Genes, Lifestyle, and Coronary Artery Disease

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Acknowledgements

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Atherosclerosis Risk in Communities

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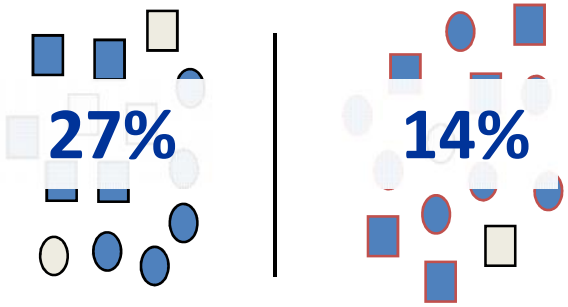
Myocardial infarction risk determined by interplay of genetic and lifestyle factors

YOUNG CANDIDATES FOR CORONARY HEART DISEASE

Menard M. Gertler, M.D., New York, Stanley M. Garn, Ph.D.
and
Paul D. White, M.D., Boston

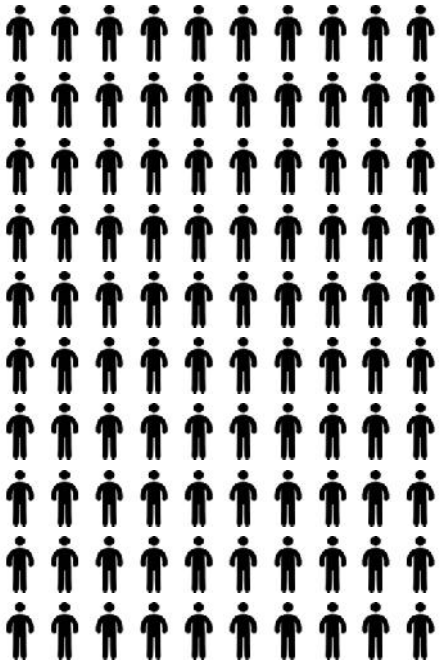
JAMA (1951)

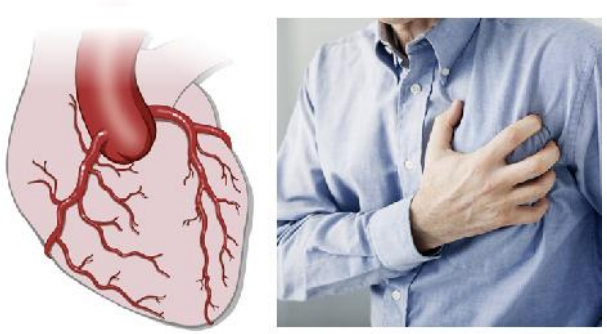
Family History



Clinical interpretation of genetic testing for heart attack risk

100 patients with myocardial infarction



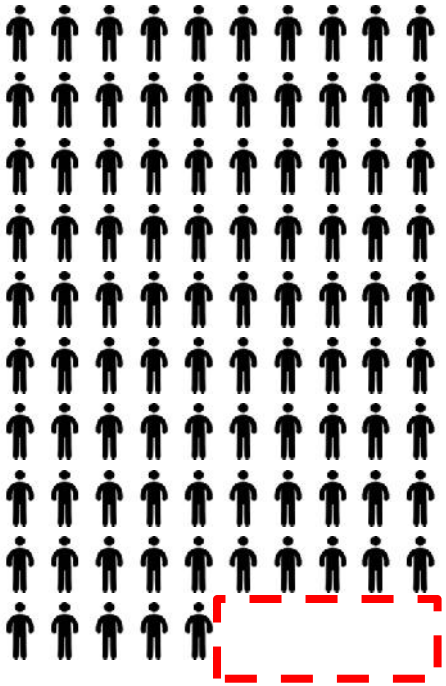


Monogenic

- LDL cholesterol
- Triglyceride clearance
- Lipoprotein(a)

A monogenic risk pathway mutation identified in 5% of individuals presenting with myocardial infarction

100 patients with myocardial infarction

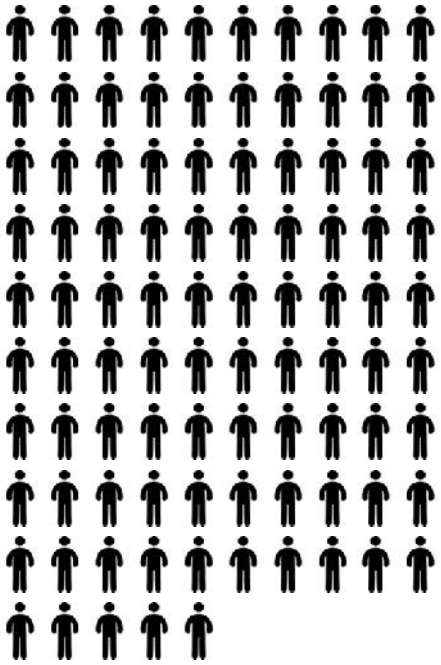


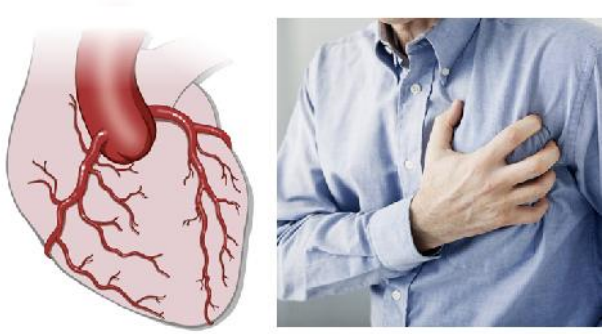
Monogenic

	↑ Risk
LDL cholesterol *LDLR, APOB*	3.2-fold
Triglyceride clearance *LPL, APOA5*	2.3-fold
Lipoprotein(a) *LPA*	2.8-fold

Clinical interpretation of genetic testing for heart attack risk

100 patients with myocardial infarction





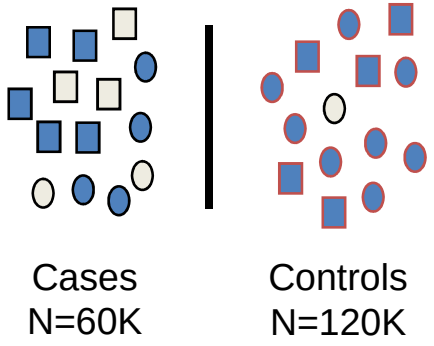
Monogenic

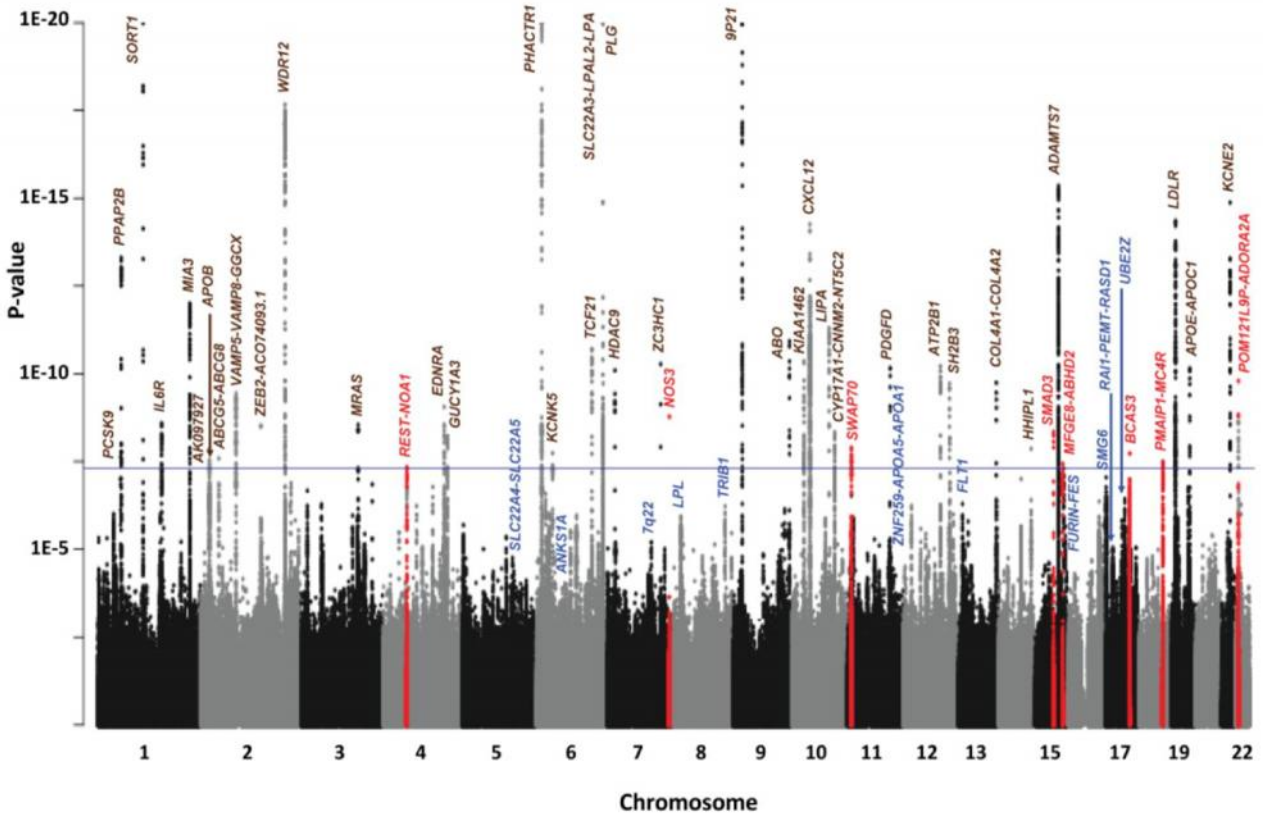
LDL Cholesterol
Triglyceride Clearance
Lipoprotein(a)

