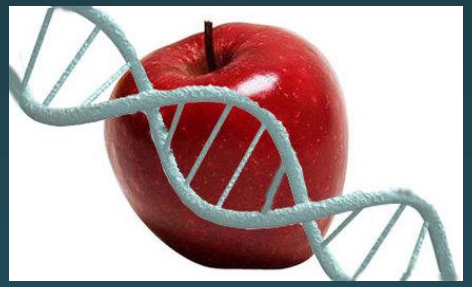
Διατροφή, Τρόπος Ζωής & Γενετική προδιάθεση



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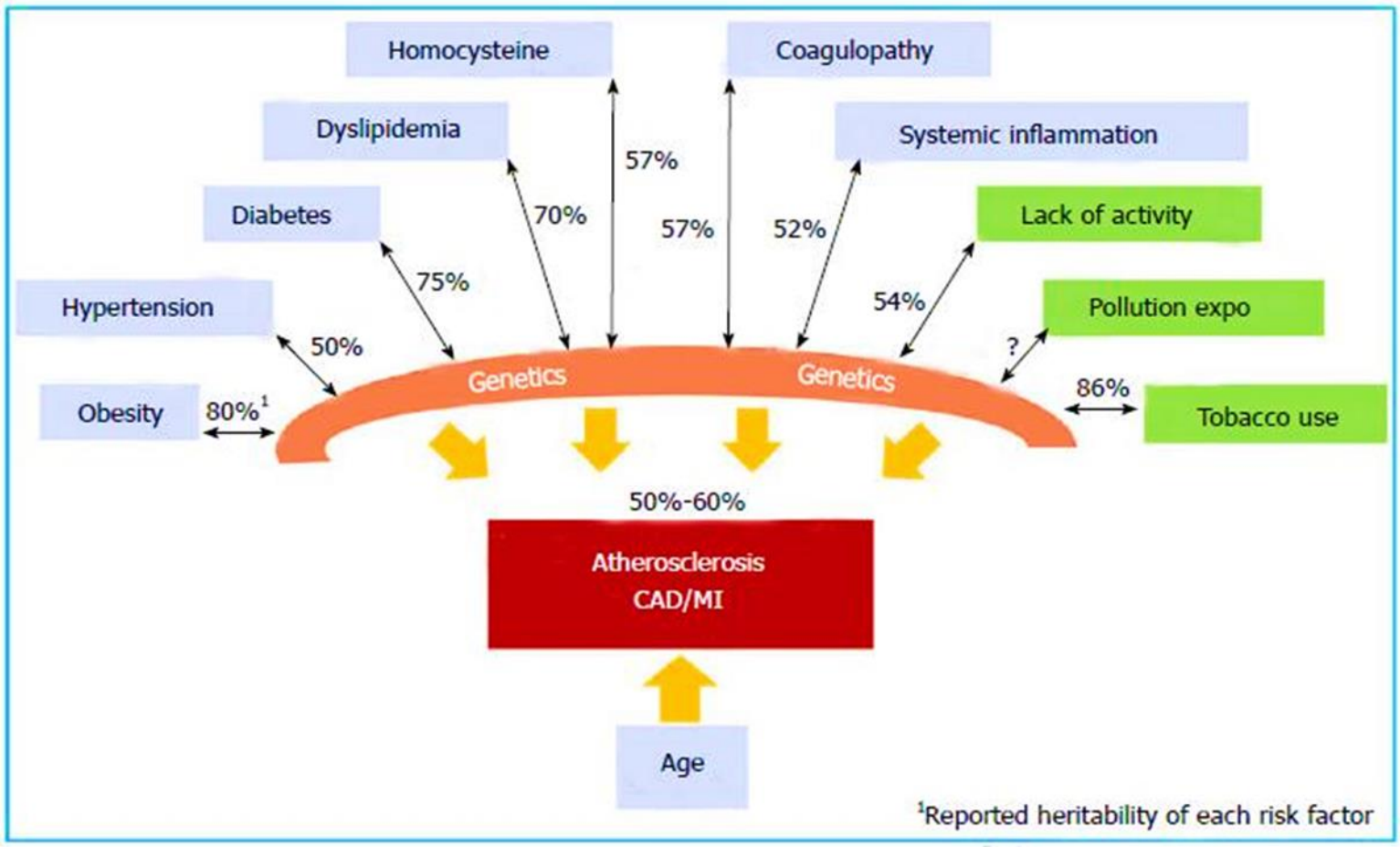
ΧΑΡΟΚΟΠΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ

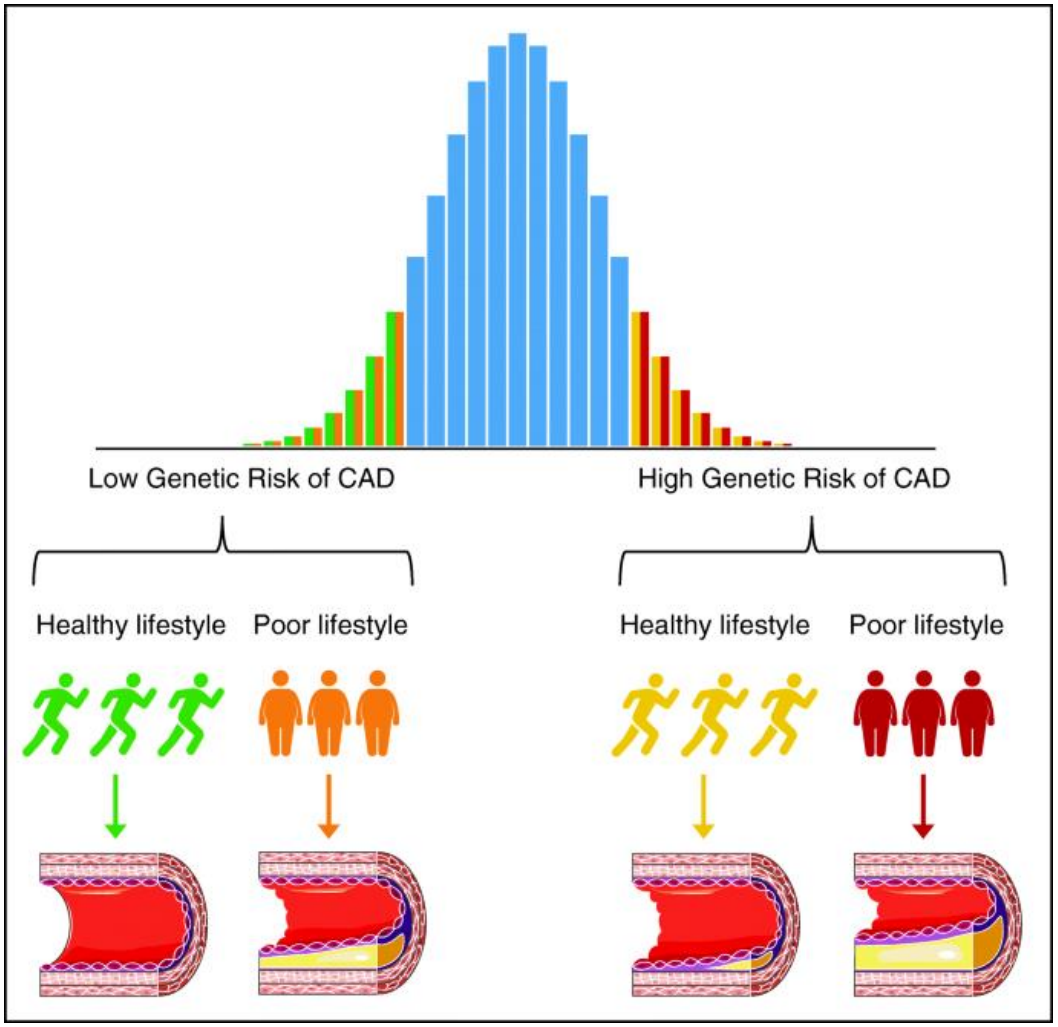
Coronary Artery Disease / Myocardial Infarction Heritability

- **CAD/MI heritability, or the proportion of phenotype explained by the additive sum of genetic factors, is estimated to be 50% to 60%**



