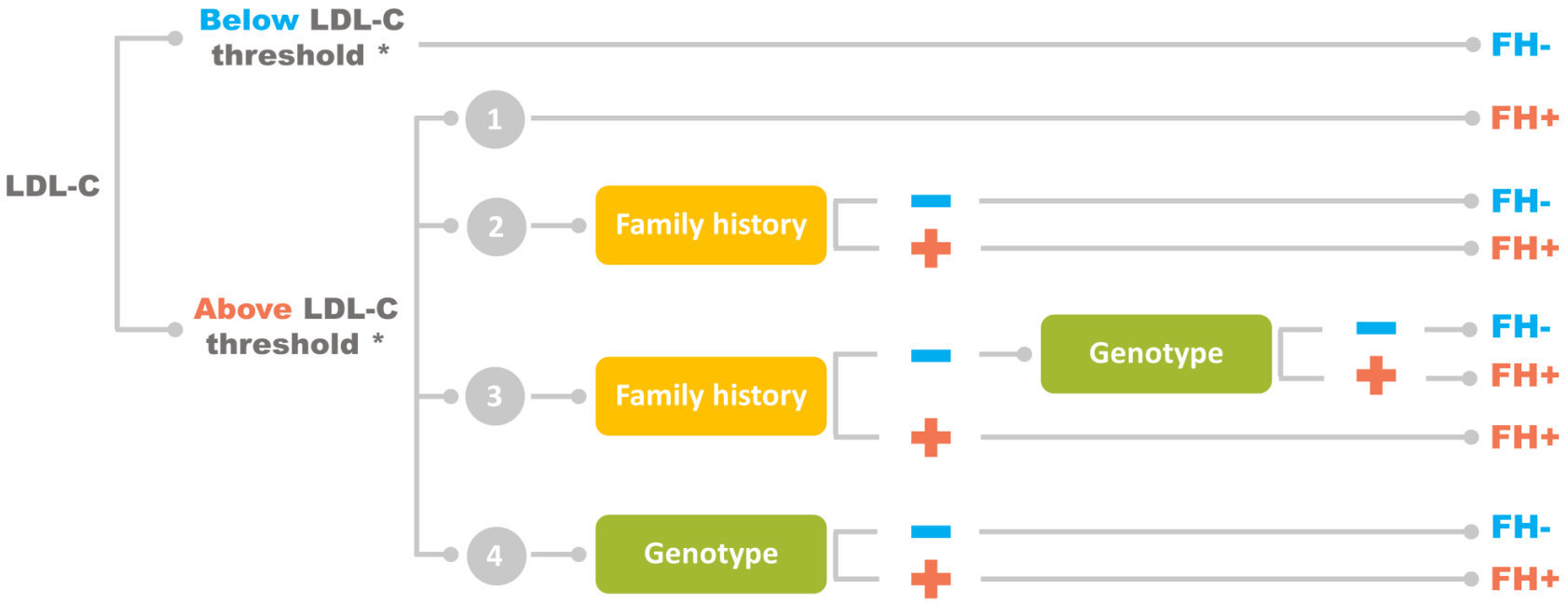
- Quantify the health and economic value of targeted FH screening using FIND-FH machine learning algorithms to identify probable adult or child FH patients
- Compare cost-effectiveness of targeted screening in US counties with high vs. low FH prevalence

Aim 3
Cascade Screening

- Quantify the health and economic value of cascade FH screening in family members of FH cases identified through Aim 1 & 2 screening strategies

*NHLBI R01HL141823

FH Screening Project Aim 1: individual FH screening



FH screening and diagnostic algorithms

Scenario 1: Phenotypic screening based on LDL-C alone
Scenario 2: Phenotypic screening based on LDL-C + Family history of FH
Scenario 3: Phenotypic screening based on LDL-C + Family history of FH + Confirmatory genetic testing
Scenario 4: Phenotypic screening based on LDL-C + Confirmatory genetic testing

** LDL-C threshold for main analysis: ≥160 mg/dL for children and ≥190 mg/dL for adults*

Thank you!

