Personalized Cardiovascular Medicine and Genomics

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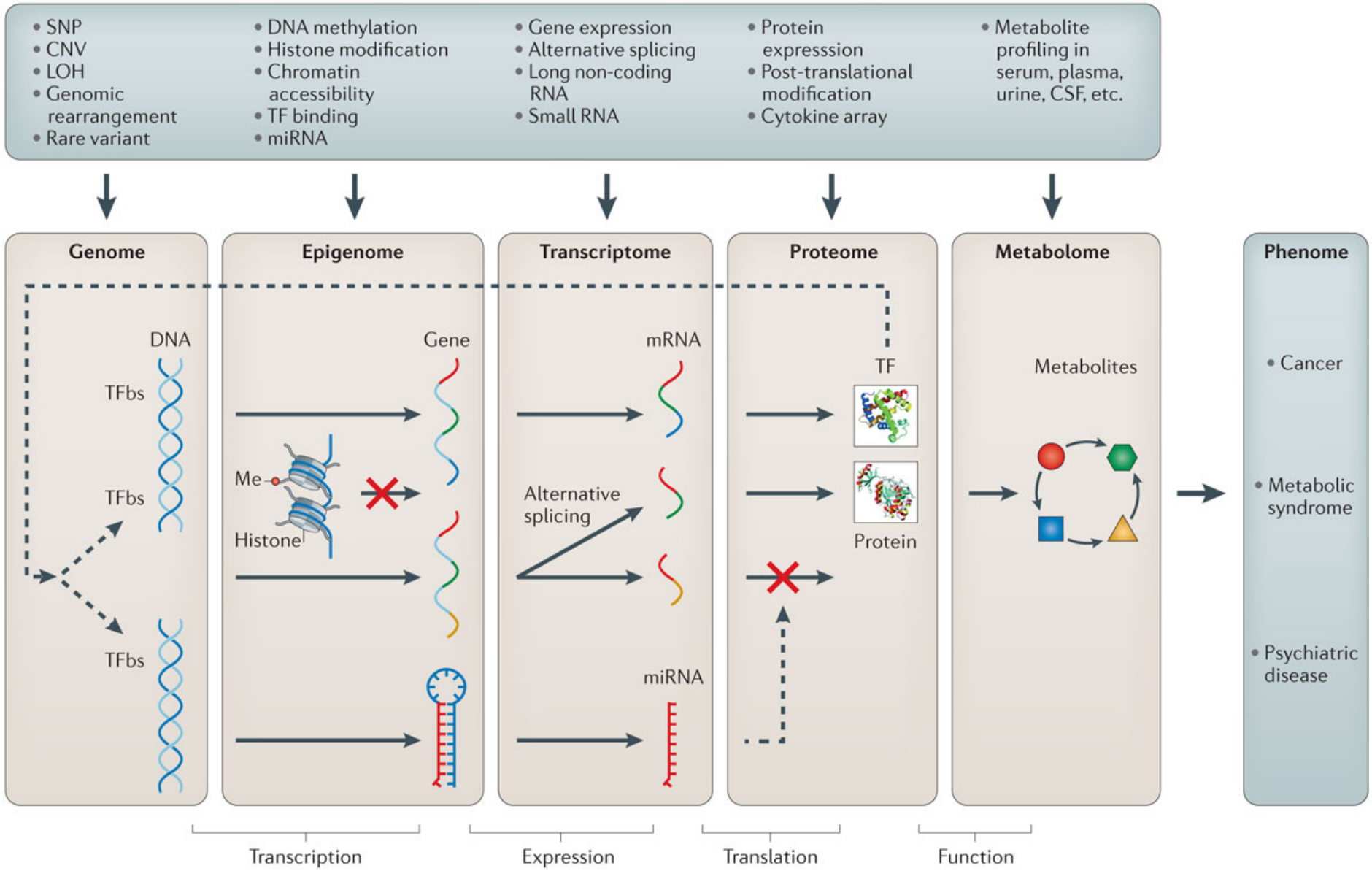
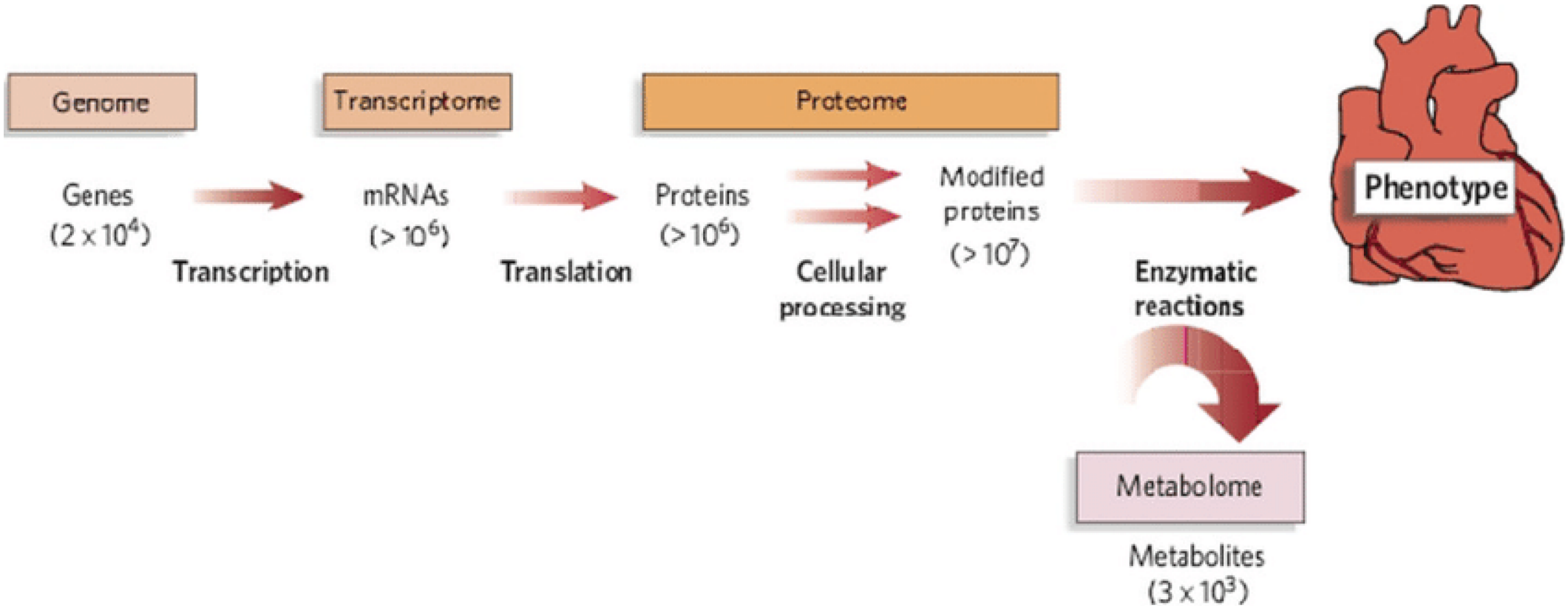
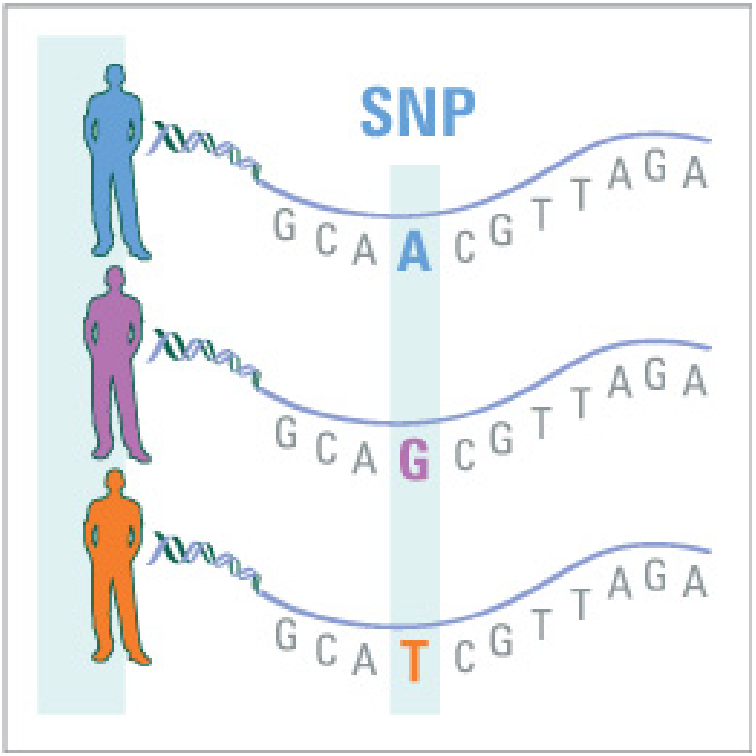
Disclosures