Polygenic

Polygenic Risk Score

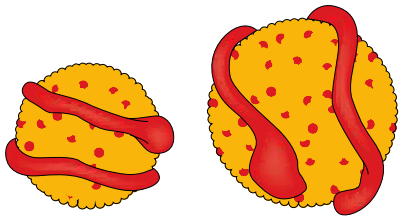
>50 genetic variants associated with myocardial infarction





Kathiresan *Nature Genetics* (2009)
Samani *Nature Genetics* (2011)
Deloukas *Nature Genetics (*2013)
Nikpay *Nature Genetics* (2015)

Genetic variants associated with myocardial infarction highlight multiple underlying pathways



LDL cholesterol and lipoprotein(a)

- *SORT1*
- *PCSK9*
- *APOB*
- *ABCG5–ABCG8*
- *LPA*
- *LIPA*
- *LDLR*
- *APOE*

Triglyceride-rich lipoproteins

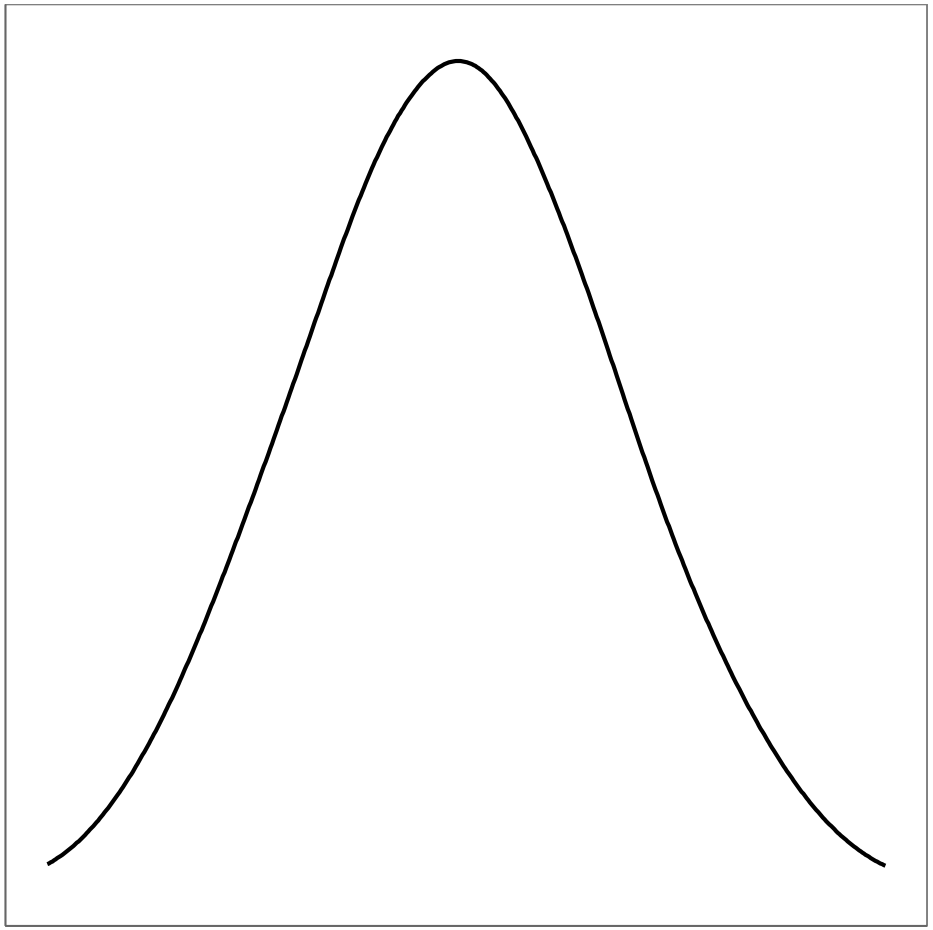
- *LPL*
- *TRIB1*
- *APOA5/A4/C3/A1*
- *ANGPTL4*

Kathiresan *Nature Genetics* (2009)
Samani *Nature Genetics* (2011)
Deloukas *Nature Genetics (*2013)
Nikpay *Nature Genetics* (2015)

Khera & Kathiresan | Nature Reviews Genetics | 2017

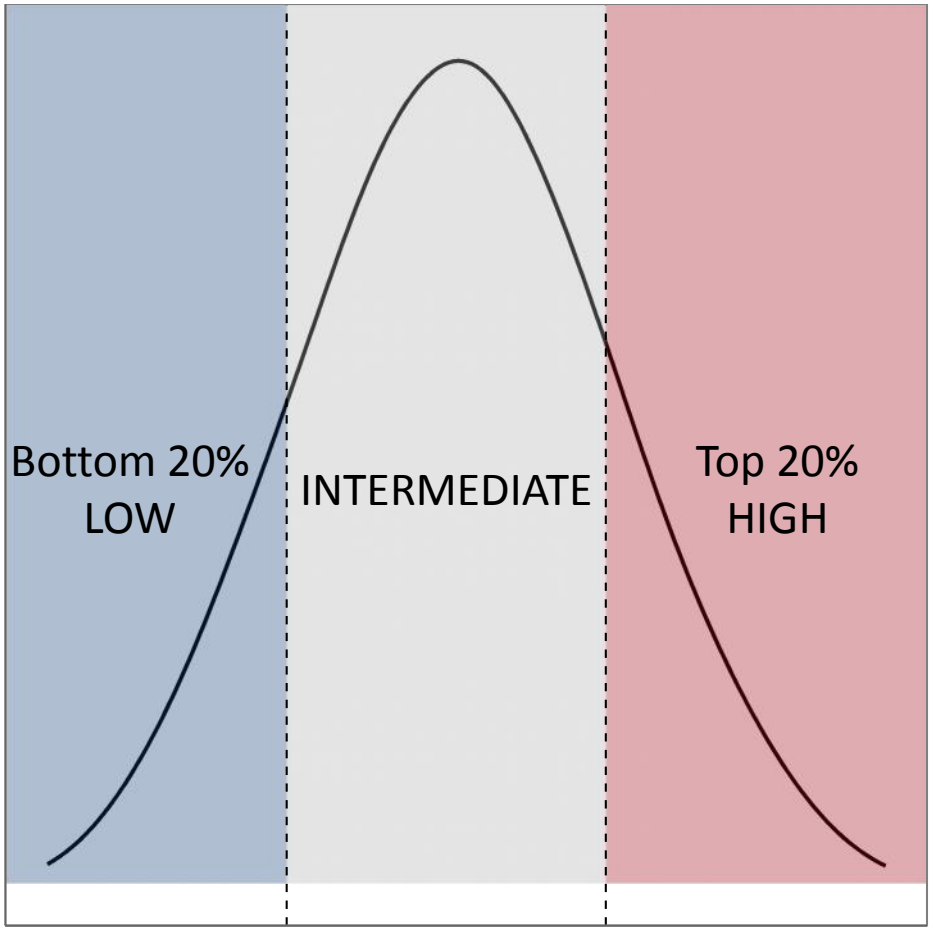
Polygenic risk score:

Measure of inherited risk for coronary disease



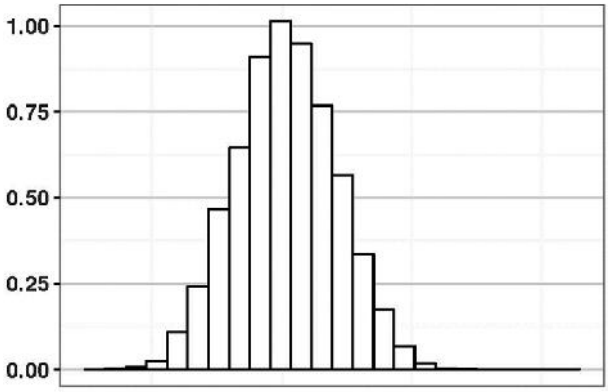
Polygenic Risk Score

Polygenic risk score: Divide population into genetic risk groups (low, intermediate, high)



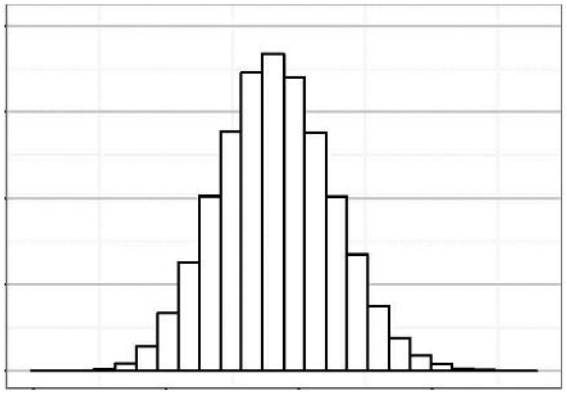
Building a polygenic risk score using 50 variants:
Distribution in > 50,000 individuals

Atherosclerosis Risk in Communities (N = 7,814)



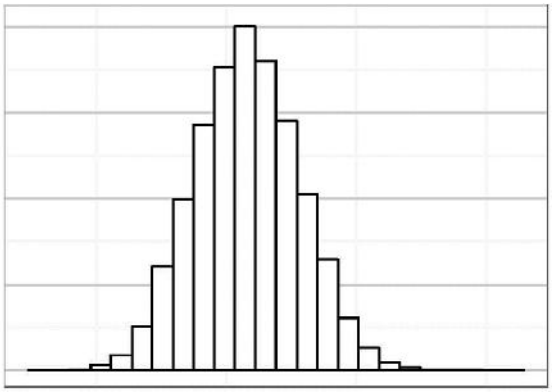
Polygenic Risk Score

Women's Genome Health Study (N = 21,222)



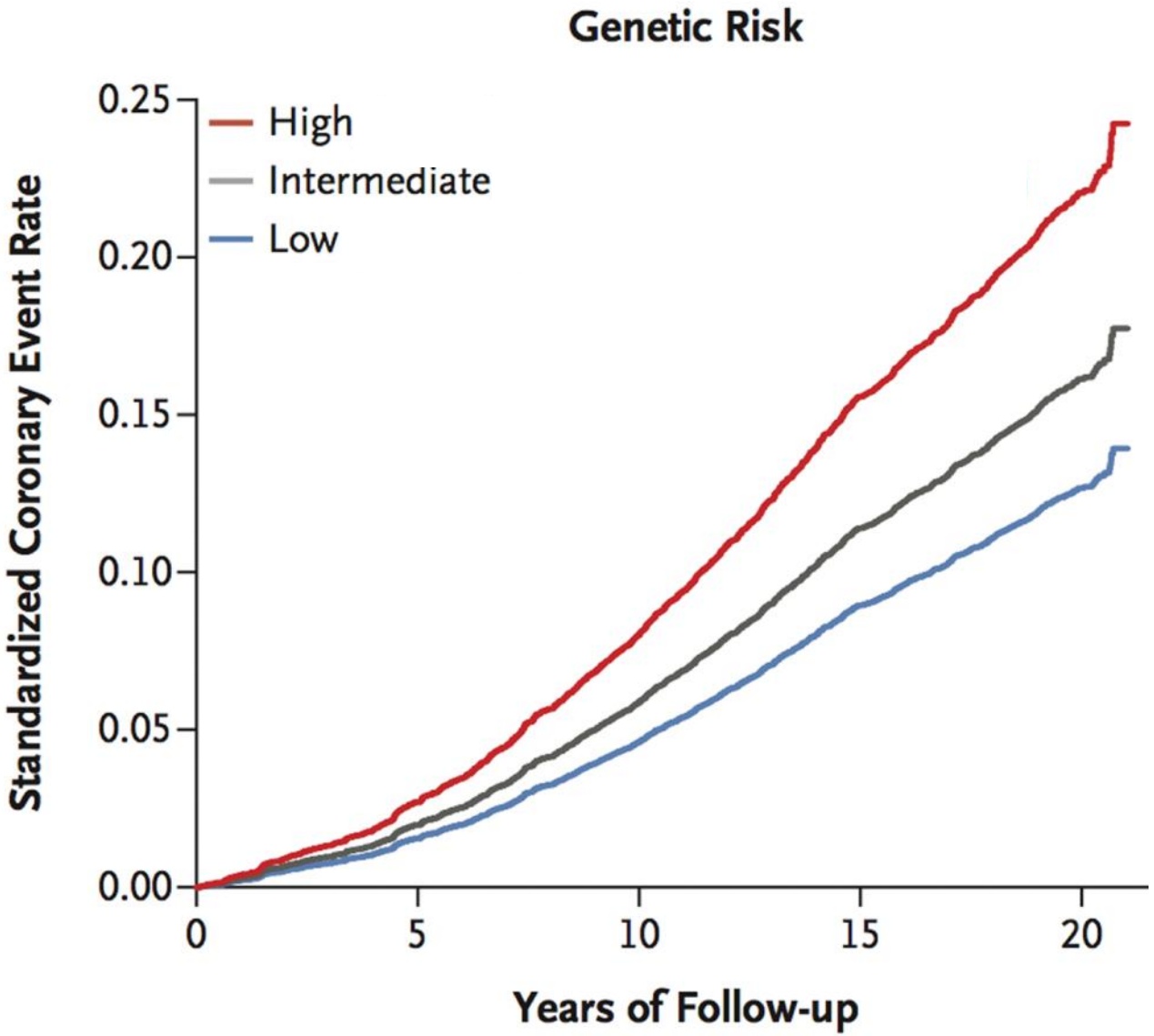
Polygenic Risk Score

Malmö Diet and Cancer Study (N = 22,389)