Dai et al. World J Cardiol 2016; 8(1):1-23

Combined genetic & lifestyle risks increase the risk of CAD

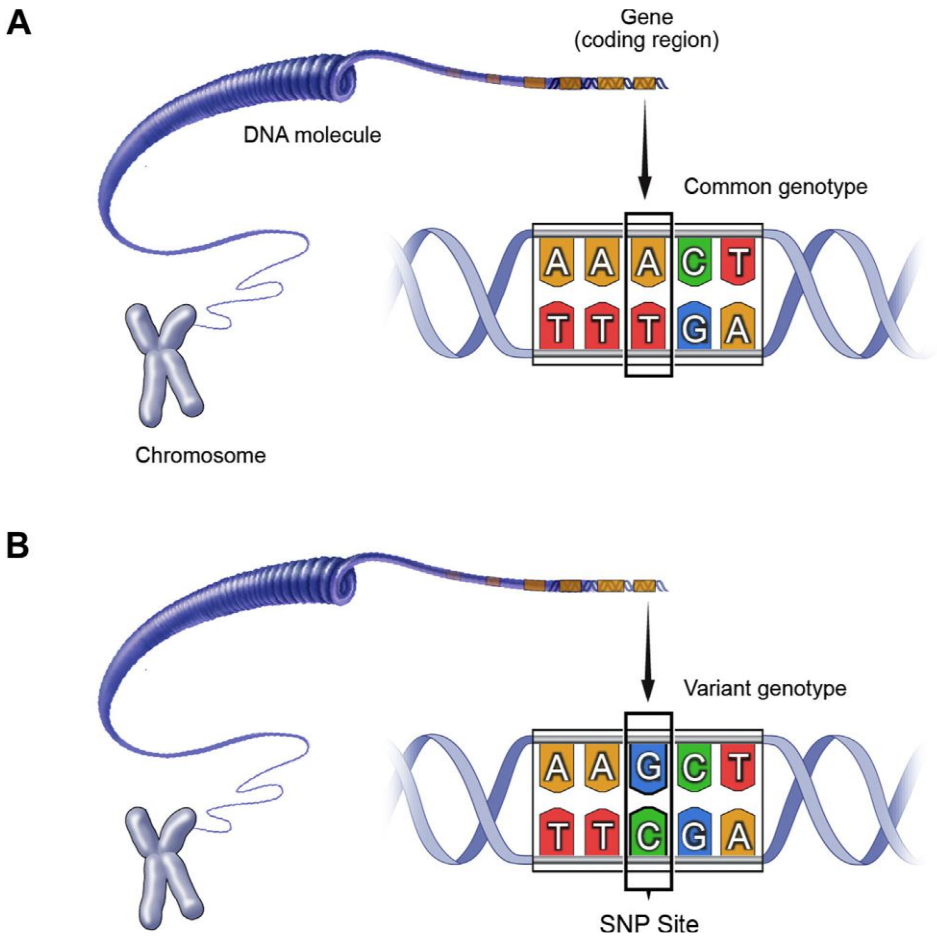


The risk of CAD in individuals with low or high genetic risk is higher amongst individuals with poor lifestyle compared to a healthy lifestyle. Compared with individuals with low genetic risk, individuals with high genetic risk start off at higher risks of CAD, with the highest risks of CAD amongst individuals with poor lifestyle and high genetic risk

Said et al. Current Cardiology Reports (2019) 21: 89

Genetic variation: *Single nucleotide polymorphisms (SNPs)*

Variants occurring in at least 1% of any distinct population are called **polymorphisms**.



Alleles

A , G

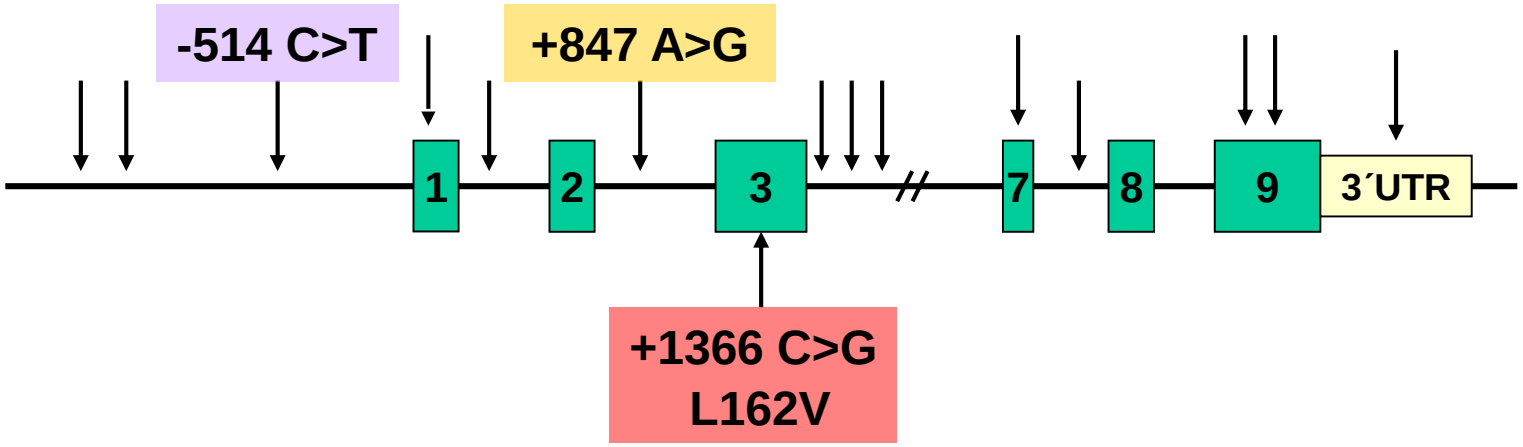
Genotypes:

A/A

A/G

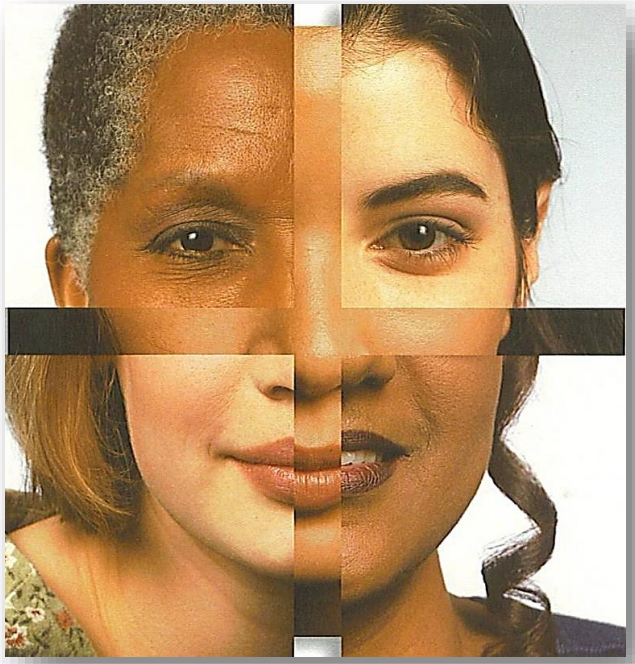
G/G

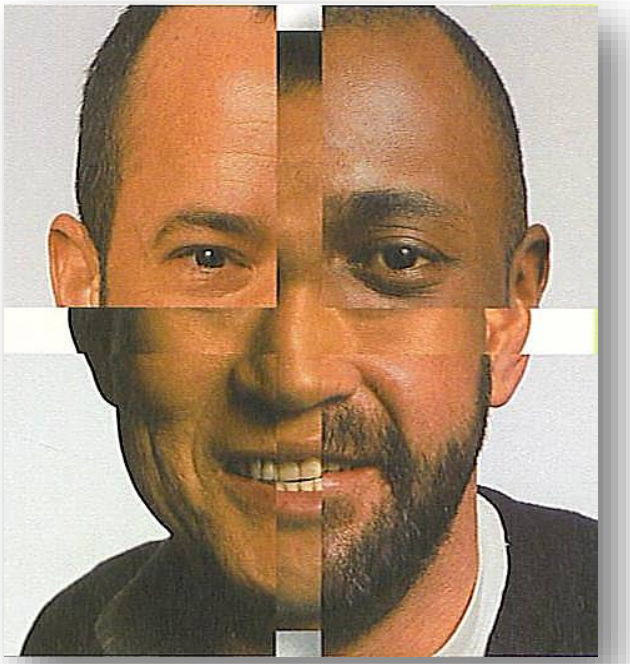
Single Nucleotide Polymorphisms (SNPs)