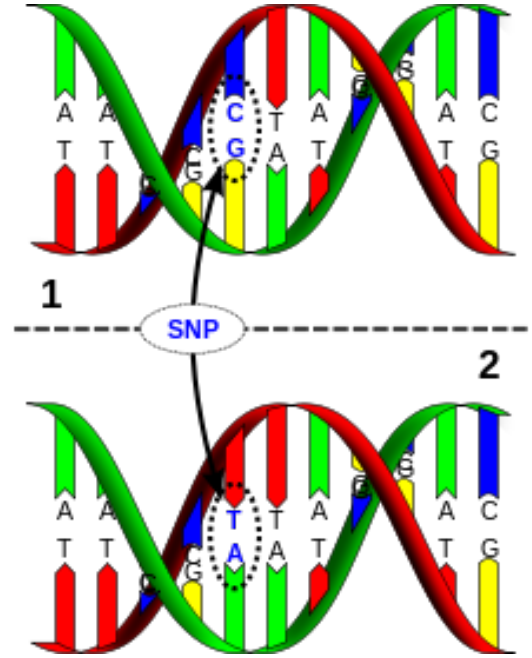
- None
- Grant Funding
  - NIH/NHLBI R01HL128801
  - NIH/NCCIH R01AT009247
  - NIH/NHLBI R01HL072125

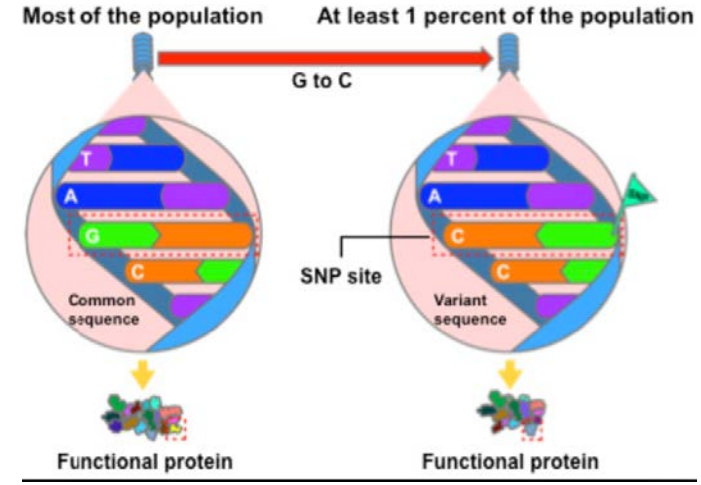


Nature Reviews | Genetics


Genome
Transcriptome
Proteome
Genes
(2 x 10^4)
Transcription
mRNAs
(> 10^6)
Translation
Proteins
(> 10^6)
Cellular processing
Modified proteins
(> 10^7)
Enzymatic reactions
Phenotype
Metabolome
Metabolites
(3 x 10^3)







A SNP is a single-letter change in DNA, part of the natural genetic variation (at least 1%) within a population.
Human genome has 3 billion nucleotides.
500,000 SNP provide, on average, a marker every 6,000 nucleotides.

Image courtesy of Lauren Solomon, the Broad Institute

Genome Wide Association Studies (GWAS): SNPs common and occuring on average in 50% of the population.

Chromosomal Location	SNP	Nearby Genes	Risk Allele Frequency (allele)	Odds Ratio	Delivery Route
Risk Variant Associated with LDL Cholesterol					
6q25.3	rs3798220	LPA	0.02 (C)	1.92 (1.48-2.49)	2009
2p24.1	rs515135	APOB	0.83 (G)	1.03	2012
1p13.3	rs599839	SORT1	0.78 (A)	1.29 (1.18-1.40)	2007
19p13.2	rs1122608	LDLR	0.77 (G)	1.14 (1.09-1.19)	2009
19q13.32	rs2075650	APOE	0.14 (G)	1.14 (1.09-1.19)	2011
2p21	rs6544713	ABCG5-ABCG8	0.29 (G)	1.07 (1.04-1.11)	2011
1p32.3	rs11206510	PCSK9	0.82 (T)	1.15 (1.10-1.21)	2009
Risk Variant Associated with HDL Cholesterol					
6p21.31	rs12205331	ANKS1A	0.81 (C)	1.04	2012
Risk Variant Associated with Triglycerides					
8q24.13	rs10808546	TRIB1	0.65 (A)	1.08 (1.04-1.12)	2011
11q23.3	rs964184	ZNF259, APOA5-A4-C3-A1	0.13 (G)	1.13 (1.10-1.16)	2011
Risk Variant Associated with Hypertension					
12q24.12	rs3184504	SH2B3	0.44 (T)	1.13 (1.08-1.18)	2009
10q24.32	rs12413409	CYP17A1, CNNM2, NT5C2	0.89 (G)	1.12 (1.08-1.16)	2011
4q31.1	rs7692387	GUCYA3	0.81 (G)	1.13	2012
15q26.1	rs17514846	FURIN-FES	0.44 (A)	1.04	2012

Genome Wide Association Studies (GWAS): SNPs and CVD risk factor associations

Most SNPs do not code for protein. this means the risk variant mediates its increased risk for CVD directly or indirectly through regulation of DNA sequences that do code for proteins

Chromosomal Location	SNP	Nearby Genes	Risk Allele Frequency (allele)	Odds Ratio	Delivery Route
Risk Variant Associated with Myocardial Infarction					
9q34.2‡	rs579459	ABO	0.21 (C)	1.10 (1.07-1.13)	2011
Risk Variant Mechanism of Risk Unknown					
9p21.3	rs4977574	CDKN2A,CDKN2B	0.46 (G)	1.25 (1.18-1.31) to 1.37 (1.26-1.48)	2007
1q41	rs17465637	MIA3	0.74 (C)	1.20 (1.12-1.30)	2007
10q11.21	rs1746048	CXCL12	0.87 (C)	1.33 (1.20-1.48)	2007
2q33.1	rs6725887	WDR12	0.15 (C)	1.16 (1.10-1.22)	2009
6p24.1	rs12526453	PHACTR1	0.67 (C)	1.13 (1.09-1.17)	2009
21q22.11	rs9982601	MRPS6	0.15 (T)	1.19 (1.13-1.27)	2009
3q22.3	rs2306374	MRAS	0.18 (C)	1.15 (1.11-1.19)	2009
10p11.23	rs2505083	KIAA1462	0.42 (C)	1.07 (1.04-1.09)	2010
1p32.2	rs17114036	PPAP2B	0.91 (A)	1.17 (1.13-1.22)	2011
5q31.1	rs2706399	IL5	0.48 (A)	1.02 (1.01-1.03)	2011
6q23.2	rs12190287	TCF21	0.62 (C)	1.08 (1.06-1.10)	2011
7q22.3	rs10953541	BCAP29	0.75 (C)	1.08 (1.05-1.11)	2011
7q32.2	rs11556924	ZC3HC1	0.62 (C)	1.09 (1.07-1.12)	2011
10q23.31	rs1412444	LIPA	0.34 (T)	1.09 (1.07-1.12)	2011
11q22.3	rs974819	PDGF	0.29 (T)	1.07 (1.04-1.09)	2011
13q34	rs4773144	COL4A1, COL4A2	0.44 (G)	1.07 (1.05-1.09)	2011
14q32.2	rs2895811	HHIPL1	0.43 (C)	1.07 (1.05-1.10)	2011
15q25.1	rs3825807	ADAMTS7	0.57 (A)	1.08 (1.06-1.10)	2011
17p13.3	rs216172	SMG6, SRR	0.37 (C)	1.07 (1.05-1.09)	2011
17p11.2	rs12936587	RASD1, SMCR3, PEMT	0.56 (G)	1.07 (1.05-1.09)	2011
17q21.32	rs46522	UBE2Z, GIP, ATP5G1, SNF8	0.53 (T)	1.06 (1.04-1.08)	2011
5p13.3*	rs11748327	IRX1, ADAMTS16	0.76 (C)	1.25 [1.18-1.33]	2011
6p22.1*	rs6929846	BTN2A1	0.06 (T)	1.51 (1.28-1.77)	2011
6p24.1**	rs6903956	C6orf105	0.07 (A)	1.65 (1.44-1.90)	2011
6p21.3	rs3869109	HCG27 and HLA-C	0.60 (C)	1.15	2012
1q21	rs4845625	IL6R	0.47 (T)	1.09	2012