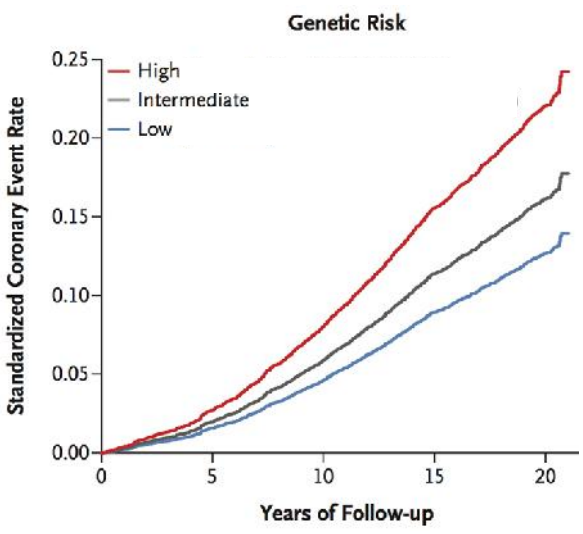
Polygenic Risk Score

High genetic risk → 91% higher event rate

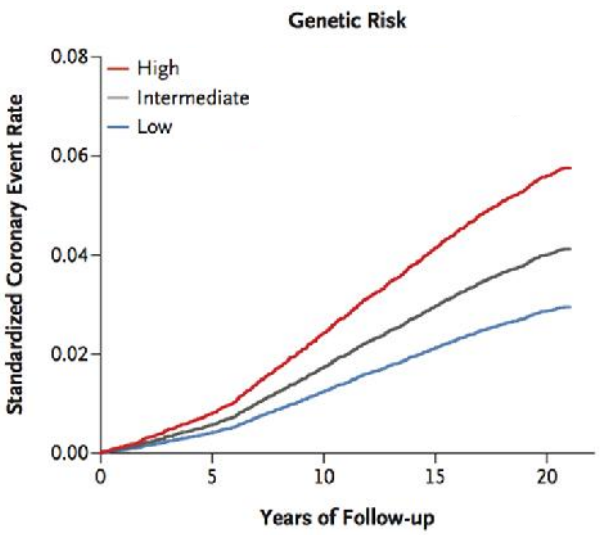


High genetic risk → 91% higher event rate

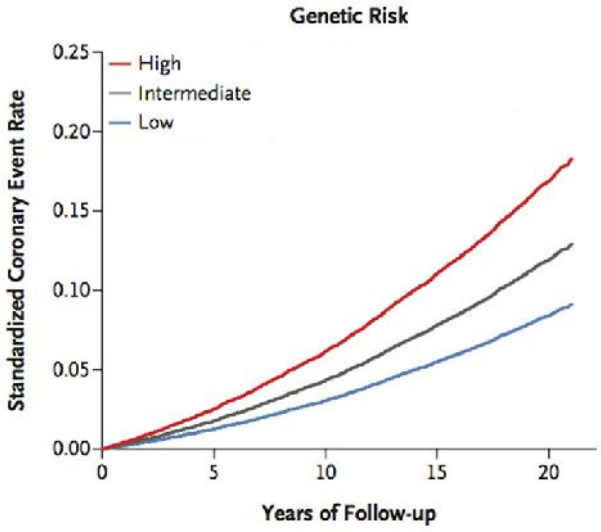
Atherosclerosis Risk in Communities



Women's Genome Health Study

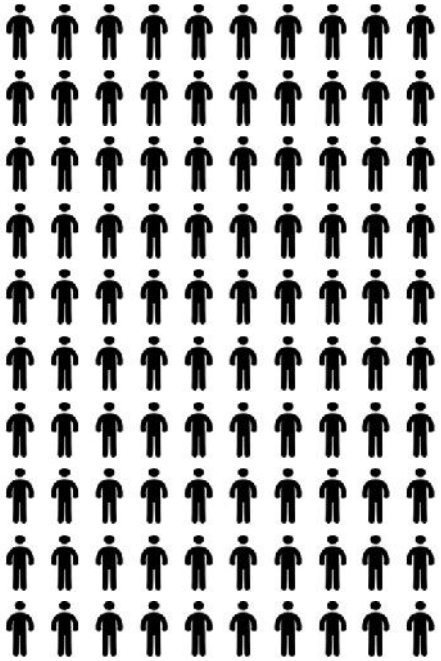


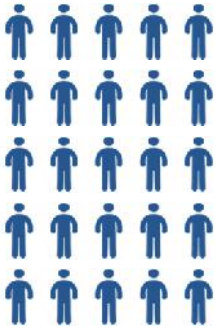
Malmö Diet and Cancer Study



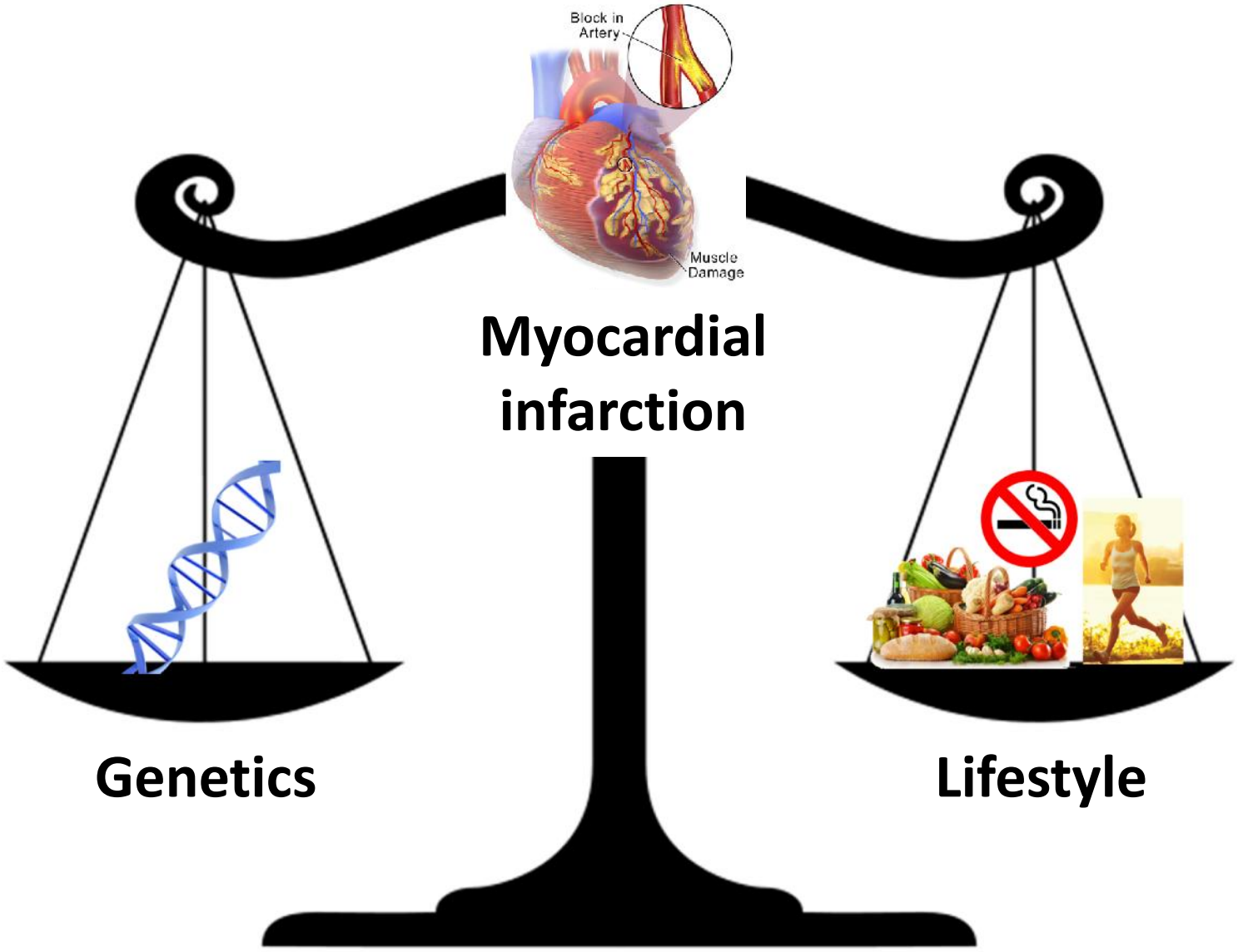
Clinical interpretation of genetic testing for heart attack risk; where do we stand in 2017?

100 patients with myocardial infarction



	↑ Risk
Monogenic risk	3-fold
 Polygenic risk	2-fold
Monogenic & polygenic	6-fold

To what extent can a healthy lifestyle offset inherited risk of myocardial infarction?



Nurses Health Study: N Eng J Med, 2000

PRIMARY PREVENTION OF CORONARY HEART DISEASE IN WOMEN THROUGH DIET AND LIFESTYLE

MEIR J. STAMPFER, M.D., FRANK B. HU, M.D., JOANN E. MANSON, M.D., ERIC B. RIMM, SC.D., AND WALTER C. WILLETT, M.D.

Most favorable lifestyle (3% of women) associated with 83% decrease in coronary risk.

Building a healthy lifestyle score:

No current smoking

Avoiding obesity

Regular exercise

Healthy diet

Favorable lifestyle

3-4 healthy lifestyle factors

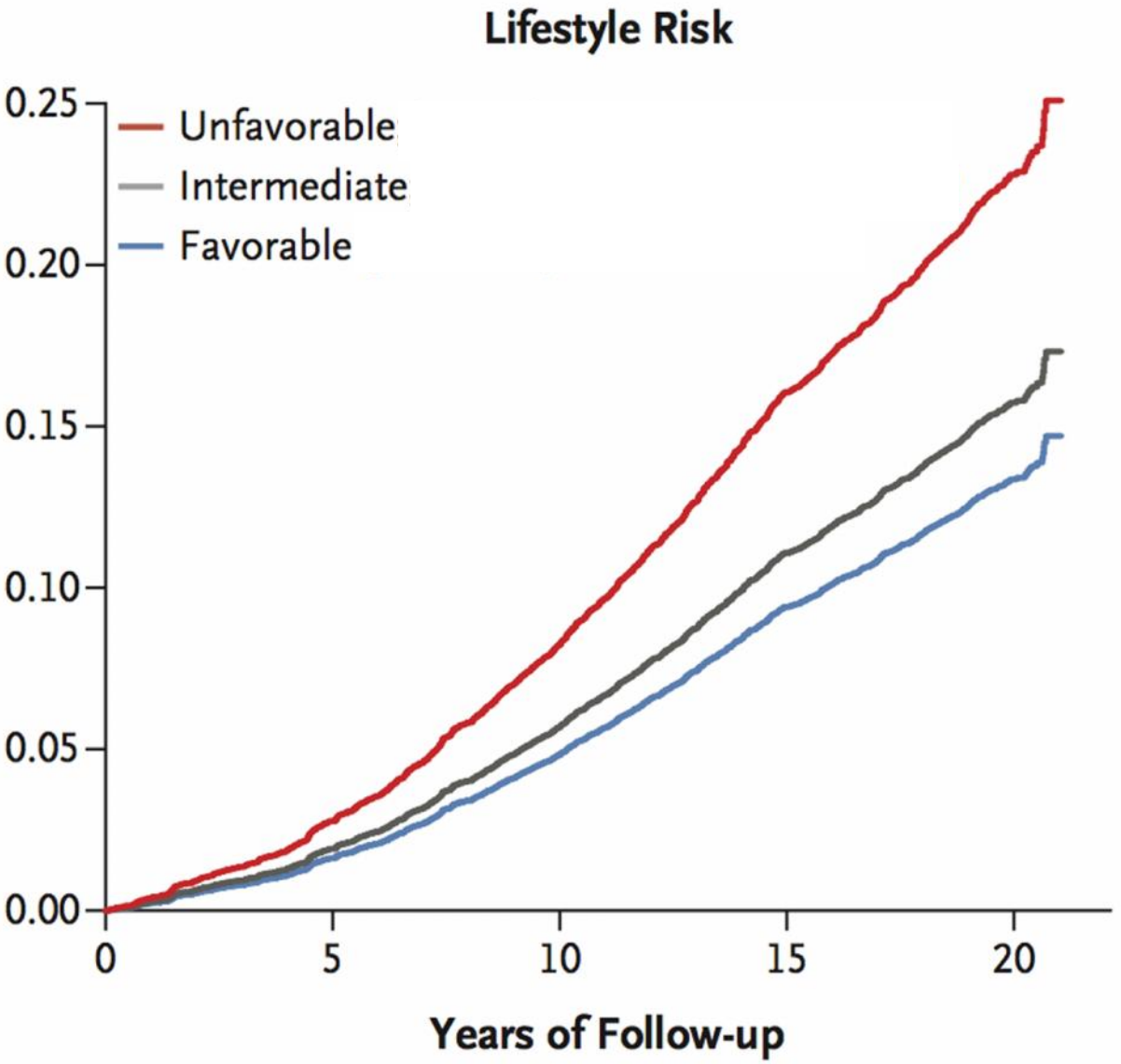
Intermediate lifestyle

2 healthy lifestyle factors

Unfavorable lifestyle

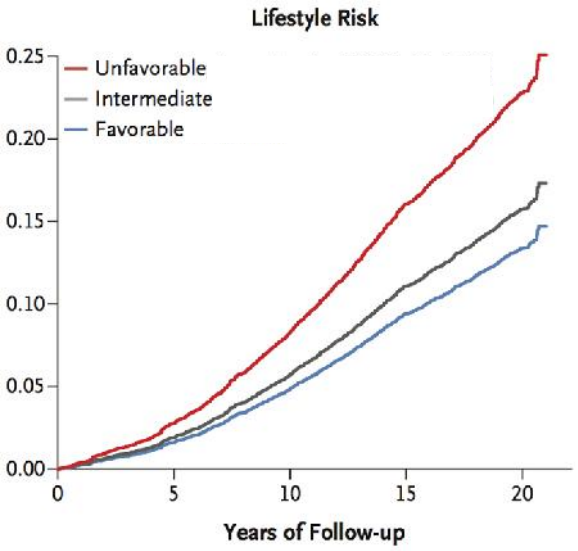
0-1 healthy lifestyle factors

Favorable lifestyle → 50% lower event rate

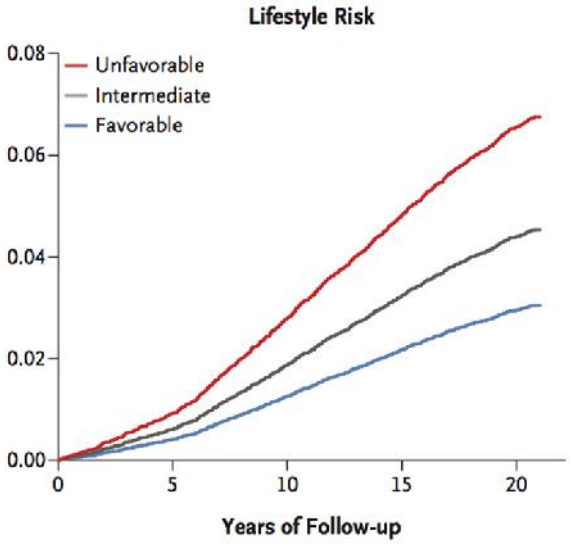


Favorable lifestyle → 50% lower event rate

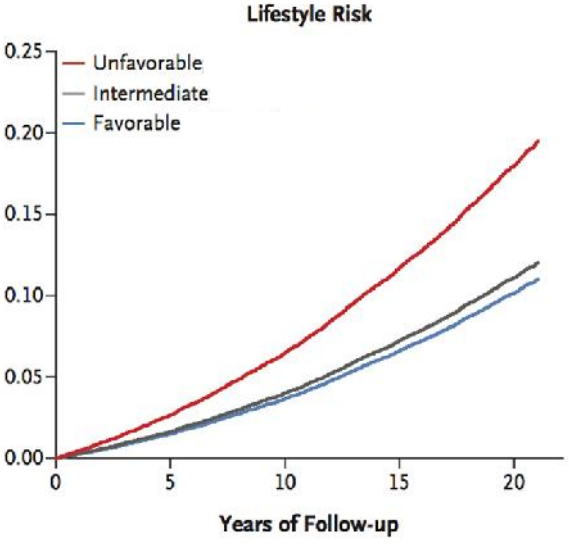
Atherosclerosis Risk in Communities



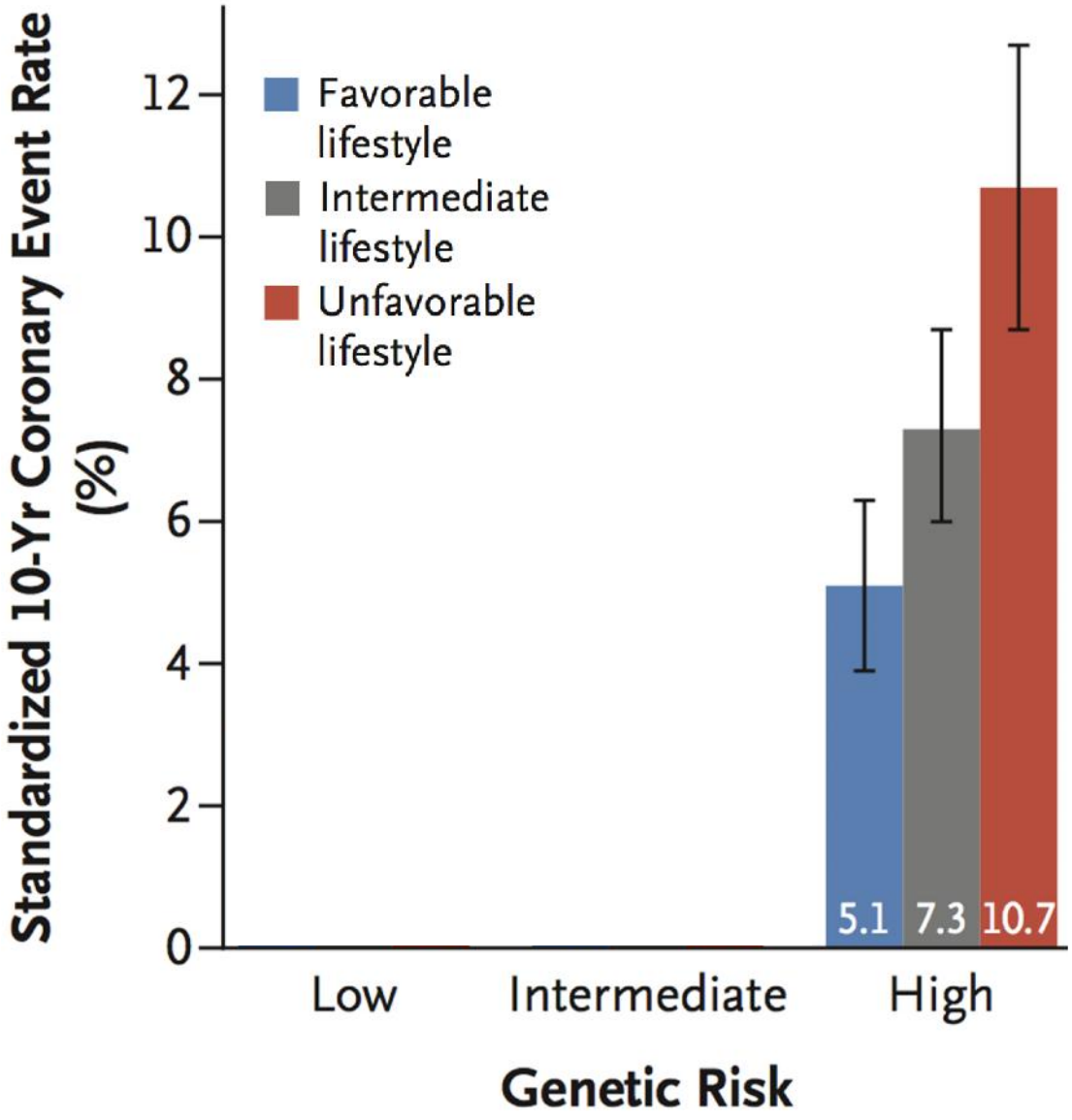
Women's Genome Health Study



Malmö Diet and Cancer Study



Among high polygenic risk individuals, favorable lifestyle decreases risk by ≈ 50%