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Extra Slides

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Young Adults Study:
pooled and harmonized data from six U.S. NIH cohorts (n = 36,061)

Study	N	Female (%)	AA (%)
ARIC	13,325	56	25
CARDIA	4,669	56	50
CHS	4,301	61	14
Framingham Offspring	4,905	52	0
Health ABC	2,166	56	41
MESA	6,695	53	28
Total	**36,061**	**56**	**25**

Young Adults Study methods: mathematical model inputs

- Validated individual person-level simulation (“microsimulation”) model of lifetime Atherosclerotic Cardiovascular Disease (ASCVD)
- Nationally representative cohort of **one million ASCVD-free U.S. young adults** sampled from the U.S. national survey (NHANES)
- LDL-C and SBP effects incorporated in risk functions as time-weighted average (TWA); updated each year from age 18 to present

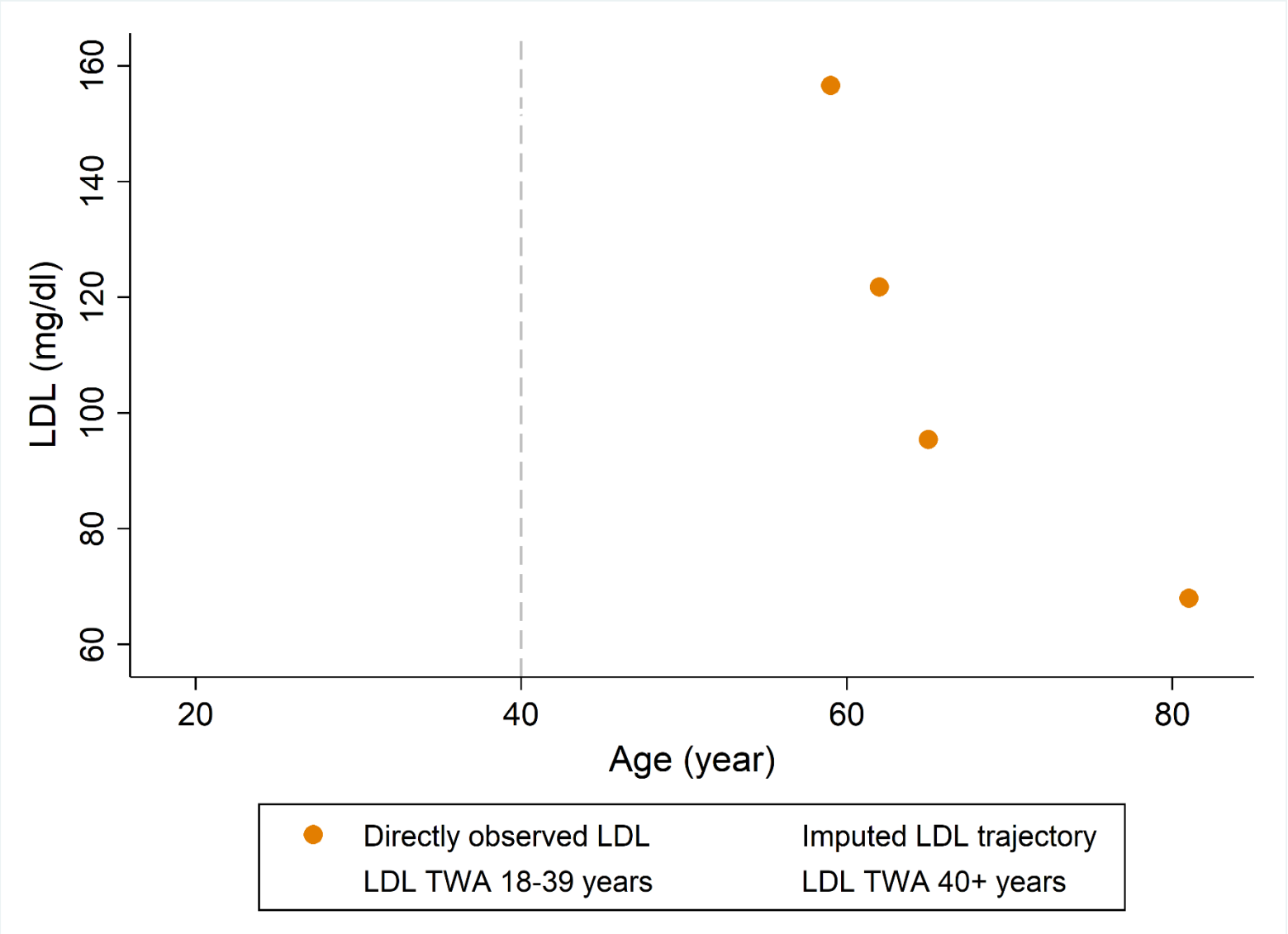
$$rate_k = \frac{e^{(\alpha+\beta_{age}*AGE+\sum \beta_{RF}*RF+ \beta_{SBP,TWA}*SBP_{TWA}+\beta_{LDL-C,TWA}*LDL-C_{TWA})}}{1+e^{(\alpha+\beta_{age}*AGE+\sum \beta_{RF}*RF+ \beta_{SBP,TWA}*SBP_{TWA}+\beta_{LDL-C,TWA}*LDL-C_{TWA})}}$$