Atherosclerosis 223 (2012) 421–426

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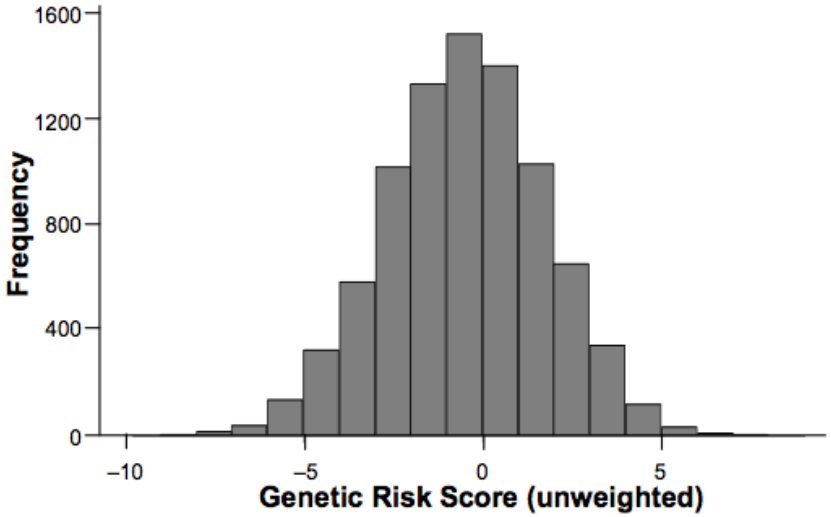
Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

A genetic risk score based on direct associations with coronary heart disease improves coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC), but not in the Rotterdam and Framingham Offspring, Studies

Ariel Brautbar [a,b,c,d,*], Lisa A. Pompeii [e], Abbas Dehghan [f,g], Julius S. Ngwa [h], Vijay Nambi [b,d], ii [b,d,i], Fernando Rivadeneira [g,j], André G. Uitterlinden [g,j], Albert Hofman [f,g], M. Witteman [f,g], Michael J. Pencina [h], Aaron R. Folsom [k], L. Adrienne Cupples [h,l], allantyne [b,d], Eric Boerwinkle [e,m,n]



SNP	Gene Region Name or Locus	HR in ARIC [95% CI]	Published Risk Estimates
rs9818870	*MRAS*	1.062 [0.949, 1.190]	OR 1.15 [1.11–1.19]
rs2259816	*HNF1A*	1.019 [0.934, 1.113]	OR 1.08 [1.05–1.11]
rs9982601	*SLC5A3, MRPS6, KCNE2*	1.171 [1.044, 1.314]	OR 1.2 [1.14–1.27]
rs12526453	*PHACTR1*	1.141 [1.043, 1.250]	OR 1.12 [1.08–1.17]
rs1746048	*CXCL12*	1.229 [1.077, 1.401]	OR 1.17 [1.11–1.24]
rs6725887	*WDR12*	1.073 [0.950, 1.213]	OR 1.17 [1.11–1.23]
rs6922269	*MTHFD1L*	1.010 [0.920, 1.110]	OR 1.23 [1.15–1.33]
rs501120	*CXCL12*	1.214 [1.066, 1.383]	OR 1.33 [1.20–1.48
rs3900940	*MYH15*	1.127 [1.032, 1.230]	HR 1.17 [1.07–1.28]
rs1010	*VAMP8*	1.042 [0.959, 1.133]	HR 1.2 [P < 0.019]
rs7439293	*PALLD*	1.104 [1.012, 1.205]	HR 1.11 [1.02–1.22]
rs2298566	*SNX19*	1.131 [1.027, 1.247]	HR 1.12 [1.01–1.24]
rs10757274	*9p21*	1.214 [1.117, 1.319]	OR 1.21 [1.04–1.40]

Hazards ratios (HR) per unit score increase as calculated for the unweighted and weighted genetic risk score (GRS) in the ARIC, Rotterdam, and Framingham Offspring Studies.

	Study	HR	Lower CI	Upper CI
Unweighted GRS	ARIC	1.10	1.07	1.13
	Rotterdam	1.08	1.03	1.14
	Framingham	1.12	1.10	1.14
Weighted GRS	ARIC	2.30	1.87	2.83
	Rotterdam	2.05	1.50	2.70
	Framingham	1.12	1.10	1.15

HRs were adjusted for age, sex, smoking, diabetes, systolic blood pressure, antihypertensive medication use, total cholesterol, and high-density lipoprotein cholesterol (HDL-C). In the Rotterdam Study, HRs were calculated for participants younger than 65 years. CI indicates 95% confidence interval.

Weights are generally assigned to each genetic variant according to the strength of their association with disease risk (effect estimate). Individuals are scored based on how many risk alleles they have for each variant (for example, zero, one, or two copies) included in the polygenic score

nature genetics

LETTERS

https://doi.org/10.1038/s41588-018-0183-z

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Amit V. Khera[1,2,3,4,5], Mark Chaffin[4,5], Krishna G. Aragam[1,2,3,4], Mary E. Haas[4], Carolina Roselli[4], Seung Hoan Choi[4], Pradeep Natarajan[2,3,4], Eric S. Lander[4], Steven A. Lubitz[2,3,4], Patrick T. Ellinor[2,3,4] and Sekar Kathiresan[1,2,3,4*]

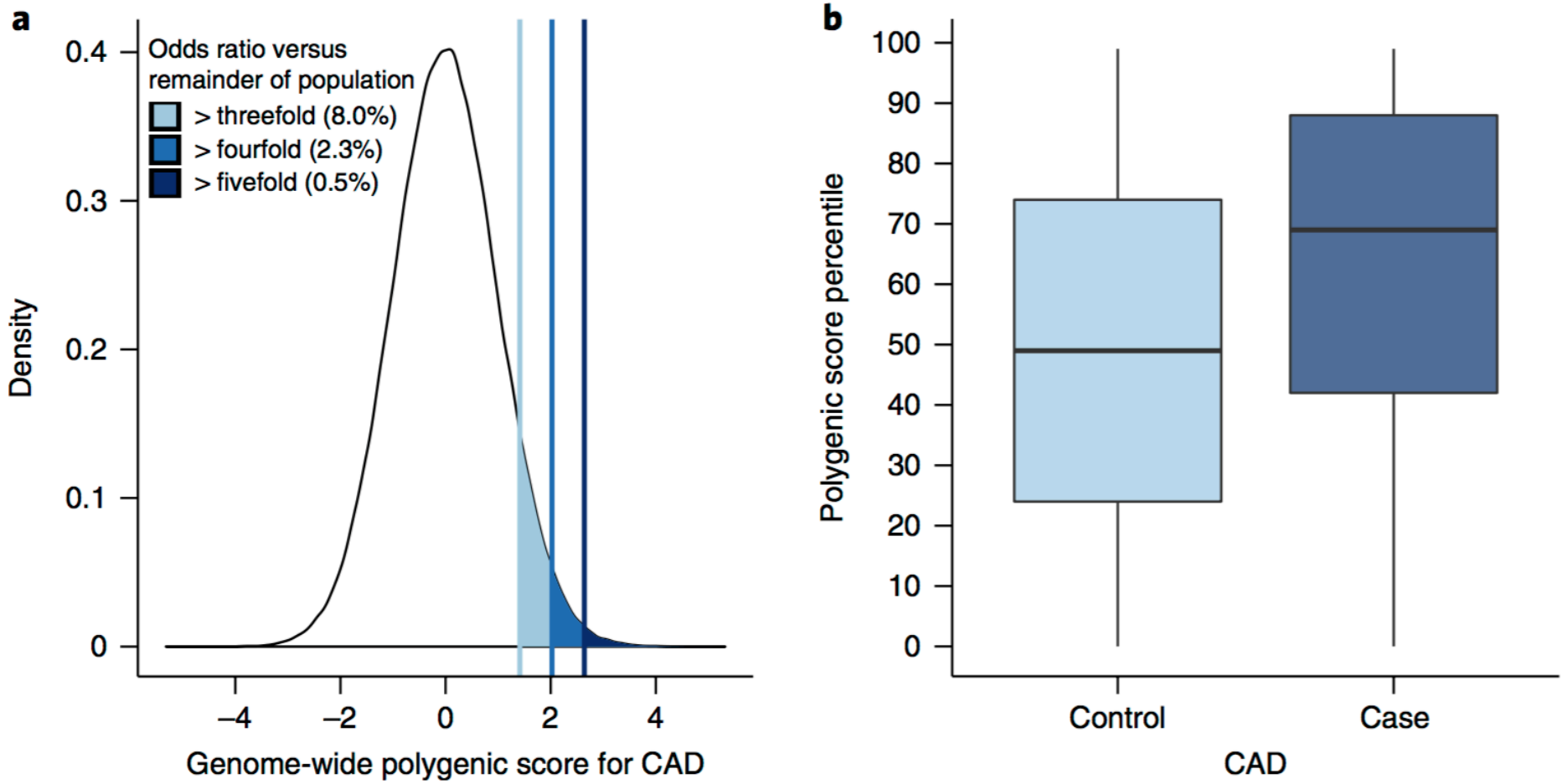
Table 1 | GPS derivation and testing for five common, complex diseases