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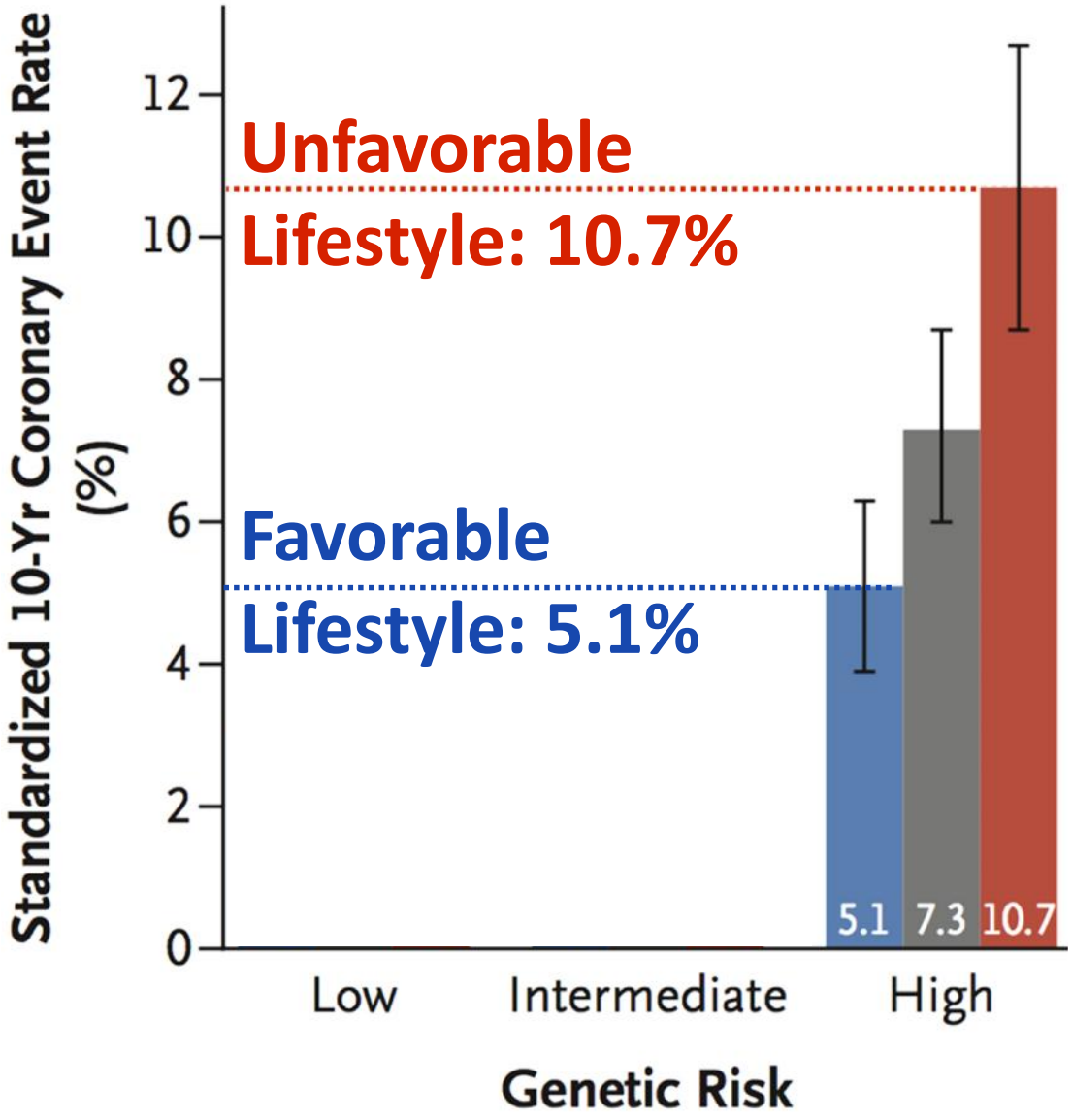