- Lifetime (ages 18 to 89 years) risk factor trajectories assigned to NHANES participants by randomly matching them 1:1 to pooled cohort study participants

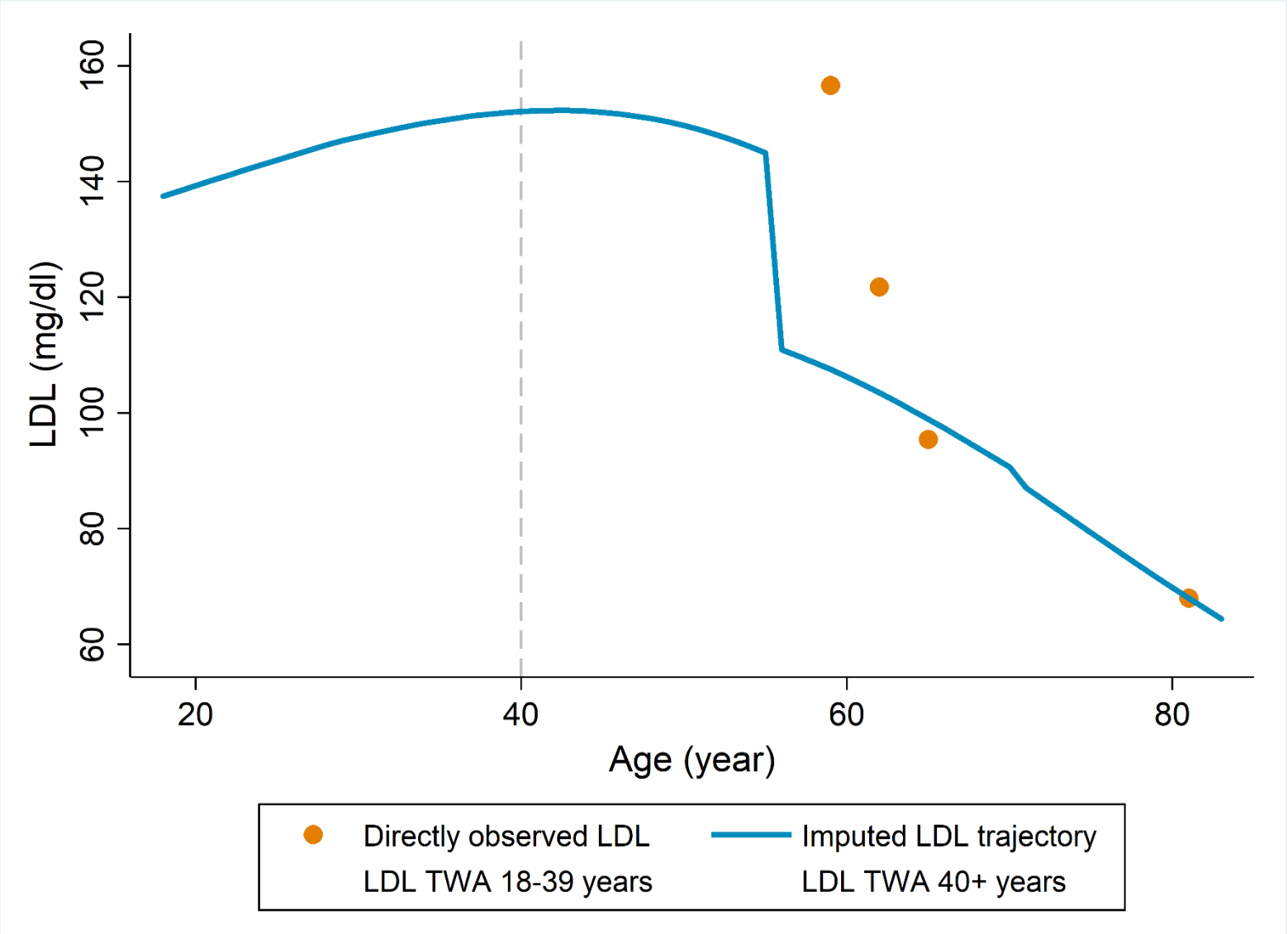
Young Adults Study: Conclusions (2)