Disease	Discovery GWAS (*n*)	Prevalence in validation dataset	Prevalence in testing dataset	Polymorphisms in GPS	Tuning parameter	AUC (95% CI) in validation dataset
CAD	60,801 cases; 123,504 controls[16]	3,963/120,280 (3.4%)	8,676/288,978 (3.0%)	6,630,150	LDPred ($\rho = 0.001$)	0.81 (0.80–0.81)
Atrial fibrillation	17,931 cases; 115,142 controls[30]	2,024/120,280 (1.7%)	4,576/288,978 (1.6%)	6,730,541	LDPred ($\rho = 0.003$)	0.77 (0.76–0.78)
Type 2 diabetes	26,676 cases; 132,532 controls[31]	2,785/120,280 (2.4%)	5,853/288,978 (2.0%)	6,917,436	LDPred ($\rho = 0.01$)	0.72 (0.72–0.73)
Inflammatory bowel disease	12,882 cases; 21,770 controls[32]	1,360/120,280 (1.1%)	3,102/288,978 (1.1%)	6,907,112	LDPred ($\rho = 0.1$)	0.63 (0.62–0.65)
Breast cancer	122,977 cases; 105,974 controls[33]	2,576/63,347 (4.1%)	6,586/157,895 (4.2%)	5,218	Pruning and thresholding ($r^2 < 0.2$; $P < 5 \times 10^{-4}$)	0.68 (0.67–0.69)

Area Under Curve (AUC) measures **discrimination**, that is, the ability of the test to correctly classify those with and without the disease.

Nature Genetics, 2018

Polygenic risk and CAD



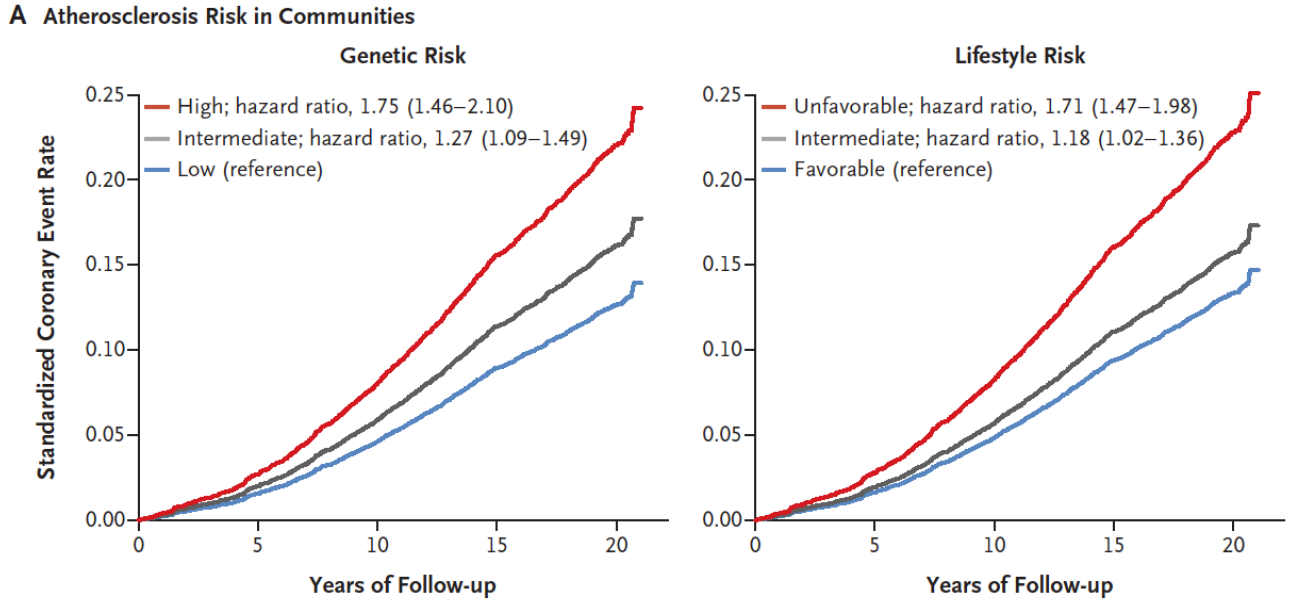
Genetics and Lifestyle

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

Amit V. Khera, M.D., Connor A. Emdin, D.Phil., Isabel Drake, Ph.D., Pradeep Natarajan, M.D., Alexander G. Bick, M.D., Ph.D., Nancy R. Cook, Ph.D., Daniel I. Chasman, Ph.D., Usman Baber, M.D., Roxana Mehran, M.D., Daniel J. Rader, M.D., Valentin Fuster, M.D., Ph.D., Eric Boerwinkle, Ph.D., Olle Melander, M.D., Ph.D., Marju Orho-Melander, Ph.D., Paul M Ridker, M.D., and Sekar Kathiresan, M.D.



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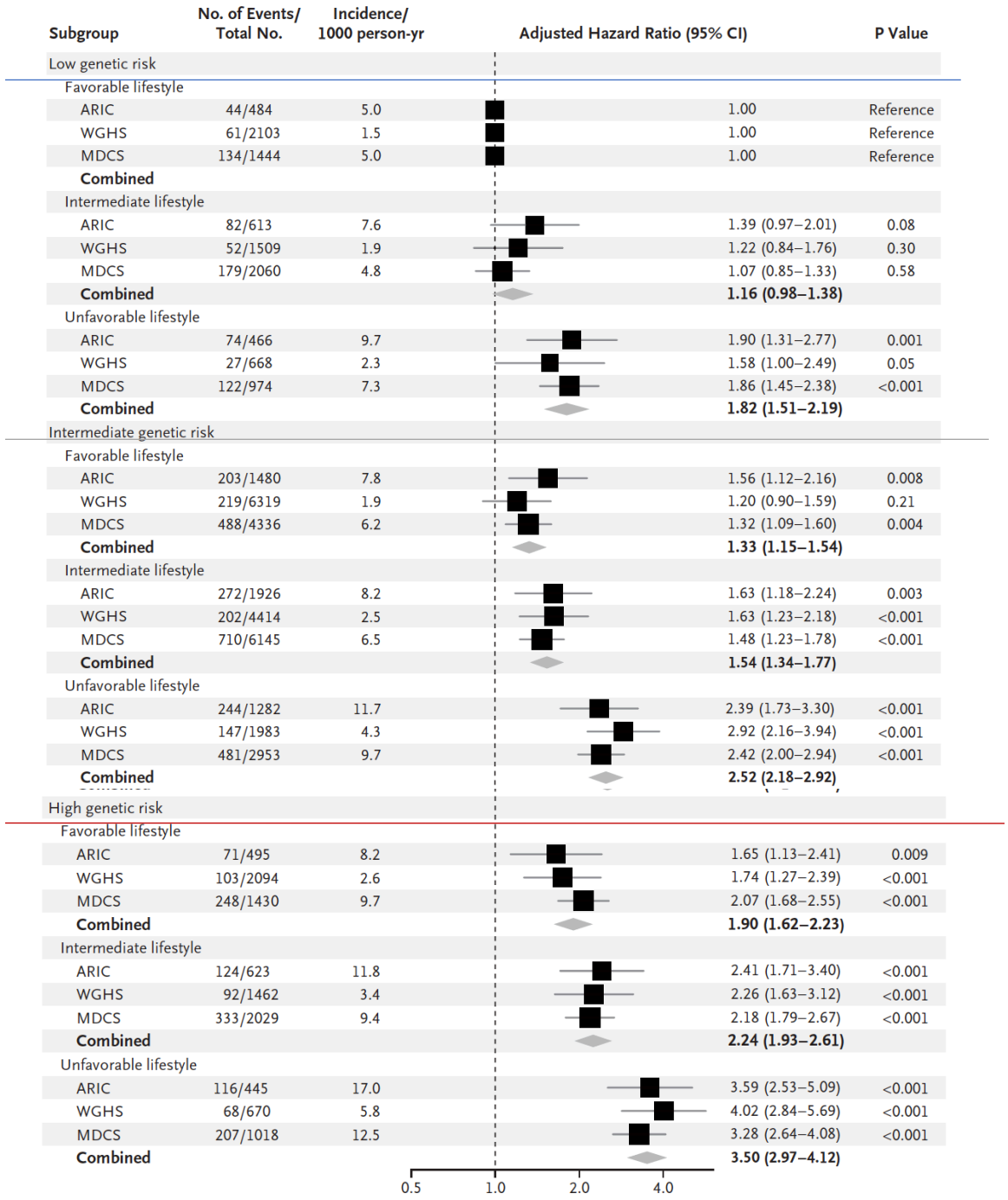
Healthy Lifestyle:
no smoking, no obesity, physical activity at least once weekly, and a healthy diet pattern.