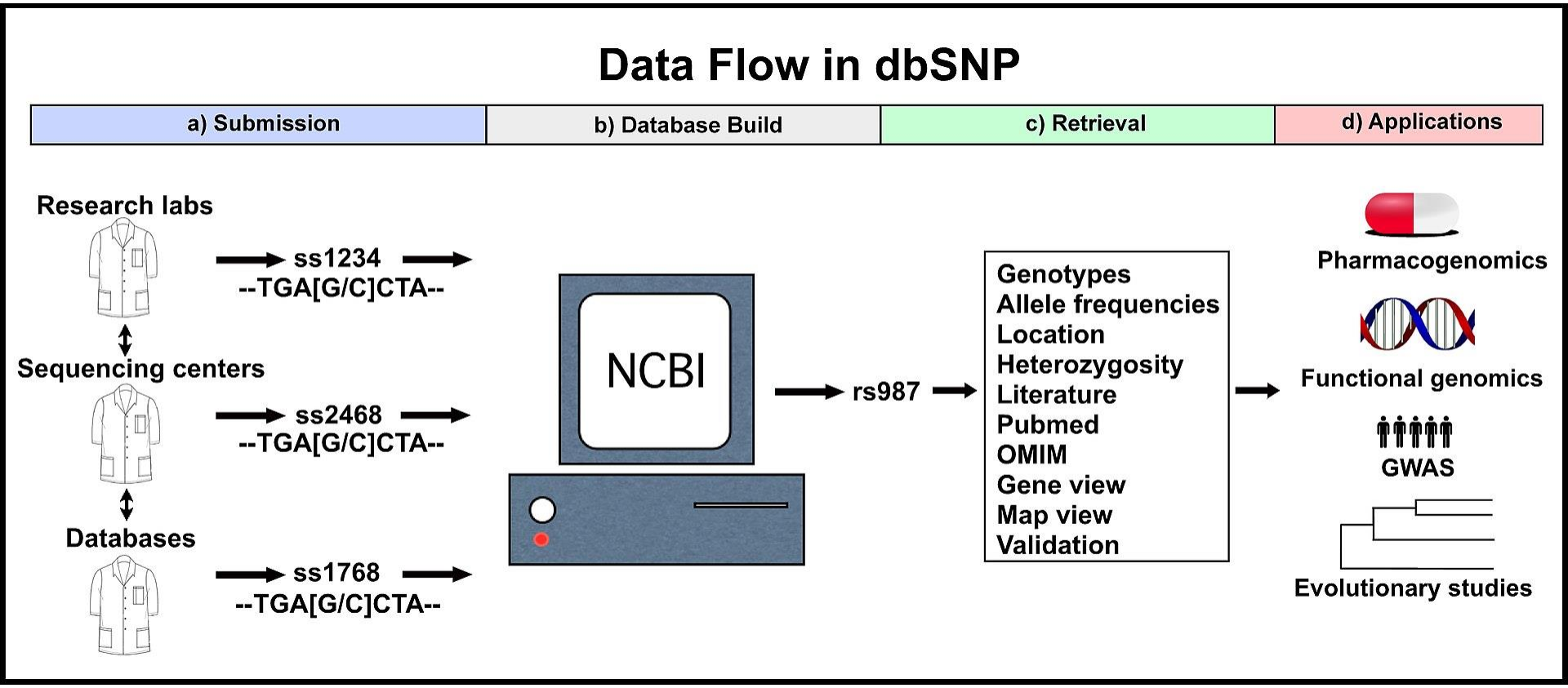
- SNPs occur almost once in every 1,000 nucleotides on average, which means there are roughly 4 to 5 million SNPs in a person's genome. These variations may be unique or occur in many individuals.
- Most commonly, SNPs are found in the DNA between genes. They can act as biological markers, helping scientists locate genes that are associated with disease. When SNPs occur within a gene or in a regulatory region near a gene, they may play a more direct role in disease by affecting the gene’s function.

- The genetic blueprints, or genomes, of any two humans are >99% the same.
- Still, the small fraction of genetic material that varies among people holds valuable clues to individual differences in susceptibility to disease, response to drugs & sensitivity to environmental factors.



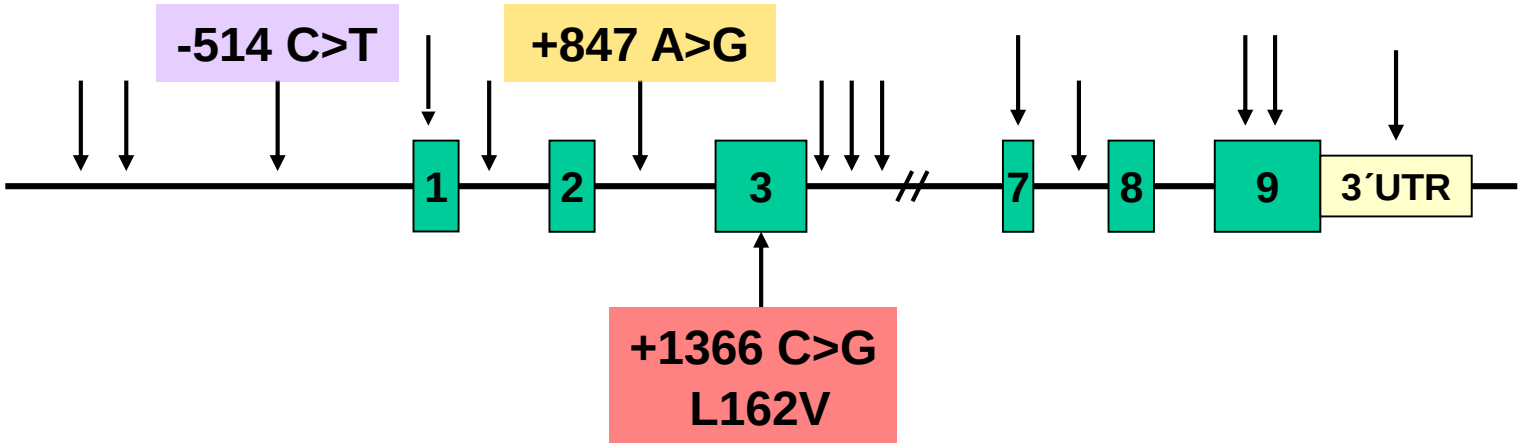


Single Nucleotide Polymorphisms (SNPs)



a) Various sources submit data, and each variation is assigned a unique submitted SNP number ID (ss#). b) dbSNP compiles identical ss# records into one reference SNP cluster (rs#) containing data from each ss#. c) Users can retrieve data for specific rs# records and analyze these variations. d) Data from dbSNP aids clinical and applied research. The ss# and rs# IDs in this figure are examples only. NCBI, National Center for Biotechnology Information; OMIM, Online Mendelian Inheritance in Man; GWAS, genome wide association study.

Single Nucleotide Polymorphisms (SNPs) / Single Nucleotide Variations (SNVs)



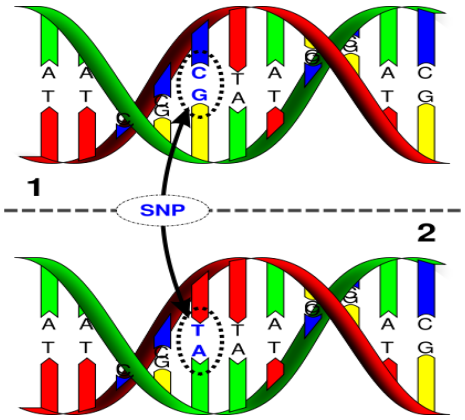
Human Genome Project: ***20.000 - 22.000 genes in human DNA***

International Haplotype (HapMap) Project: ***>100million SNPs have been detected to date in populations around the world***

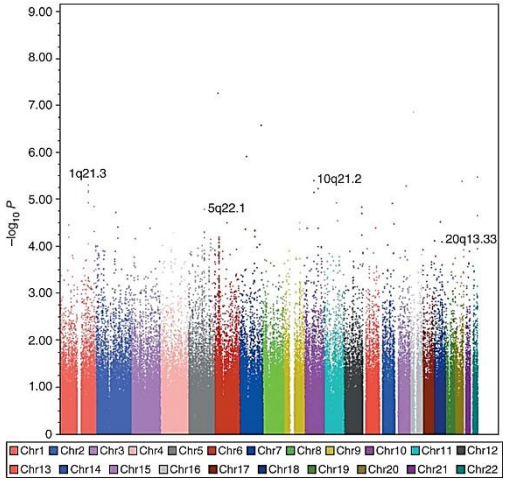
dbSNP is a SNP database from the National Center for Biotechnology Information (NCBI).
As of June 2015, dbSNP listed ~150,000,000 SNPs in humans.
As of build 153 (released in August 2019), dbSNP had amassed nearly 2 billion submissions representing >675,000,000 distinct variants for Homo sapiens.