- In the U.S., early ASCVD prevention is complicated by few young adults with health insurance or usual source of medical care; we also may underestimate “pill-taking disutility” (aversion to taking daily pills) in young adults.
- It is also important to consider that our previous analysis found that treating **“borderline” risk (10-year ASCVD risk 5.0-7.4%) older adults** (aged ≥40 years) is even more cost-effective incremental to standard care than treating young adults with raised LDL-C.
- We found that lifestyle interventions focused on individual behaviour change were not cost effective; we did not study public health LDL-C lowering programs that have been successful in improving CVD health (North Karelia Study and others)

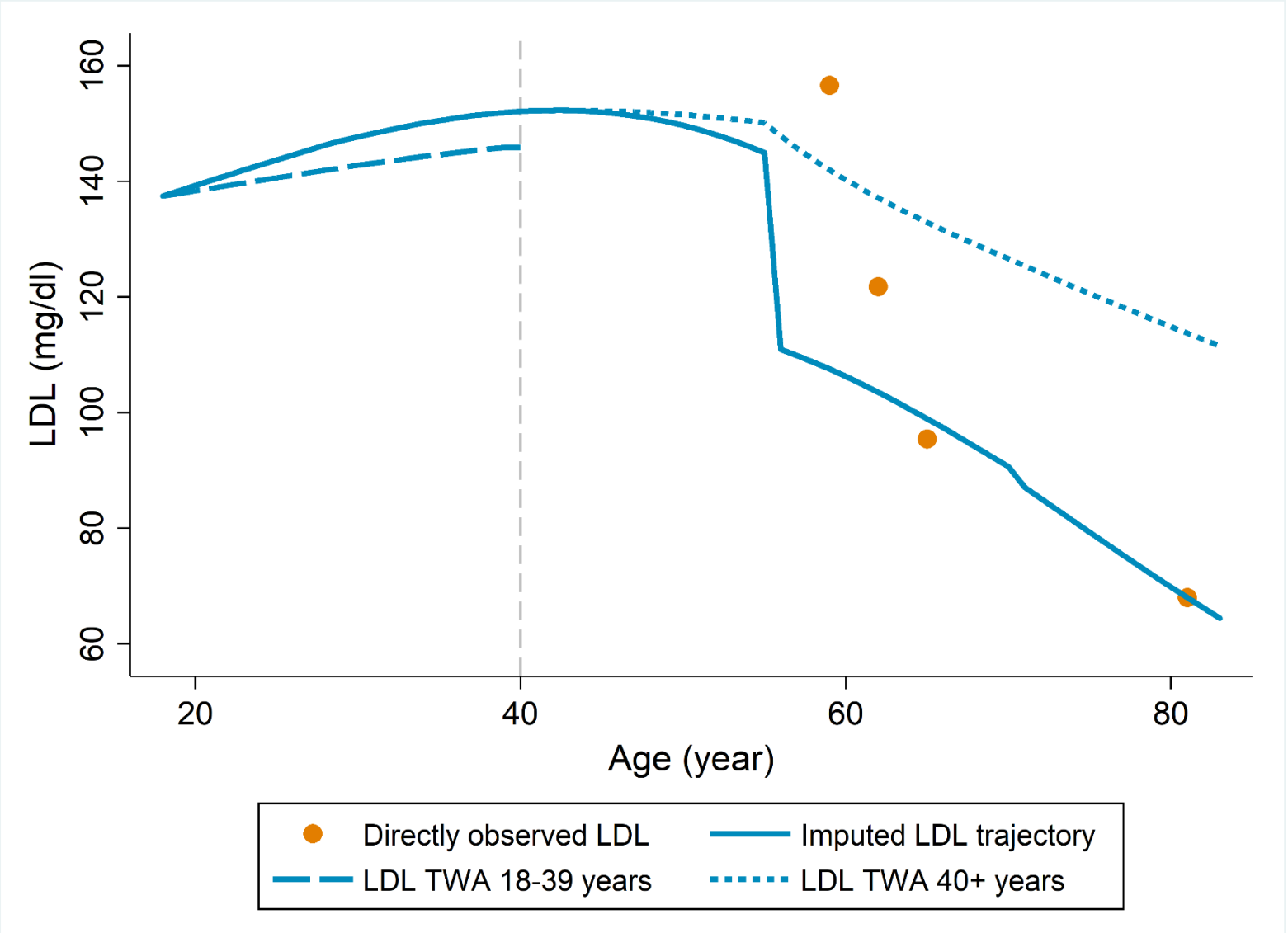
Example LDL trajectory of a random study participant