At least half of the following:
Increased:
- fruits, vegetables,
- Nuts
- Whole grains,
- fish,
- dairy products

Reduced
- refined grains,
- processed meats, unprocessed red meats,
- sugar-sweetened beverages,
- trans fats
- sodium



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PLOS | GENETICS

Gene × Physical Activity Interactions in Obesity: Combined Analysis of 111,421 Individuals of European Ancestry

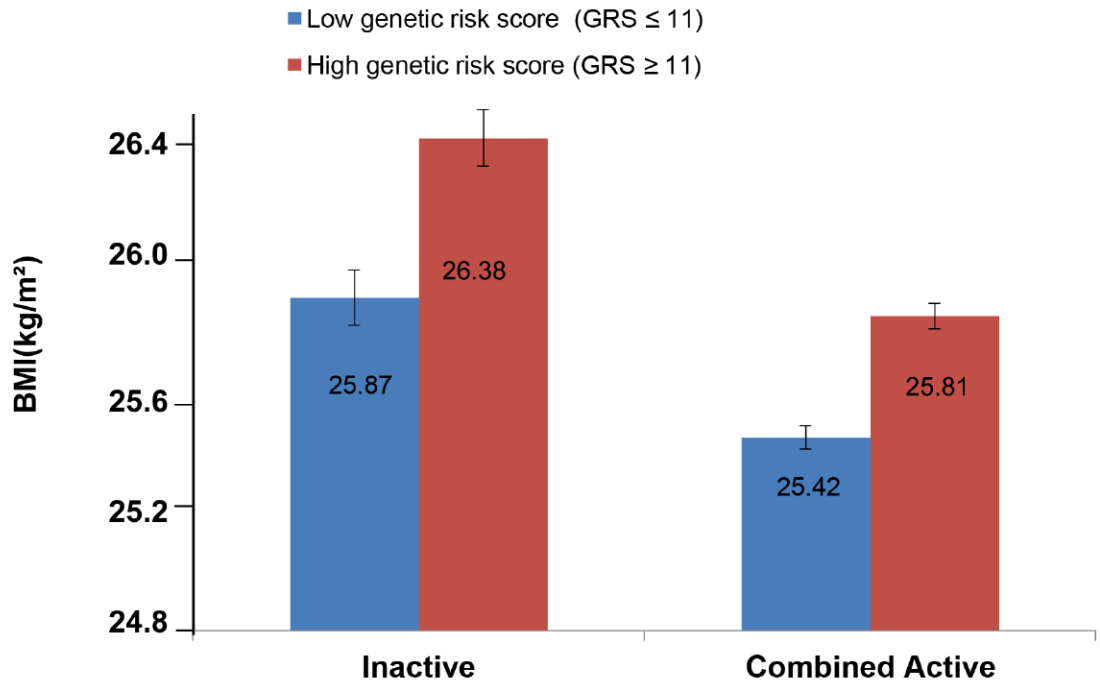


Figure 3. Adjusted least square mean BMI (95% CI) stratified by GRS level (>11 vs. ≤11 BMI-associated alleles) and by physical activity levels (N = 111,421). Physical activity was estimated according to the Cambridge Physical Activity Index (CPAI), where the 'inactive' group is defined as individuals with CPAI = 1 and the 'combined active' group as individuals with CPAI = 2–4.
doi:10.1371/journal.pgen.1003607.g003

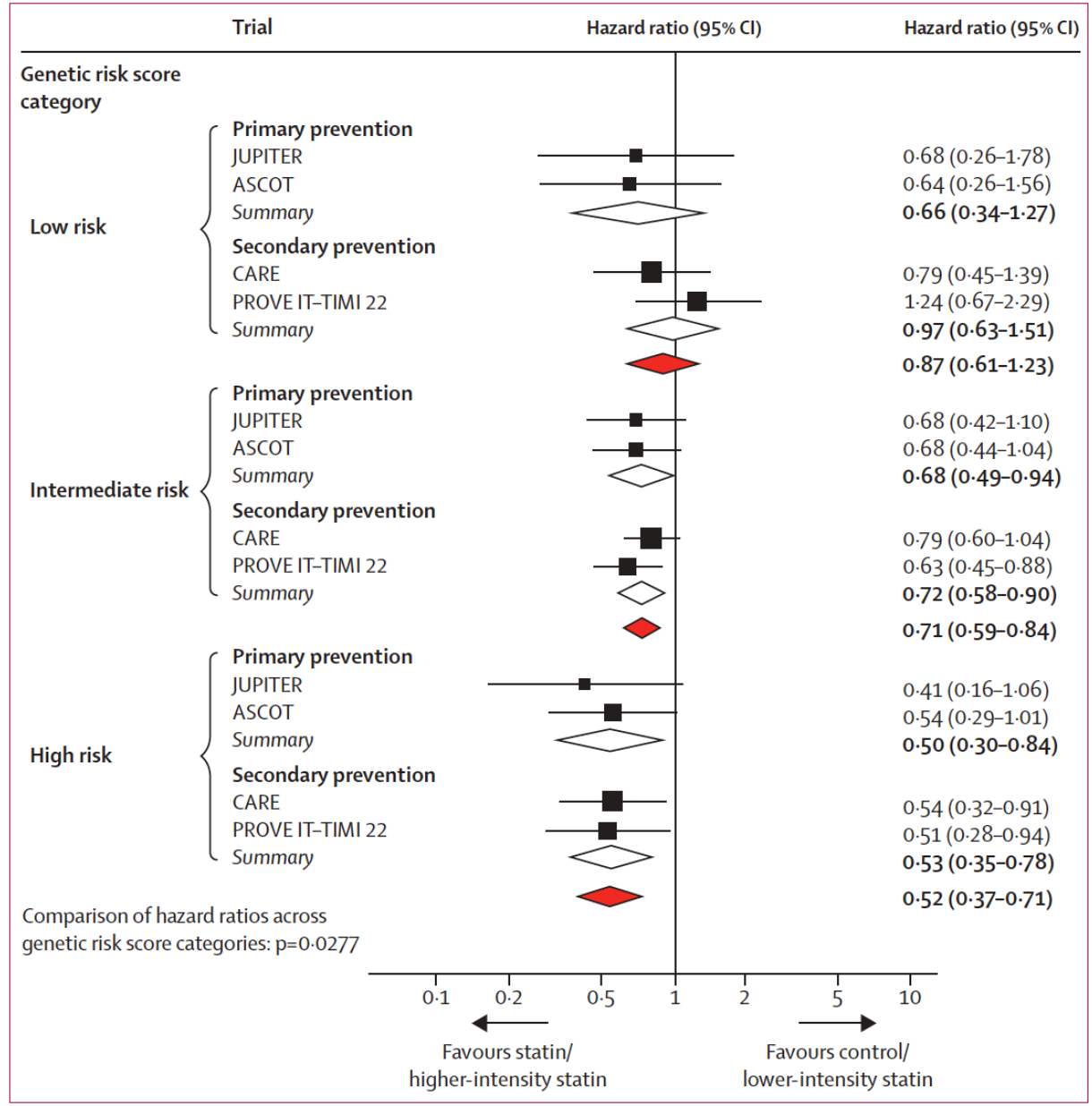
Occupational physical activity in most studies was categorized as i) sedentary or standing; ii) light but partly physically active; iii) light and physically active; and iv) sometimes or often physically straining. Leisure time physical activity during the past three months was categorized as exercising: i) occasionally; ii) 1–2 times/week; iii) 2–3 times/week; or iv) 3 times/week