Γενετικές μελέτες *(Genetic association studies)*

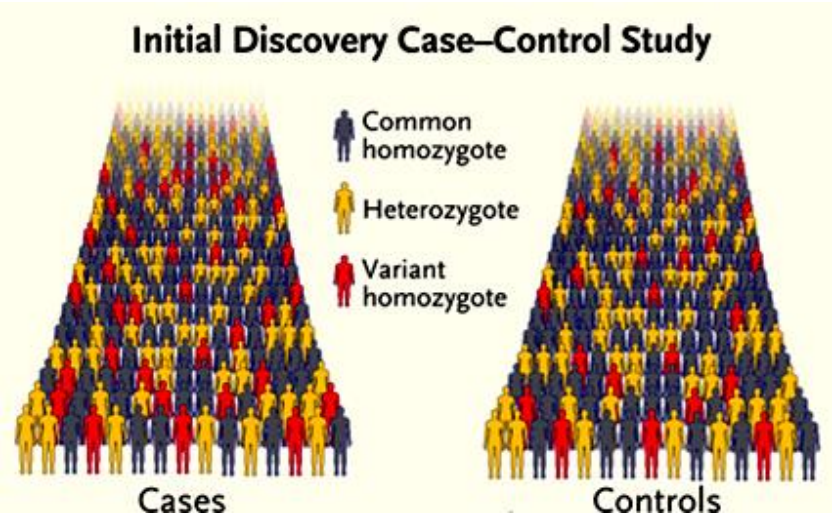
- **Μελέτες υποψήφιων γονιδίων** ***(Candidate gene studies)***

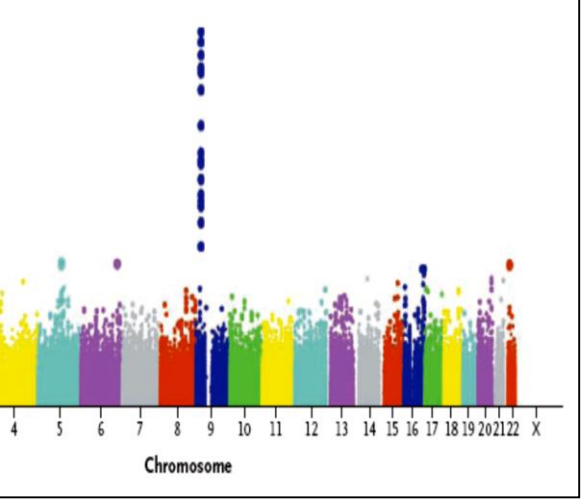


- **Μελέτες ευρυ-γονιδωματικής συσχέτισης** ***(Genome-wide association studies, GWAs)***



GWAS: Μελέτες ευρυ-γονιδιωματικής συσχέτισης





The NEW ENGLAND JOURNAL of MEDICINE

Genomewide Association Analysis of Coronary Artery Disease

Nilesh J. Samani, F.Med.Sci., Jeanette Erdmann, Ph.D., Alistair S. Hall, F.R.C.P., Christian Hengstenberg, M.D., Massimo Mangino, Ph.D., Bjoern Mayer, M.D., Richard J. Dixon, Ph.D., Thomas Meitinger, M.D., Peter Braund, M.Sc., H.-Erich Wichmann, M.D., Jennifer H. Barrett, Ph.D., Inke R. König, Ph.D., Suzanne E. Stevens, M.Sc., Silke Szymczak, M.Sc., David-Alexandre Tregouet, Ph.D., Mark M. Iles, Ph.D., Friedrich Pahlke, M.Sc., Helen Pollard, M.Sc., Wolfgang Lieb, M.D., Francois Cambien, M.D., Marcus Fischer, M.D., Willem Ouwehand, F.R.C.Path., Stefan Blankenberg, M.D., Anthony J. Balmforth, Ph.D., Andrea Baessler, M.D., Stephen G. Ball, F.R.C.P., Tim M. Strom, M.D., Ingrid Braenne, M.Sc., Christian Gieger, Ph.D., Panos Deloukas, Ph.D., Martin D. Tobin, M.F.P.H.M., Andreas Ziegler, Ph.D., John R. Thompson, Ph.D., and Heribert Schunkert, M.D., for the WTCCC and the Cardiogenics Consortium*

GWAS & Coronary Artery Disease (CAD)

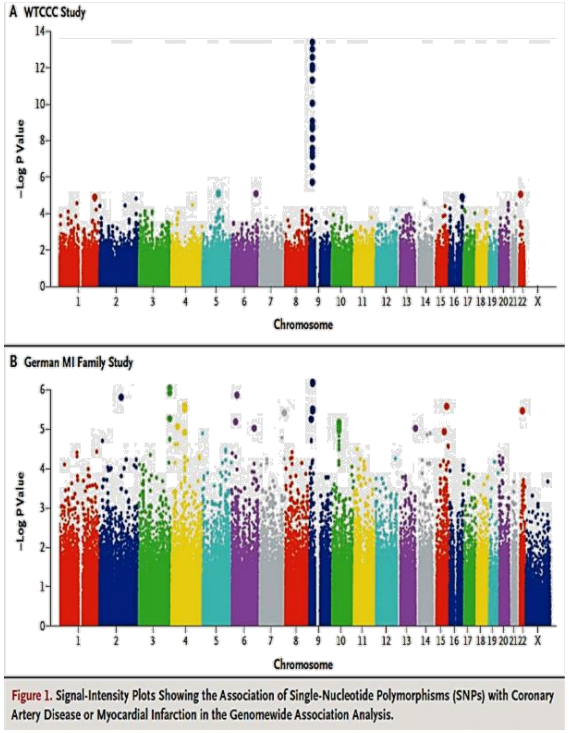
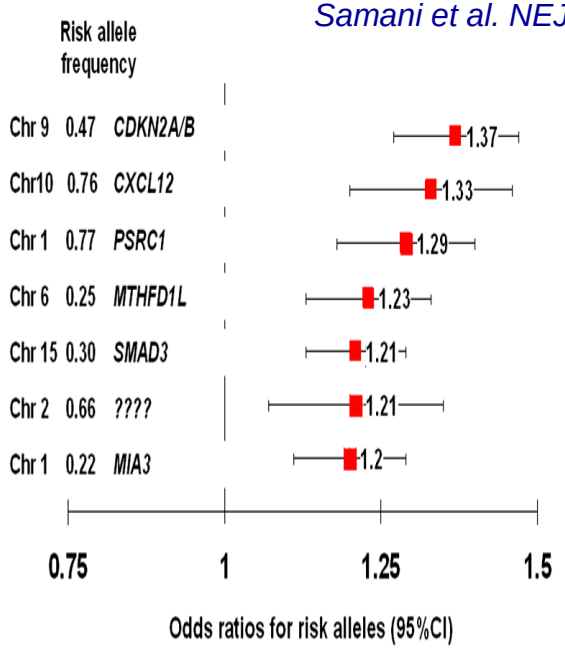


Figure 1. Signal-Intensity Plots Showing the Association of Single-Nucleotide Polymorphisms (SNPs) with Coronary Artery Disease or Myocardial Infarction in the Genomewide Association Analysis.