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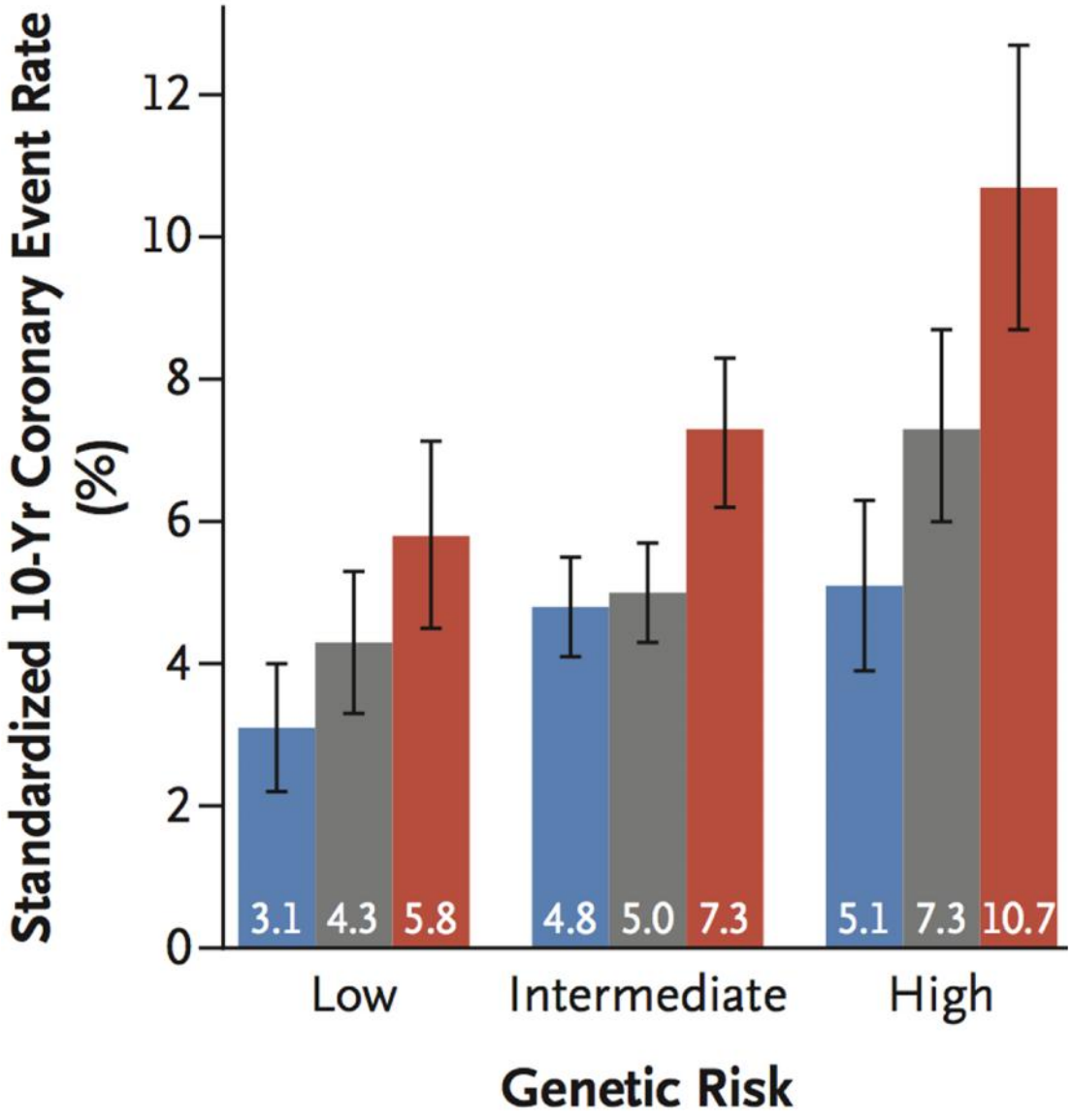
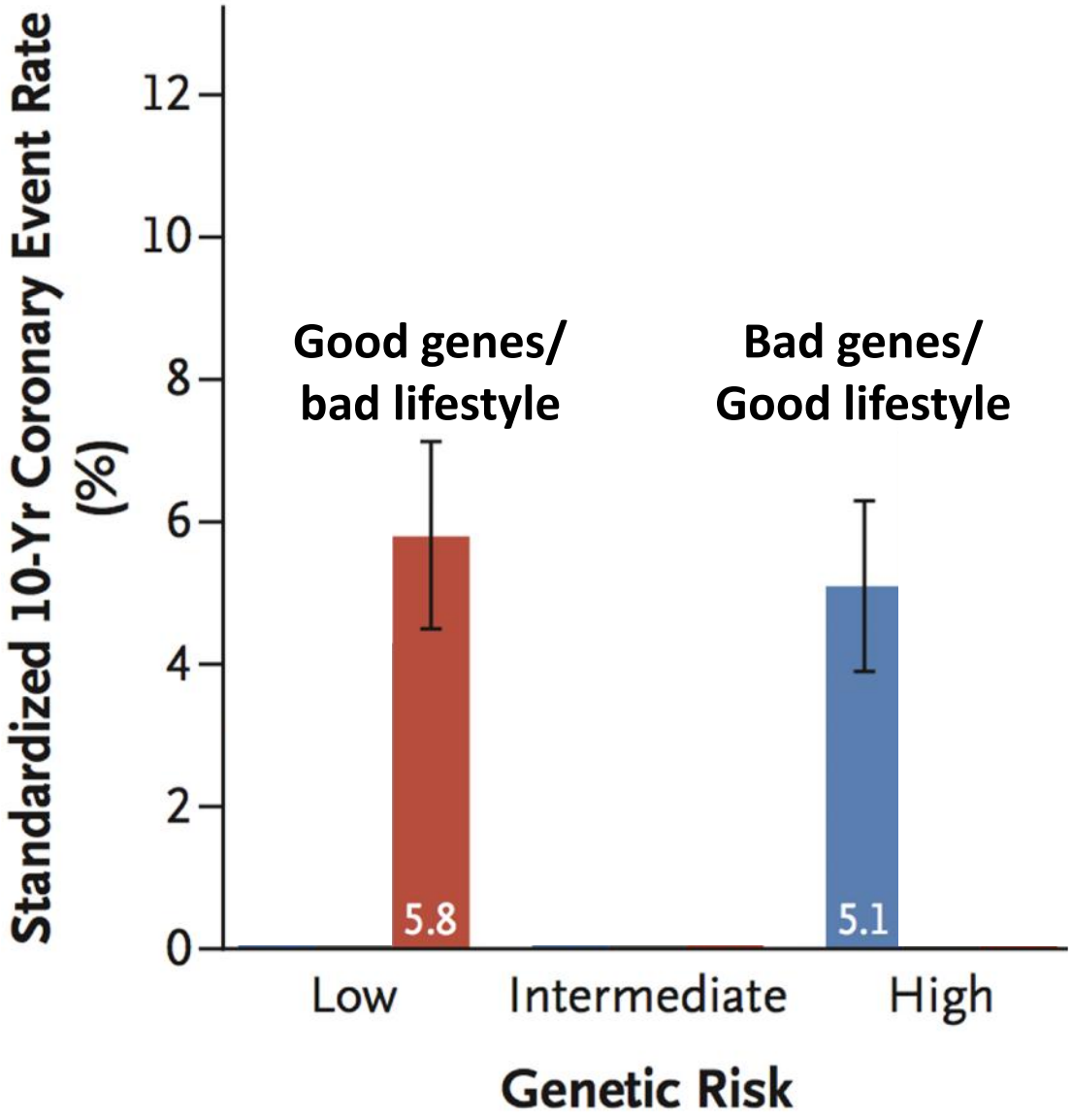


Good genes / bad lifestyle ≈ bad genes / good lifestyle



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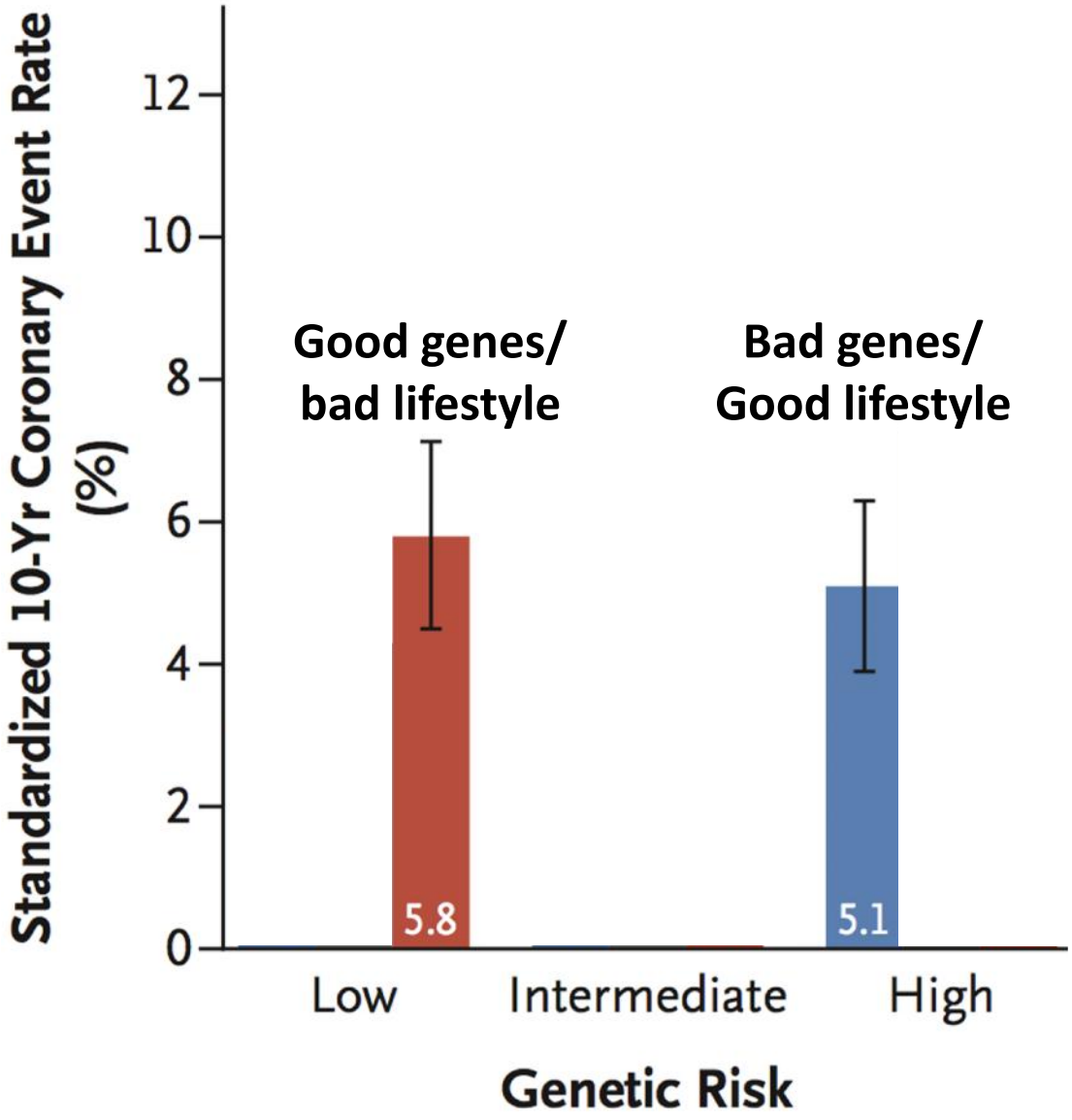
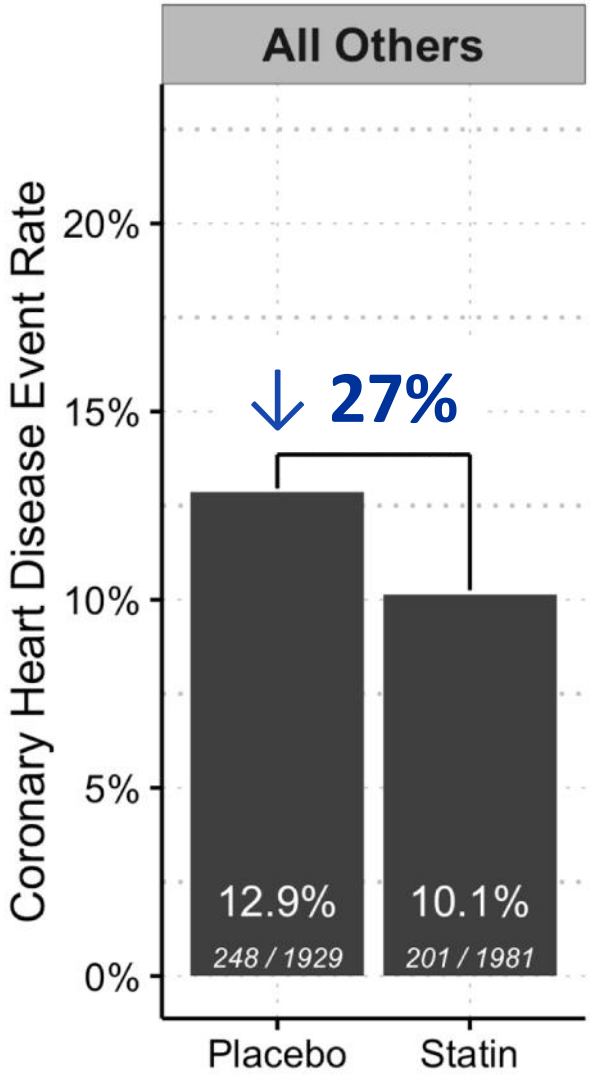