PLOS Genetics
July 2013

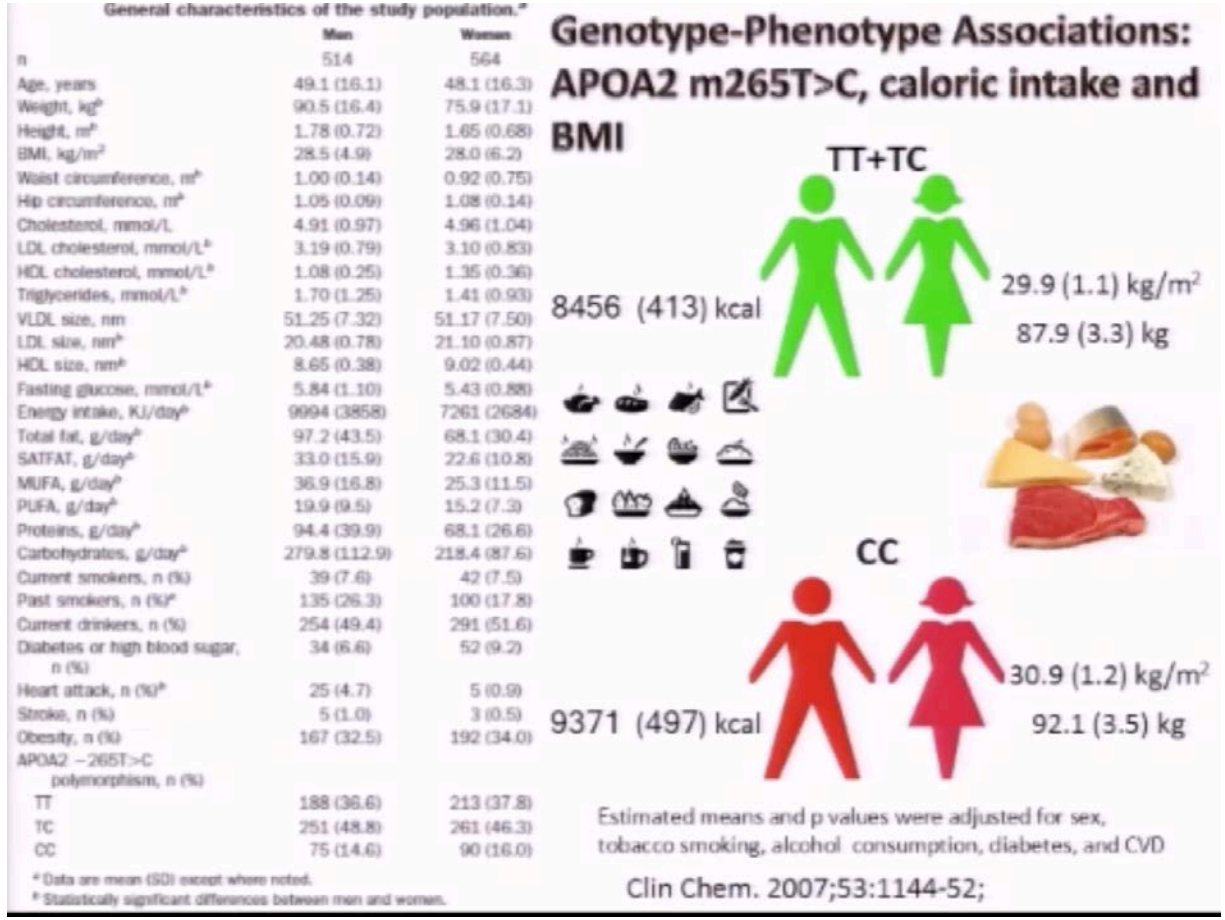
Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials

Jessica L Mega*, Nathan O Stitziel*, J Gustav Smith, Daniel I Chasman, Mark J Caulfield, James J Devlin, Francesco Nordio, Craig L Hyde, Christopher P Cannon, Frank M Sacks, Neil R Poulter, Peter S Sever, Paul M Ridker, Eugene Braunwald, Olle Melander, Sekar Kathiresan*, Marc S Sabatine*

Lancet, 2015



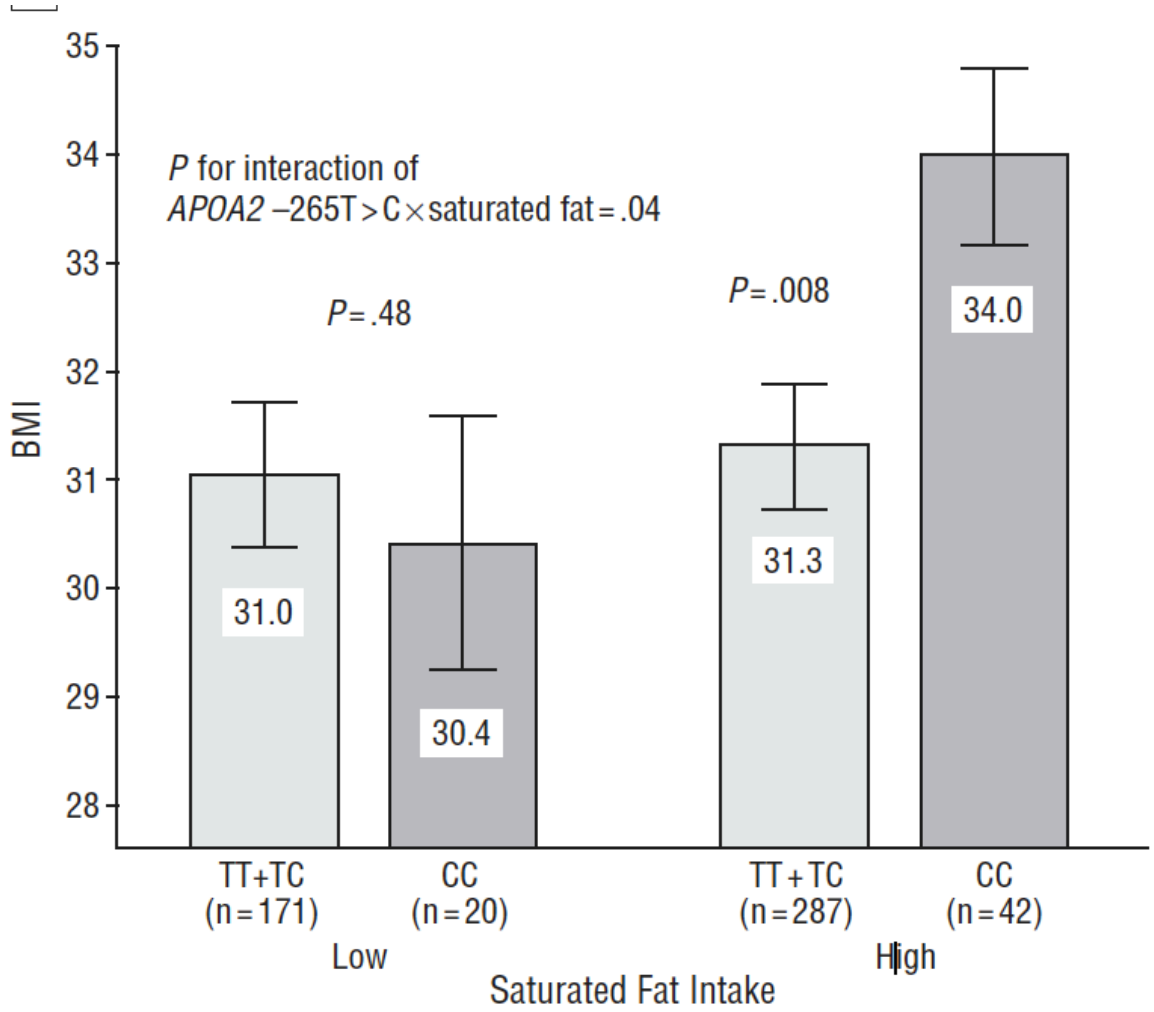
APOA2 SNP rs



General characteristics of the study population.[a]