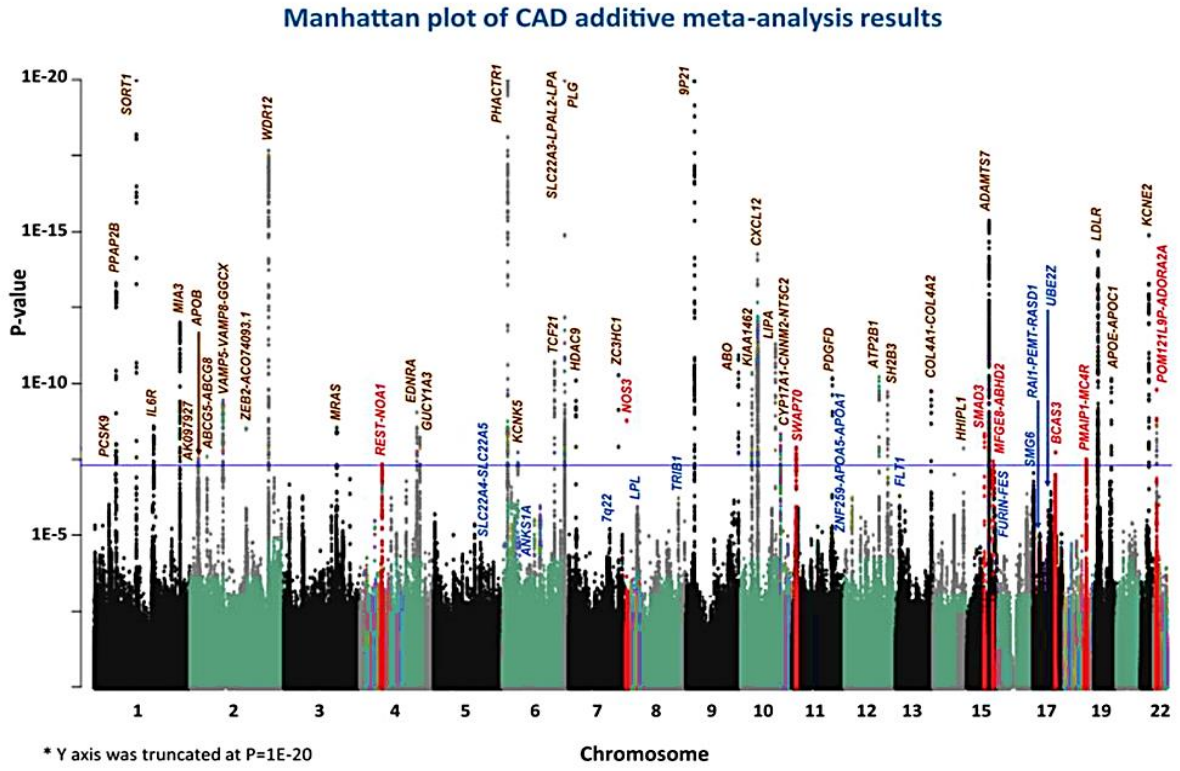
Samani et al. NEJM 2007



- Since the 9p21 discovery in 2007, large meta-analyses of additional GWAS have identified additional loci of smaller effect size but with genome-wide significance ($P<5\times10^{-8}$).
- This success has been built on large collaborative efforts, including:
  - ✓ *the Myocardial Infarction Genomics Consortium,*
  - ✓ *the CARDIoGRAM consortium,*
  - ✓ *the Coronary Artery Disease (C4D) Genetics Consortium,*
  - ✓ *CARDIoGRAMplusC4D, and others*

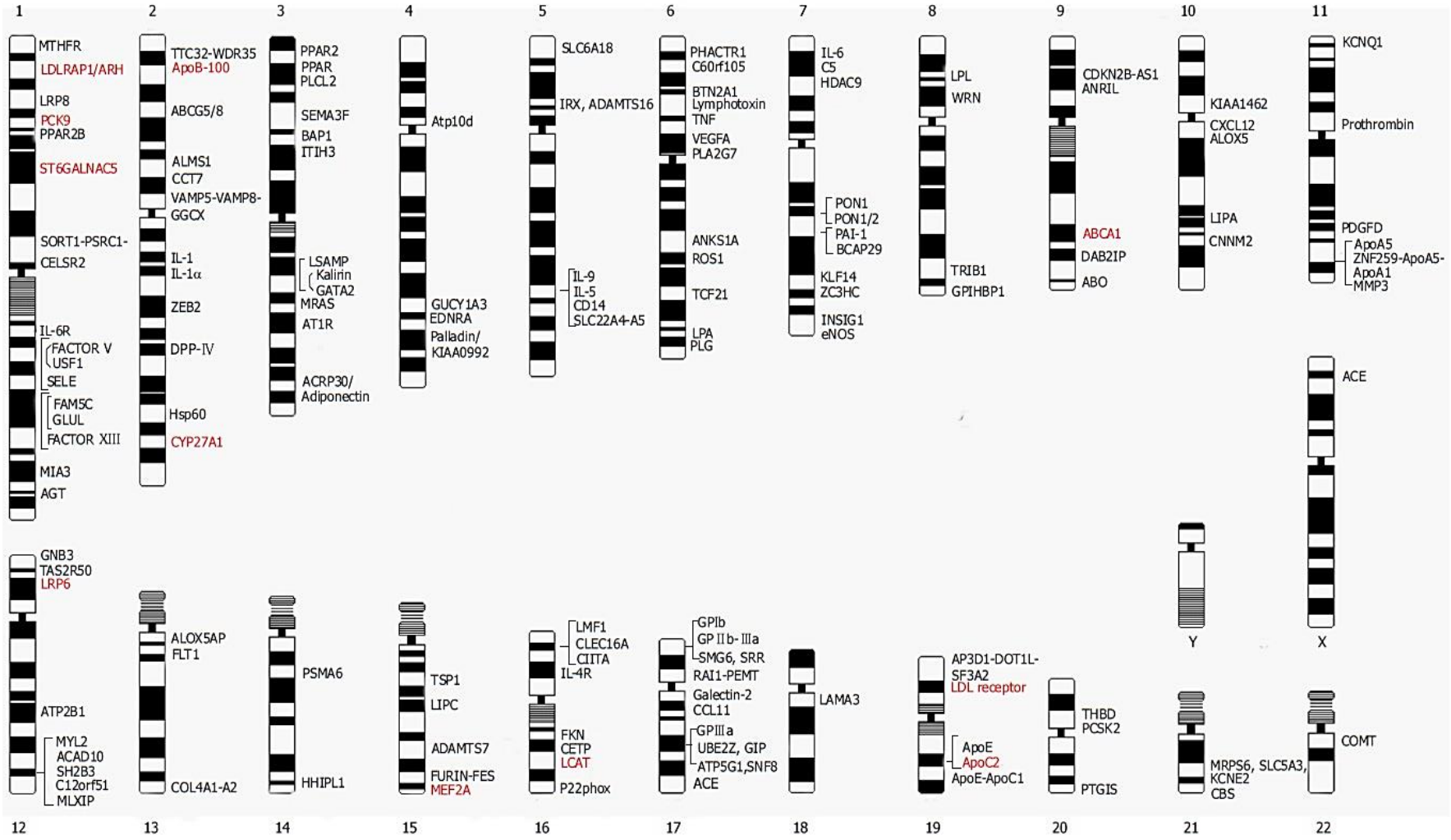
Genetics of Coronary Artery Disease

- ~60 common SNPs (minor allele frequency >0.05) with a robust association with CAD risk and reaching genomewide significance ($P < 5 \times 10^{-8}$) have been identified to date, the majority of which are of modest effect size and in non-coding regions.
- Furthermore, a total of 202 independent signals in 109 loci achieving a false discovery rate (q<0.05) together explain 28% of the estimated heritability of CAD.



Nikpay et al. Nature Genet 2015; McPherson & Tybjaerg-Hansen, Circulation Res 2016

Chromosome map of genes reported to be causal for, susceptible to and associated with CAD and MI in the literature.