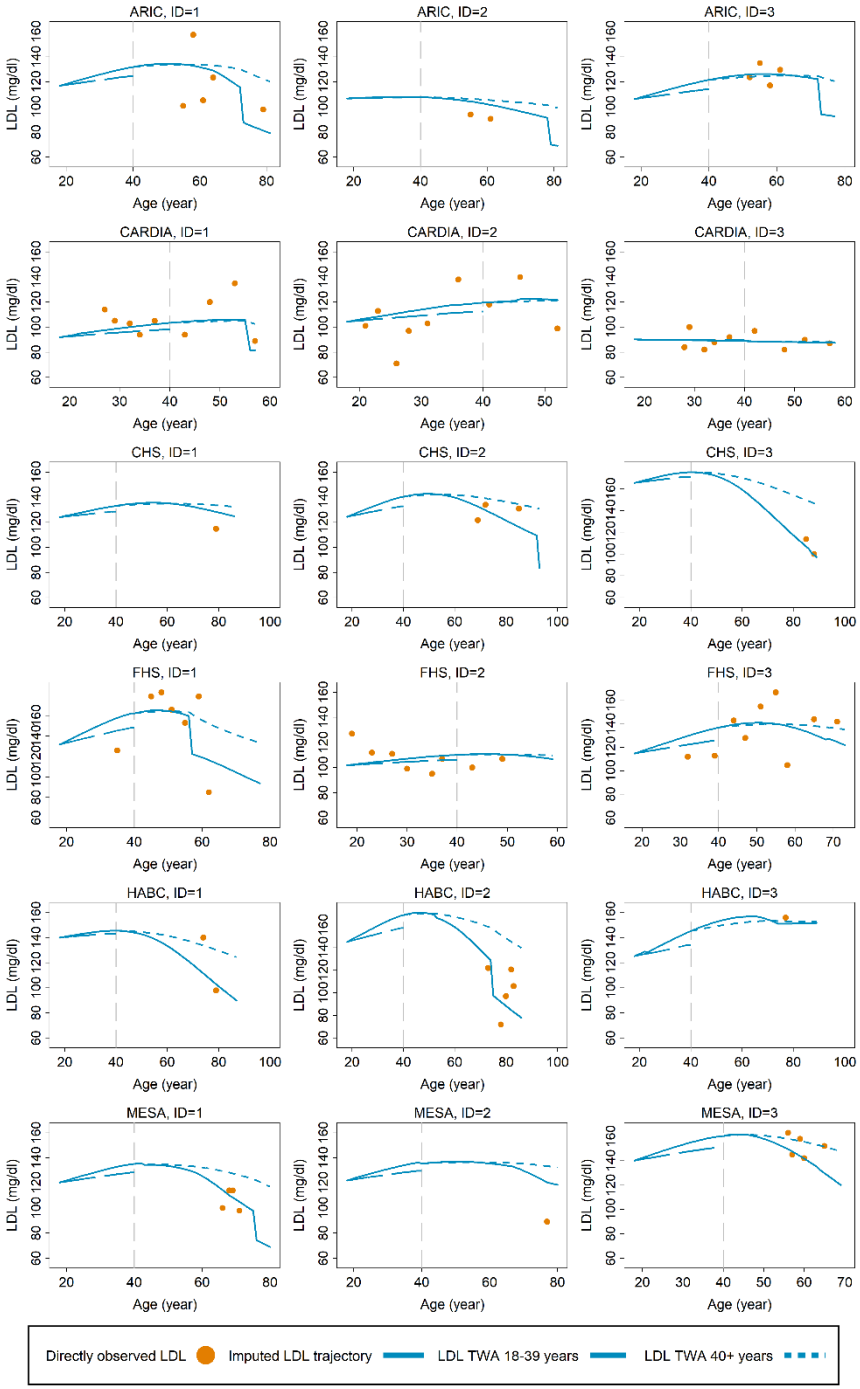


Example LDL trajectory of a random study participant

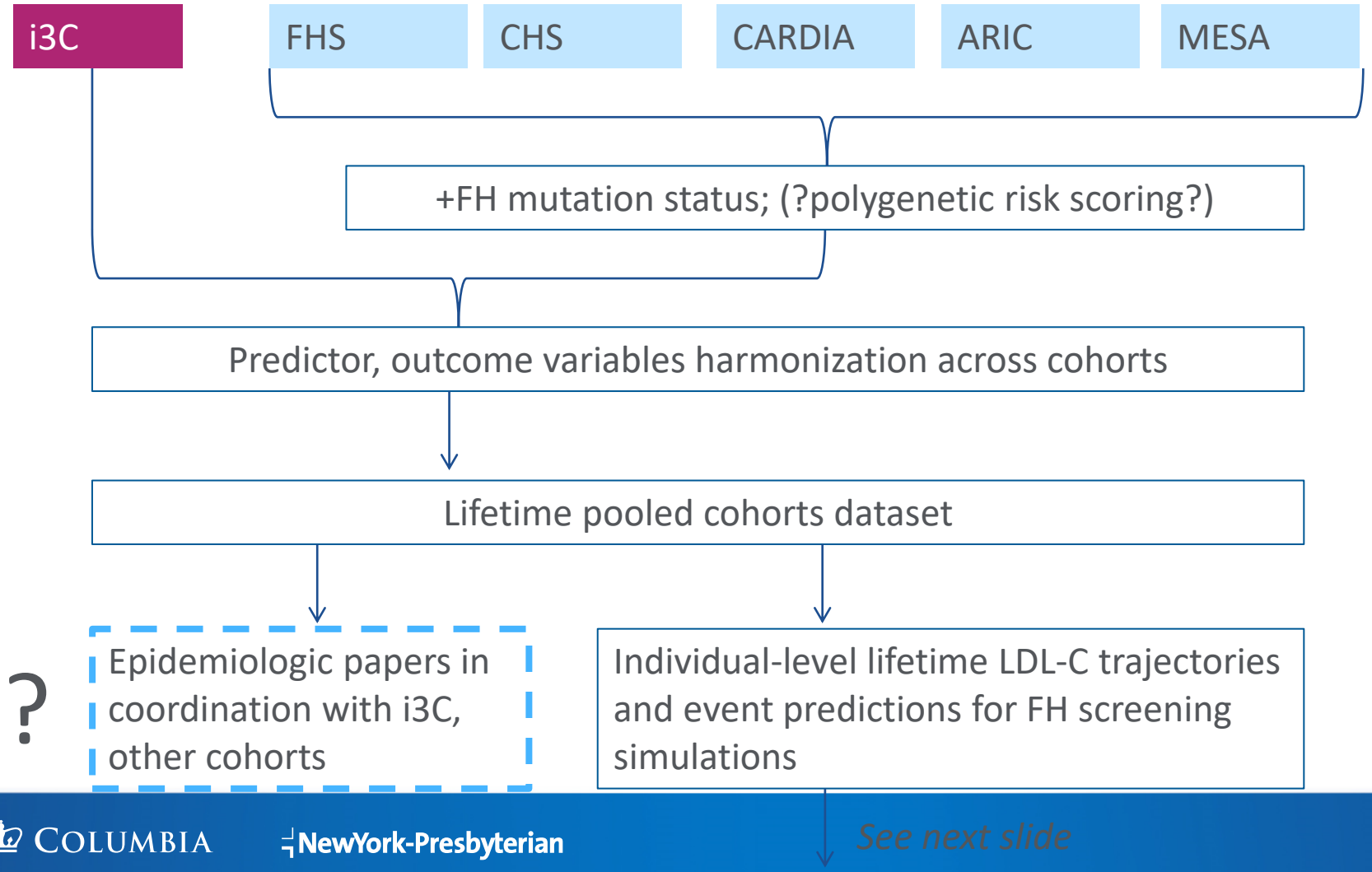


Example LDL trajectory of a random study participant




ARIC, ID=1
ARIC, ID=2
ARIC, ID=3
CARDIA, ID=1
CARDIA, ID=2
CARDIA, ID=3
CHS, ID=1
CHS, ID=2
CHS, ID=3
FHS, ID=1
FHS, ID=2
FHS, ID=3
HABC, ID=1
HABC, ID=2
HABC, ID=3
MESA, ID=1
MESA, ID=2
MESA, ID=3
LDL (mg/dl)
Age (year)
Directly observed LDL
Imputed LDL trajectory
LDL TWA 18-39 years
LDL TWA 40+ years