	Men	Women
n	514	564
Age, years	49.1 (16.1)	48.1 (16.3)
Weight, kg[b]	90.5 (16.4)	75.9 (17.1)
Height, m[b]	1.78 (0.72)	1.65 (0.68)
BMI, kg/m^2	28.5 (4.9)	28.0 (6.2)
Waist circumference, m[b]	1.00 (0.14)	0.92 (0.75)
Hip circumference, m[b]	1.05 (0.09)	1.08 (0.14)
Cholesterol, mmol/L	4.91 (0.97)	4.96 (1.04)
LDL cholesterol, mmol/L[b]	3.19 (0.79)	3.10 (0.83)
HDL cholesterol, mmol/L[b]	1.08 (0.25)	1.35 (0.36)
Triglycerides, mmol/L[b]	1.70 (1.25)	1.41 (0.93)
VLDL size, nm	51.25 (7.32)	51.17 (7.50)
LDL size, nm[b]	20.48 (0.78)	21.10 (0.87)
HDL size, nm[b]	8.65 (0.38)	9.02 (0.44)
Fasting glucose, mmol/L[b]	5.84 (1.10)	5.43 (0.88)
Energy intake, KJ/day[b]	9994 (3858)	7261 (2684)
Total fat, g/day[b]	97.2 (43.5)	68.1 (30.4)
SATFAT, g/day[b]	33.0 (15.9)	22.6 (10.8)
MUFA, g/day[b]	36.9 (16.8)	25.3 (11.5)
PUFA, g/day[b]	19.9 (9.5)	15.2 (7.3)
Proteins, g/day[b]	94.4 (39.9)	68.1 (26.6)
Carbohydrates, g/day[b]	279.8 (112.9)	218.4 (87.6)
Current smokers, n (%)	39 (7.6)	42 (7.5)
Past smokers, n (%)[b]	135 (26.3)	100 (17.8)
Current drinkers, n (%)	254 (49.4)	291 (51.6)
Diabetes or high blood sugar, n (%)	34 (6.6)	52 (9.2)
Heart attack, n (%)[b]	25 (4.7)	5 (0.9)
Stroke, n (%)	5 (1.0)	3 (0.5)
Obesity, n (%)	167 (32.5)	192 (34.0)
APOA2 −265T>C polymorphism, n (%)		
TT	188 (36.6)	213 (37.8)
TC	251 (48.8)	261 (46.3)
CC	75 (14.6)	90 (16.0)

[a] Data are mean (SD) except where noted.
[b] Statistically significant differences between men and women.



APOA2, Dietary Fat, and Body Mass Index

Replication of a Gene-Diet Interaction in 3 Independent Populations

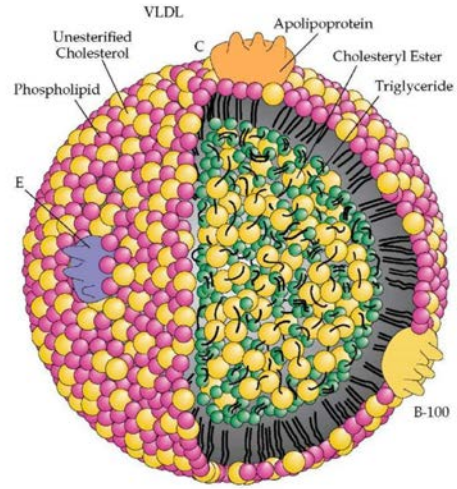
Dolores Corella, PhD; Gina Peloso, MSc; Donna K. Arnett, PhD, MSPH; Serkalem Demissie, PhD; L. Adrienne Cupples, PhD; Katherine Tucker, PhD; Chao-Qiang Lai, PhD; Laurence D. Parnell, PhD; Oscar Coltell, PhD; Yu-Chi Lee, MSc; Jose M. Ordovas, PhD

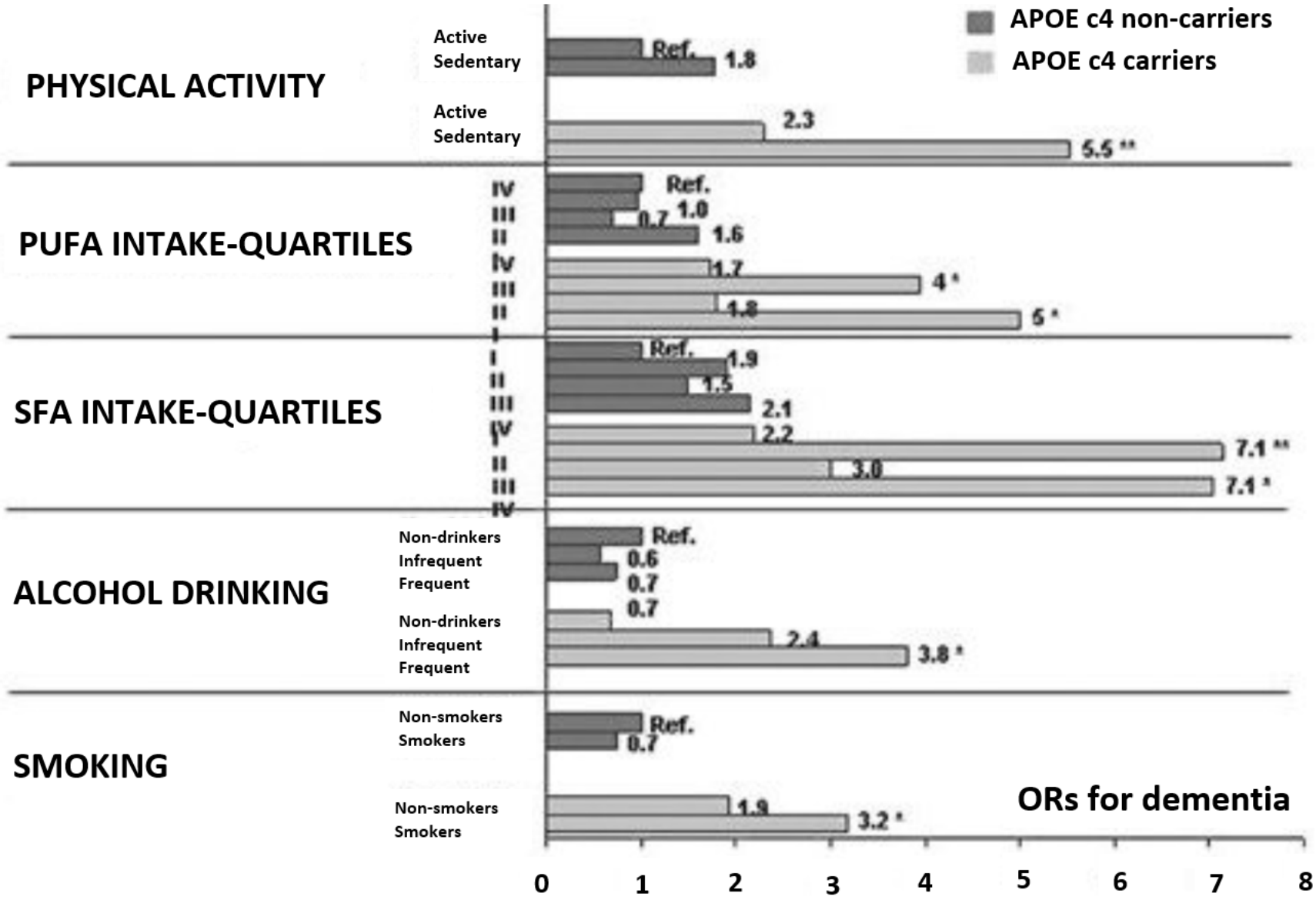
Arch Intern Med. 2009;169(20):1897-1906

Use of ApoE Polymorphism in Guiding Dietary Choices

Apo E Genotype—Metabolic Expression and Influence on Therapeutic Interventions

	Apo E2 Response		Apo E3 Response		Apo E4 Response	
Genotype	2/2	2/3	3/3	2/4	3/4	4/4
Population Frequency	1%	10%	62%	2%	20%	5%