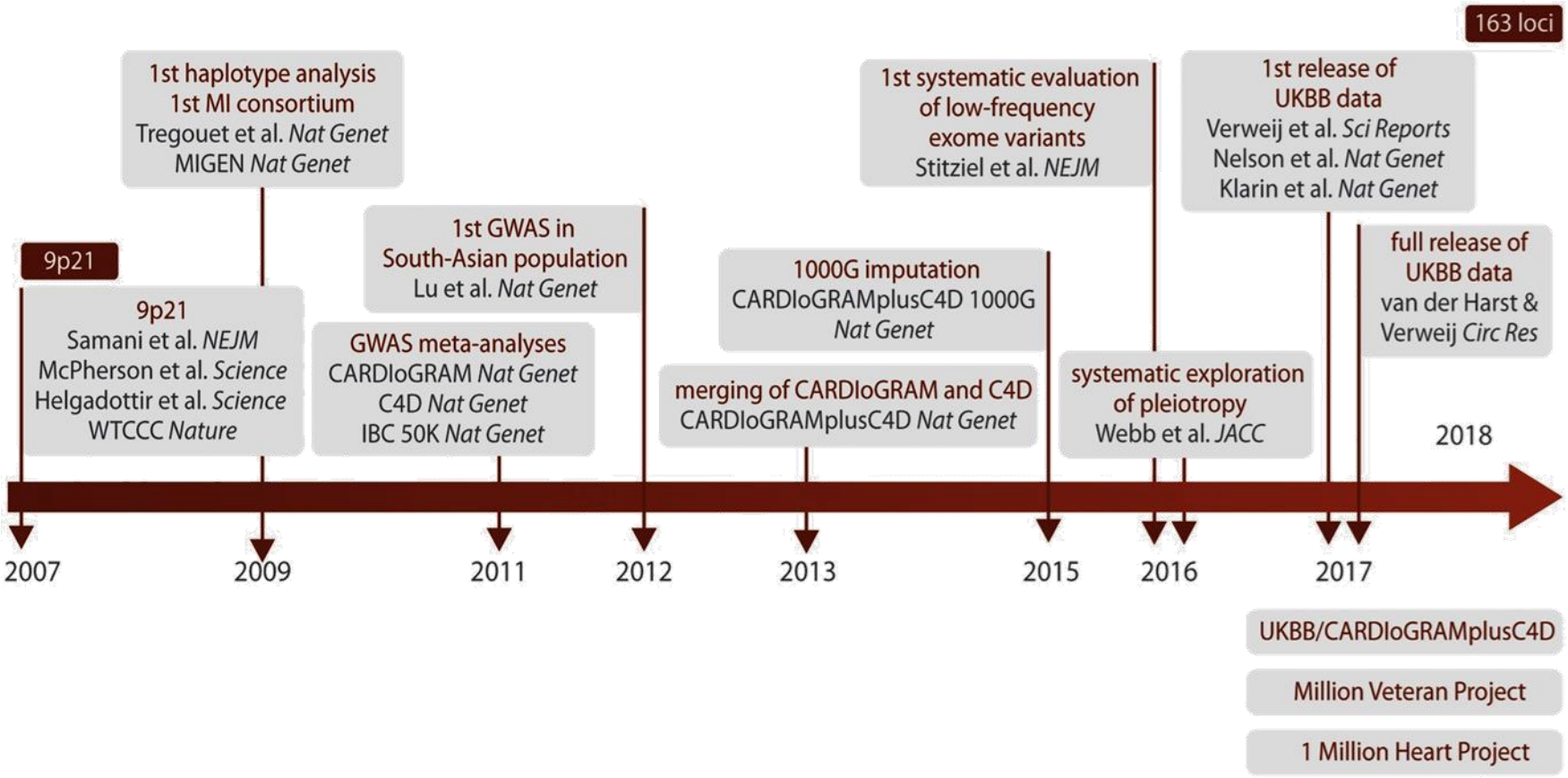


Genes in red are causal genes for monogenic familial CAD and MI.

Xuming et al.World J Cardiol. 2016

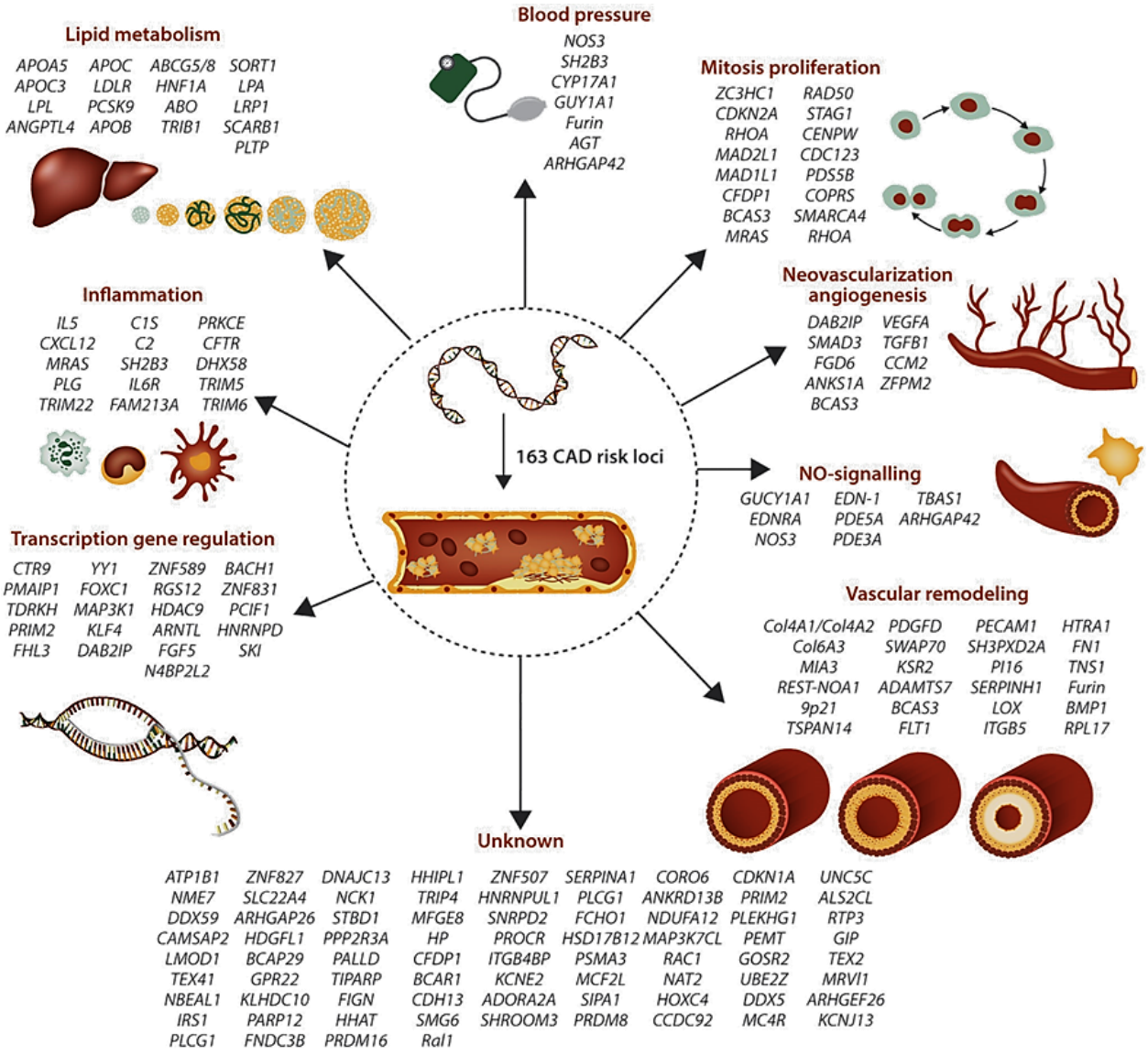
Milestones in CVD genome research

- **163 separate genomic loci** have been identified to be significantly associated with CAD and MI since 2018 (explaining ~28% of the estimated heritability)



Cardiovasc Res, Volume 114, Issue 9, 15 July 2018, Pages 1241–1257, https://doi.org/10.1093/cvr/cvy084

Genes mapped to 163 CAD risk loci and pathophysiological pathways in atherosclerosis