FH R01 workflow: epi data



Aim 2: Find FH—precision screening

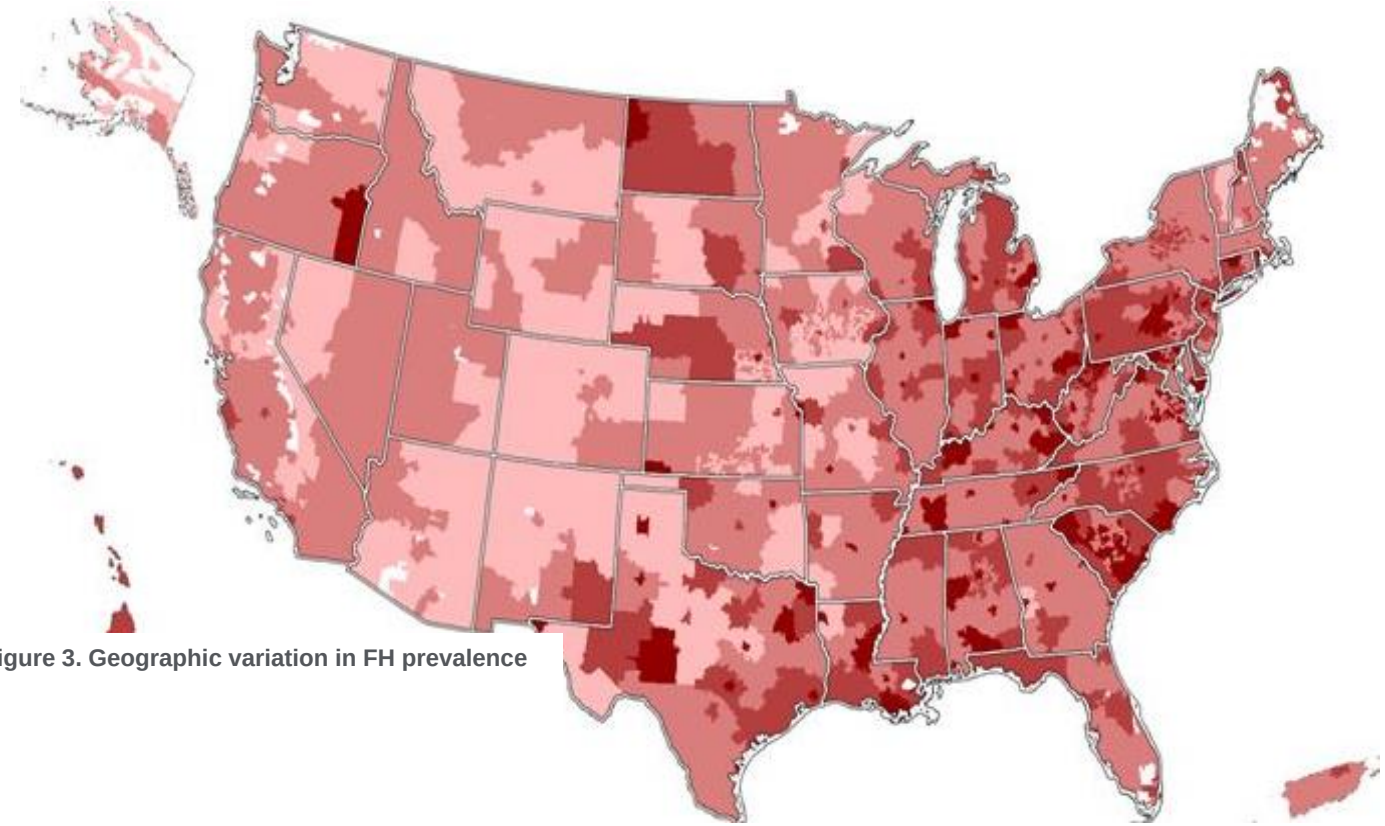
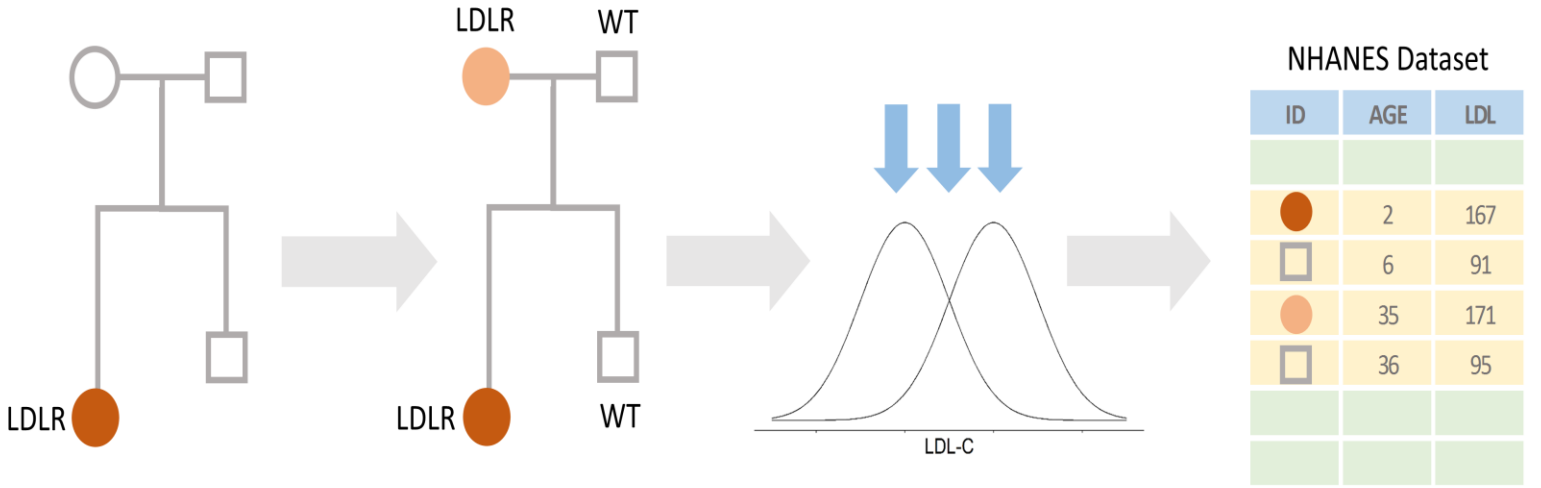