Among high polygenic risk 1° prevention group, statins → 44% decrease in coronary risk



Natarajan et al. | Circulation| 2017

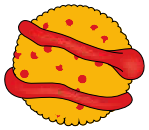
To what extent can inherited risk of myocardial infarction be offset by lifestyle or statin therapy?

DNA is not destiny.

Among those at high genetic risk,
both healthy lifestyle and statin therapy
→ **40-50% reduction** in myocardial infarction.

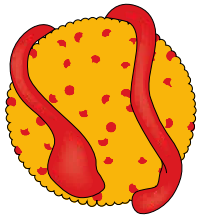
Human genetics can stratify the population to guide targeted therapy for myocardial infarction

Monogenic risk (5%)



Familial hypercholesterolemia

→ **Statin, ezetimibe, PCSK9i**



Triglyceride clearance

→ **APOC3 inhibition**

Increased lipoprotein(a)

→ **ASO Lp(a) inhibitor**

Polygenic risk (30%)

Lifestyle

NEJM 2016

Medications

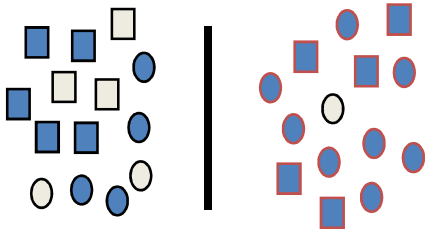
Lancet 2015
Circulation 2017

Healthy Lifestyle Factor Criteria

Healthy Lifestyle Factor	Criteria
Absence of Current Smoking	**No current smoking**
Absence of Obesity	**BMI < 30 kg/m^2** at baseline examination
Regular Physical Activity	Self-reported physical activity **≥ once/week**
Healthy Diet	At least 5 of the 10 characteristics: **Fruits**: ≥ 3 servings/day **Nuts**: ≥ 1 serving/week 3 **Vegetables**: ≥3 servings/day **Whole grains**: ≥ 3 servings/day **Fish**: ≥2 servings/week **Dairy**: ≥ 2.5 servings/day **Refined grains**: ≤ 1.5 servings/day **Processed meats**: ≤ 1 serving/week **Unprocessed red meats**: ≤ 1.5 servings/week **Sugar sweetened beverages**: ≤1 serving/week

Rare variant burden signals in 9 genes

Sample size



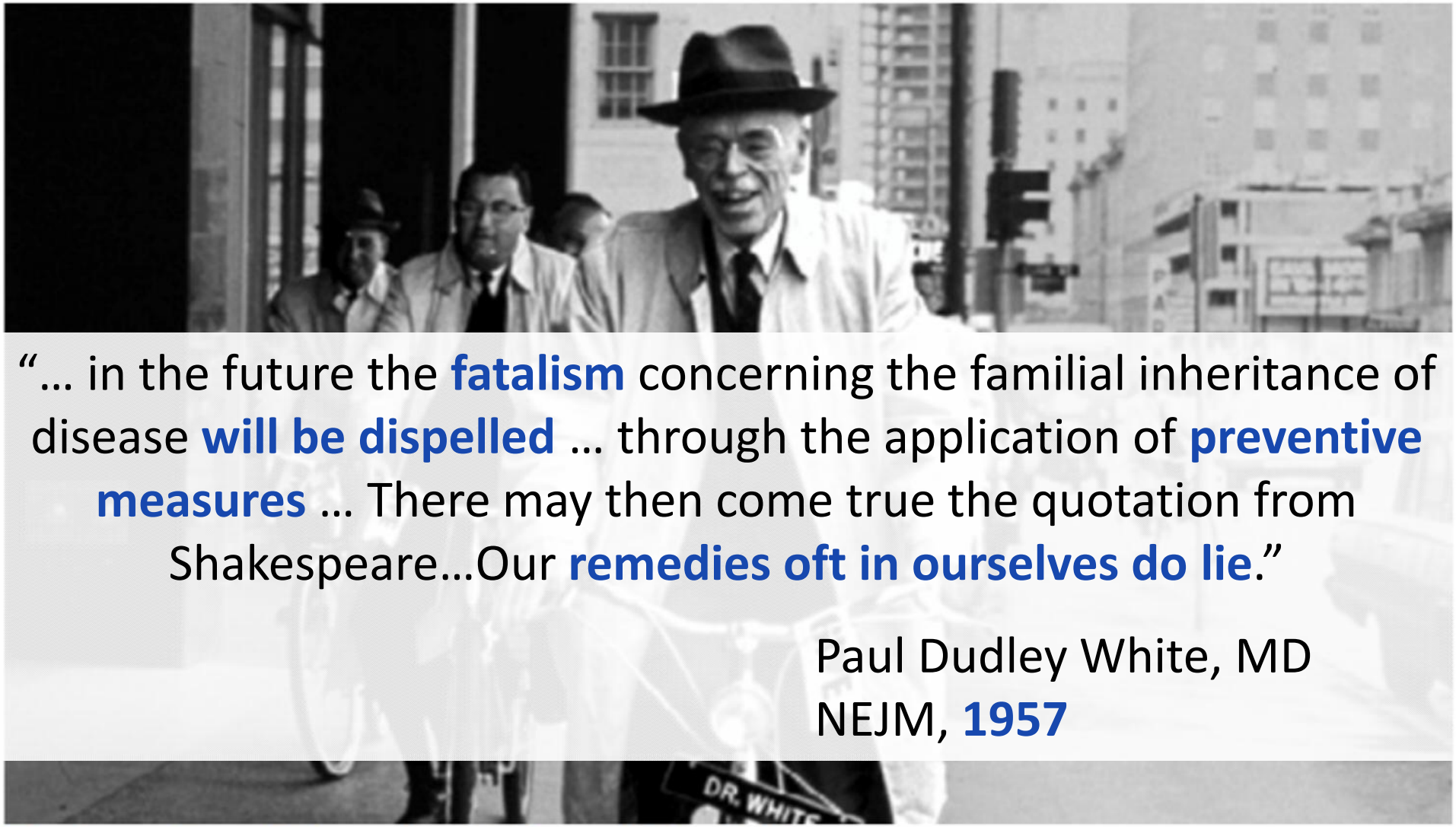
Cases
N=10K

Controls
N=12K

Exome sequencing

	Gene	Carrier Frequency	Odds Ratio for MI
← Risk	LDLR	1 in 221	≈ 4
	LPL	1 in 249	≈ 2
	APOA5	1 in 216	≈ 2
Protective	LPA	1 in 285	≈ 0.8
	NPC1L1	1 in 650	≈ 0.5
	ANGPTL4	1 in 360	≈ 0.5
	APOC3	1 in 150	≈ 0.6
	ASGR1	1 in 120	≈ 0.7
	PCSK9	1 in 50 (Blacks)	≈ 0.2

Background: Both genetic and lifestyle factors contribute to individual-level risk of coronary disease



"… in the future the **fatalism** concerning the familial inheritance of disease **will be dispelled** … through the application of **preventive measures** … There may then come true the quotation from Shakespeare…Our **remedies oft in ourselves do lie**."

Paul Dudley White, MD
NEJM, **1957**

(Photo courtesy of Massachusetts General Hospital)