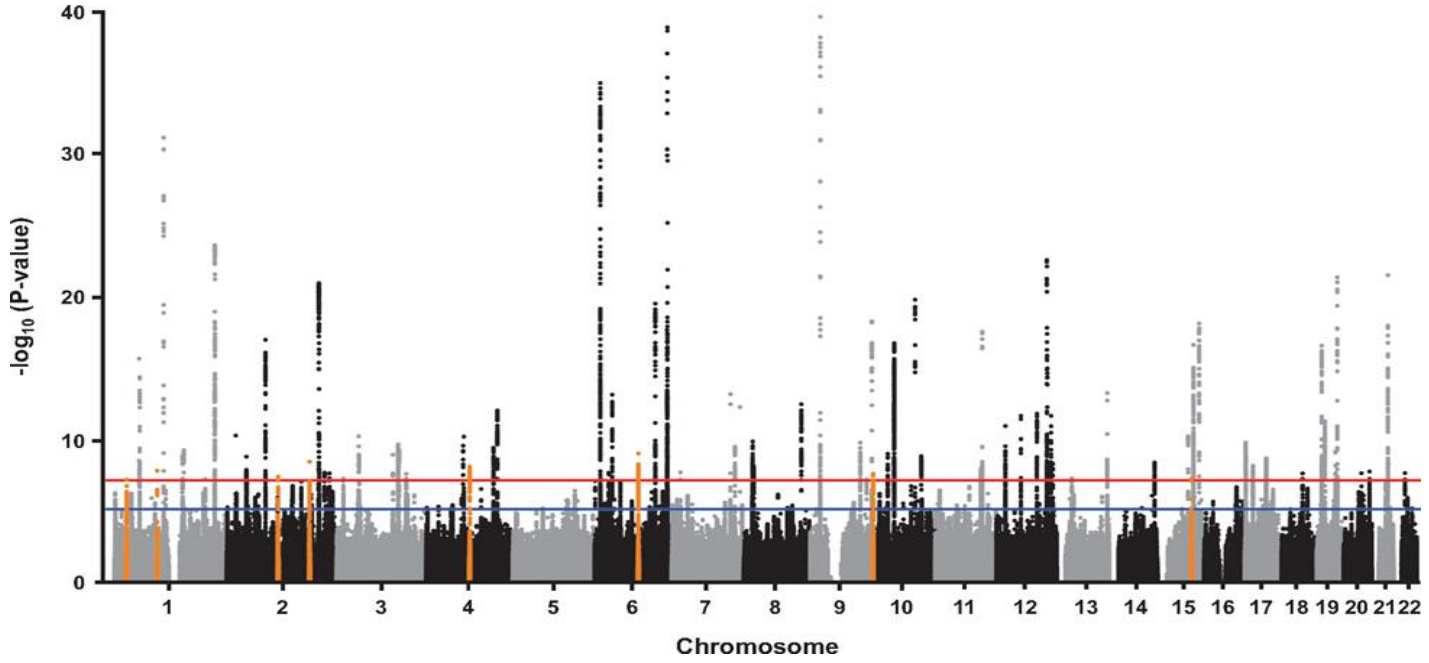


- Systematic pleiotropy analyses indicate that the majority of these loci do not influence CAD risk through well-recognized risk factors
- GWA studies continue to elucidate causal mechanisms for CVD

Cardiovasc Res, Volume 114, Issue 9, 15 July 2018, Pages 1241–1257, https://doi.org/10.1093/cvr/cvy084

Genetics of CAD

- **In the last 4 years alone, the number of susceptibility loci for CVD >250**



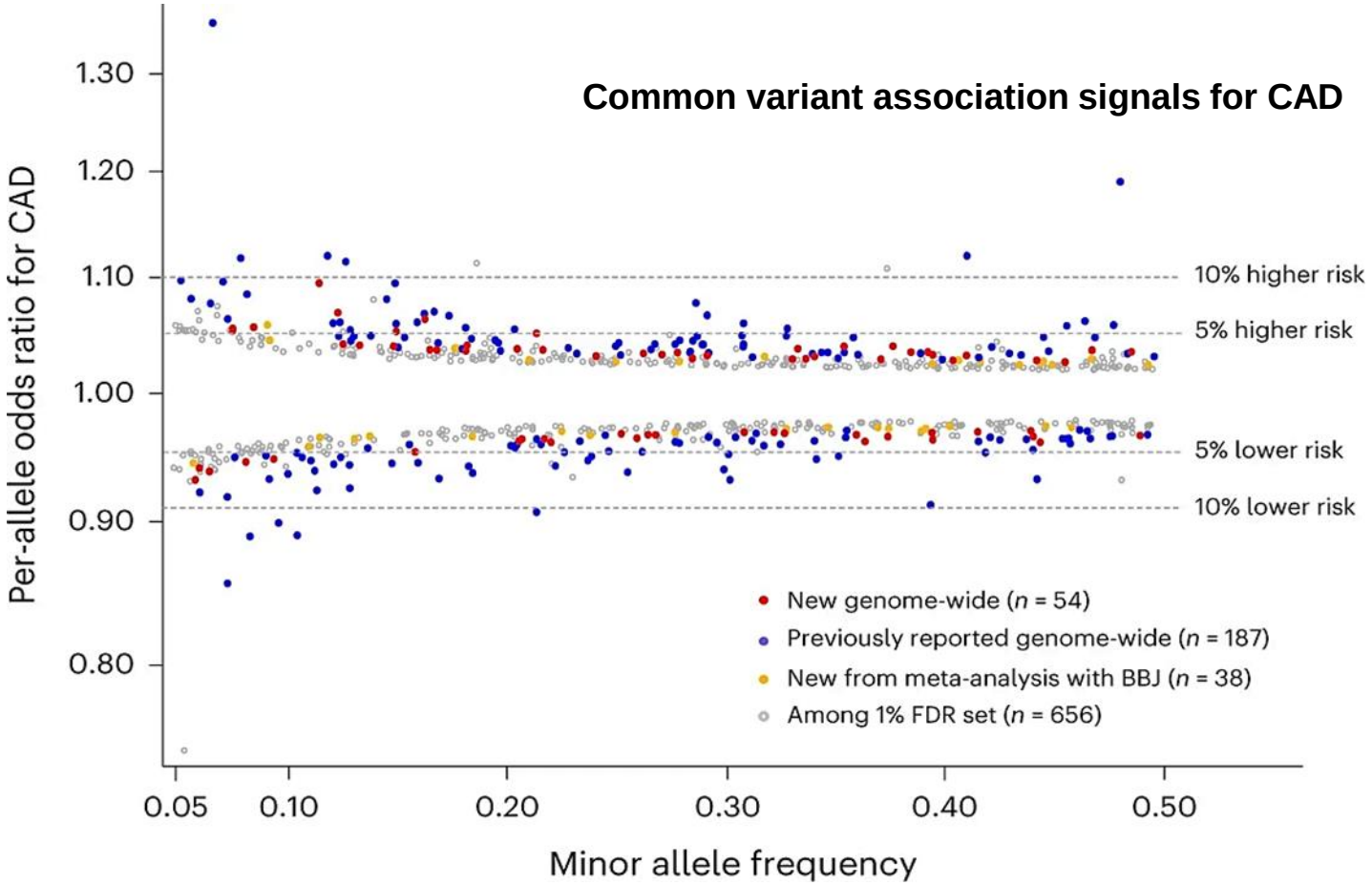
Manhattan plot of results from GWAS meta-analysis for MI

Large scale GWA for MI comprising 831,000 subjects (UKBB: n~472,000, meta-analysis with summary statistics from the CARDIoGRAMplusC4D Consortium: n~167,000), identified 8 novel loci on chromosomes 1p36.11, 1p21.3, 2q13, 2q32.1, 4q22.3, 6q16.1, 9q34.3, and 15q24.2 (orange dots) for MI, of which effect sizes at six loci were more robust for MI than for CAD without the presence of MI