Figure 3. Geographic variation in FH prevalence

Aim 3: cascade screening



STEP 1

Determine family size and ages for the proband based on US Census. Proband will be identified in Aim 1 individual screening analysis

STEP 2

Assign genotype for family members according to conventional pedigree structure for autosomal dominant disorders

STEP 3

Assign LDL-C levels for all family members based on genotype-specific LDL-C distributions

STEP 4

Matched family to individuals in NHANES based on age, sex, LDL-C, and FH genotype, and assign lifetime LDL-C trajectory

Incremental lifetime costs, health benefits, and cost-effectiveness of adult and young adult statin treatment strategies

Policy	Discounted QALYs (95% CI)	Discounted total costs, thousands of 2020 $US (95% CI)	ASCVD Events Prevented	Incremental cost-effectiveness ratio ($/QALY)
Women				
Standard care*	Reference	Reference	Reference	Reference
Standard care + young adult LDL-C ≥160 mg/dL (lifestyle)**	49 (-3-123)	14,450 (12,115-17,173)	44 (19-77)	Extendedly Dominated
Standard care + young adult LDL-C ≥160 mg/dL (statins)	148 (58-262)	27,326 (22,204-32,900)	107 (59-167)	115,000
Standard care + young adult LDL-C ≥130 mg/dL (lifestyle)**	177 (4-377)	29,555 (22,586-37,749)	186 (86-305)	177,000
Standard care + young adult LDL-C ≥130 mg/dL (statins)	433 (232-630)	81,281 (56,334-118,022)	255 (143-367)	385,000
Men				
Standard care*	Reference	Reference	Reference	Reference
Standard care + young adult LDL-C ≥160 mg/dL (lifestyle)**	384 (231-572)	27,873 (17,842-42,862)	164 (106-228)	Extendedly Dominated
Standard care + young adult LDL-C ≥160 mg/dL (statins)	817 (341-1,414)	32,385 (20,484-47,342)	491 (285-793)	39,600
Standard care + young adult LDL-C ≥130 mg/dL (lifestyle)**	1,046 (697-1,420)	102,886 (60,006-163,915)	405 (264-551)	Extendedly Dominated
Standard care + young adult LDL-C ≥130 mg/dL (statins)	2,253 (934-4,196)	136,154 (89,510-193,507)	1,532 (890-2,315)	72,200

*Treatment according to ACC/AHA 2018 guidelines; "standard care" consisted of later life (age ≥40 years) statin treatment if clinical ASCVD, diabetes, LDL-C ≥190 mg/dl, or ten-year ASCVD risk ≥7.5% and young adult statin treatment if LDL-C ≥190 mg/dl.

**Individuals with LDL-C ≥190 mg/dL also received moderate-intensity statins

LDL-C – low-density lipoprotein cholesterol