APOE c4 non-carriers
APOE c4 carriers
PHYSICAL ACTIVITY
Active
Sedentary
Ref.
1.8
Active
Sedentary
2.3
5.5 **
PUFA INTAKE-QUARTILES
IV
III
II
Ref.
1.0
0.7
1.6
IV
III
II
1.7
4 *
1.8
5 *
SFA INTAKE-QUARTILES
I
II
III
IV
Ref.
1.9
1.5
2.1
I
II
III
IV
2.2
7.1 **
3.0
7.1 *
ALCOHOL DRINKING
Non-drinkers
Infrequent
Frequent
Ref.
0.6
0.7
Non-drinkers
Infrequent
Frequent
0.7
2.4
3.8 *
SMOKING
Non-smokers
Smokers
Ref.
0.7
Non-smokers
Smokers
1.9
3.2 *
ORs for dementia
0
1
2
3
4
5
6
7
8

Use of ApoE Polymorphism in Guiding Dietary Choices

Apo E Genotype—Metabolic Expression and Influence on Therapeutic Interventions

	Apo E2 Response		Apo E3 Response		Apo E4 Response	
Genotype	2/2	2/3	3/3	2/4	3/4	4/4
Population Frequency	1%	10%	62%	2%	20%	5%
Fish Oil[1]	↓↓TG ↓small dense LDL ↑HDL		↓TG ↓small dense LDL ↑HDL		↓TG ↓↓small dense LDL ↓HDL ↑↑LDL	
Low Fat Diet[2,3]	↓LDL ↑small dense LDL		↓↓LDL ↔small dense LDL		↓↓↓LDL ↓small dense LDL	
Moderate Fat Diet[3]	↔LDL ↔small dense LDL		↓LDL ↓small dense LDL		↓LDL ↑↑small dense LDL	
Moderate Alcohol[4]	↑HDL ↓LDL		↑HDL		↓HDL ↑LDL	

J Cell Mol Med. 2008, 12(6b): 2762-2771

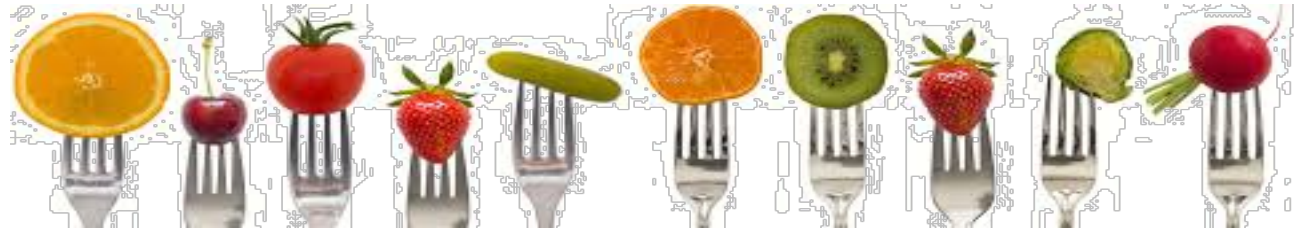
Section I: OPTIMAL Nutrition

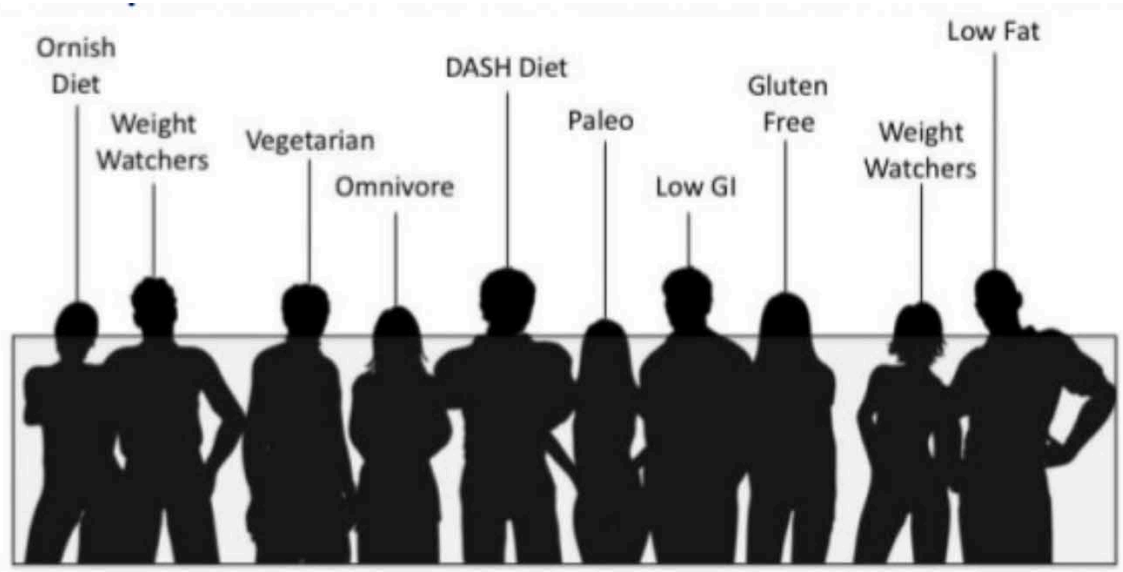
Thank you for taking the Eurogenetica NutriGENE program – this section will give you your results and all you need to know about how to make useful modifications to your diet and lifestyle in order to benefit your health and wellbeing. You should read the report carefully and also discuss it with your nutritionist who will be able to help you to plan the recommended changes. If you need to lose weight please also consult section II.

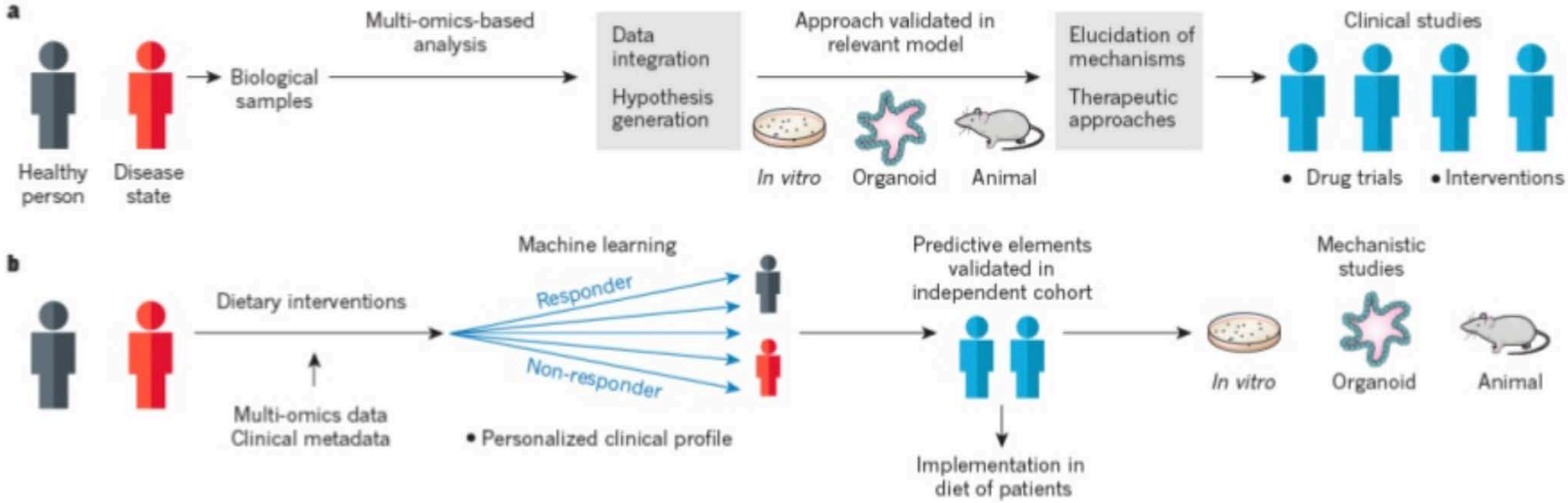
Overview – Modifications to introduce

Increase*	Folic Acid, Vit B6 e B12 Vitamin D Calcium Omega 3 Fiber
Decrease*	Salt Caffeine Refined carbs / sugars Grilled Meat
Lactose intolerance	Lactose tolerant
Celiac	Possible predisposition

*To increase or decrease relative to the official RDA guidelines







Sonnenburg JL, Bäckhed F. Diet-microbiota interactions as moderators of human metabolism. Nature. 2016 Jul 6;535(7610):56-64.

Conclusion

- Genetic Risk Scoring can have good discrimination
- Understanding pathways will be key
- Need to be tested for clinical utility