Hartiala et al., Eur. Heart J. 2021; 42:919-933

Genetics of CAD - *Dec 2022 update*

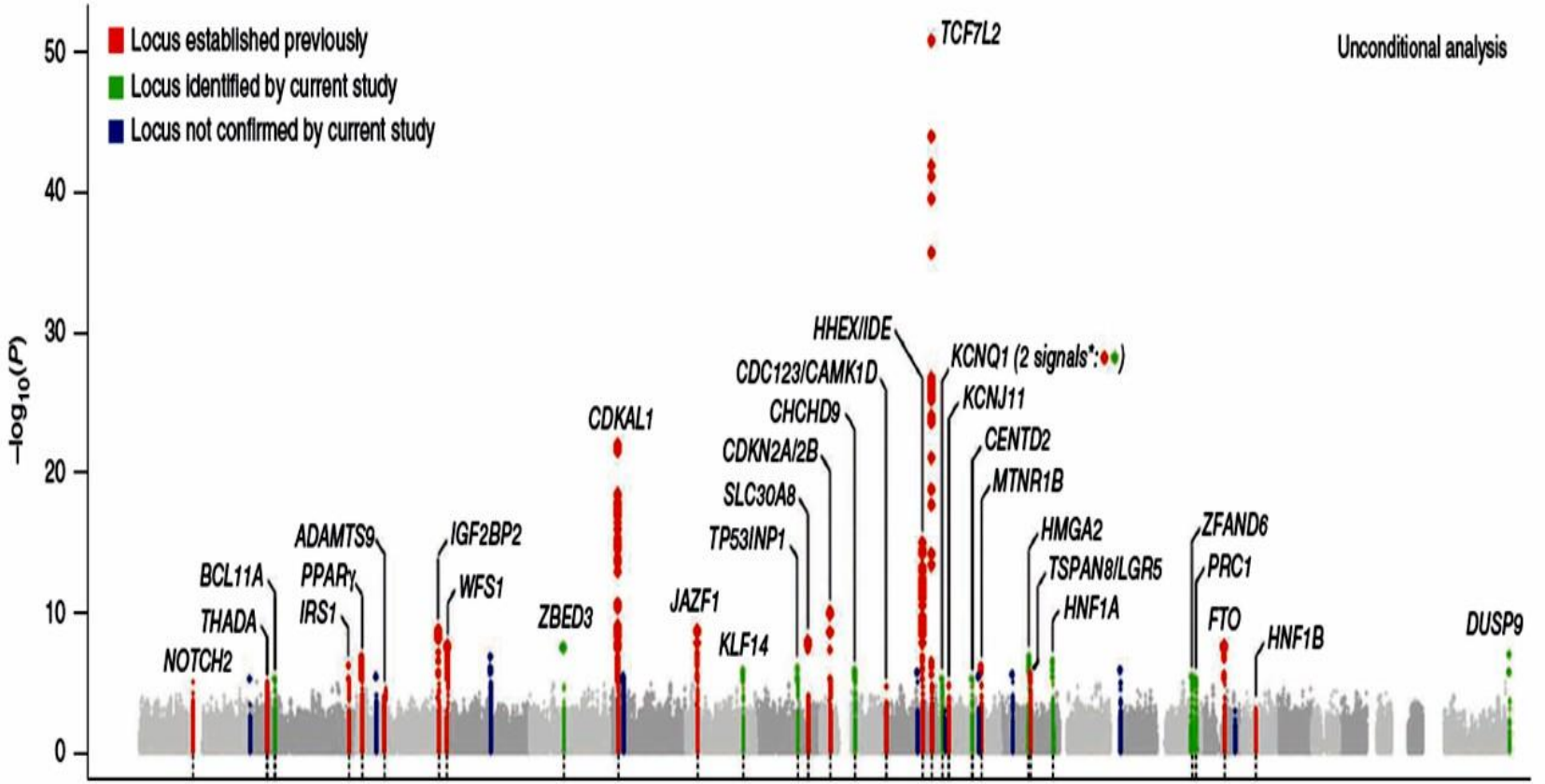
- Discovery analysis involving >200,000 CAD cases and >1 million controls: **identifies 279 GWAS risk loci (82 new)**



Aragam et al. Nature Genet 2022 Dec; 54(12):1803-1815

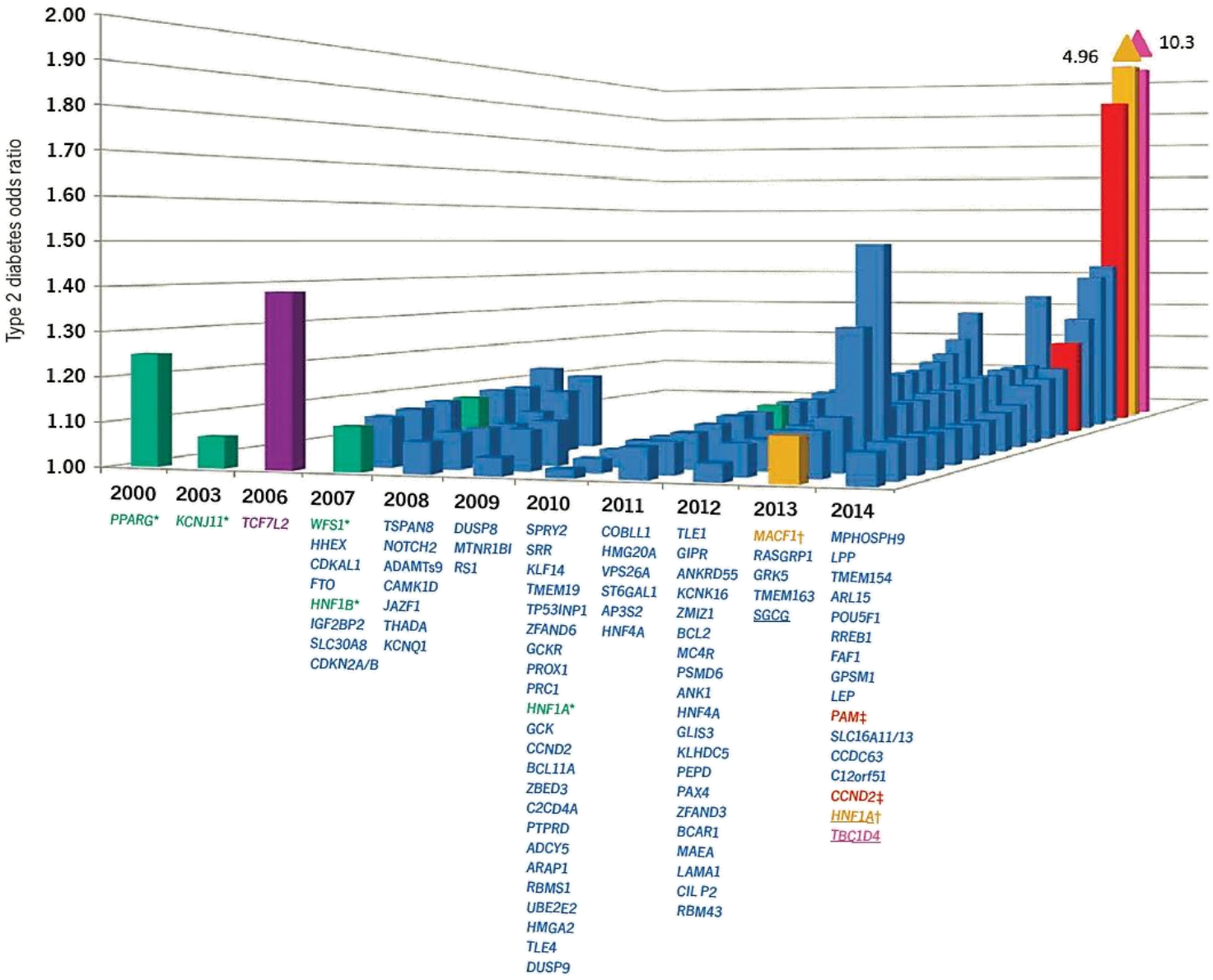
Genetics of Type-2 Diabetes (T2D)

- >60 genetic variants have been identified to date being associated with T2D

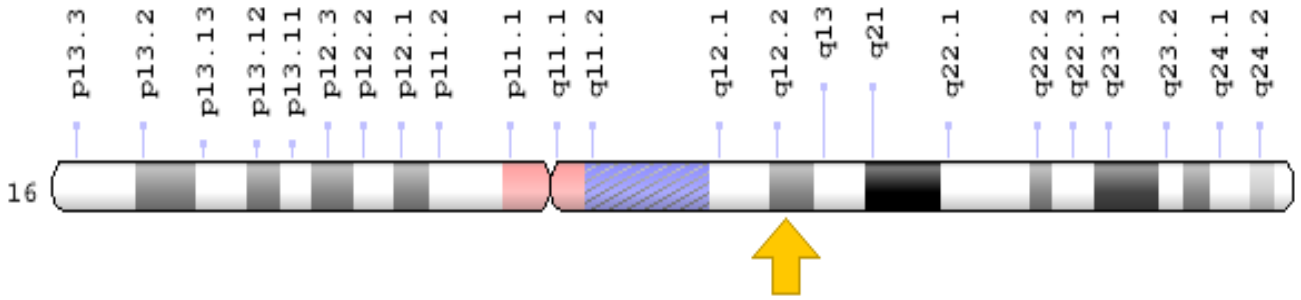


DIAGRAM+ meta-analysis
Voigt et al. Nature Genet. 2010

Genetics of Type-2 Diabetes (T2D)



Genetics of Obesity: FTO gene

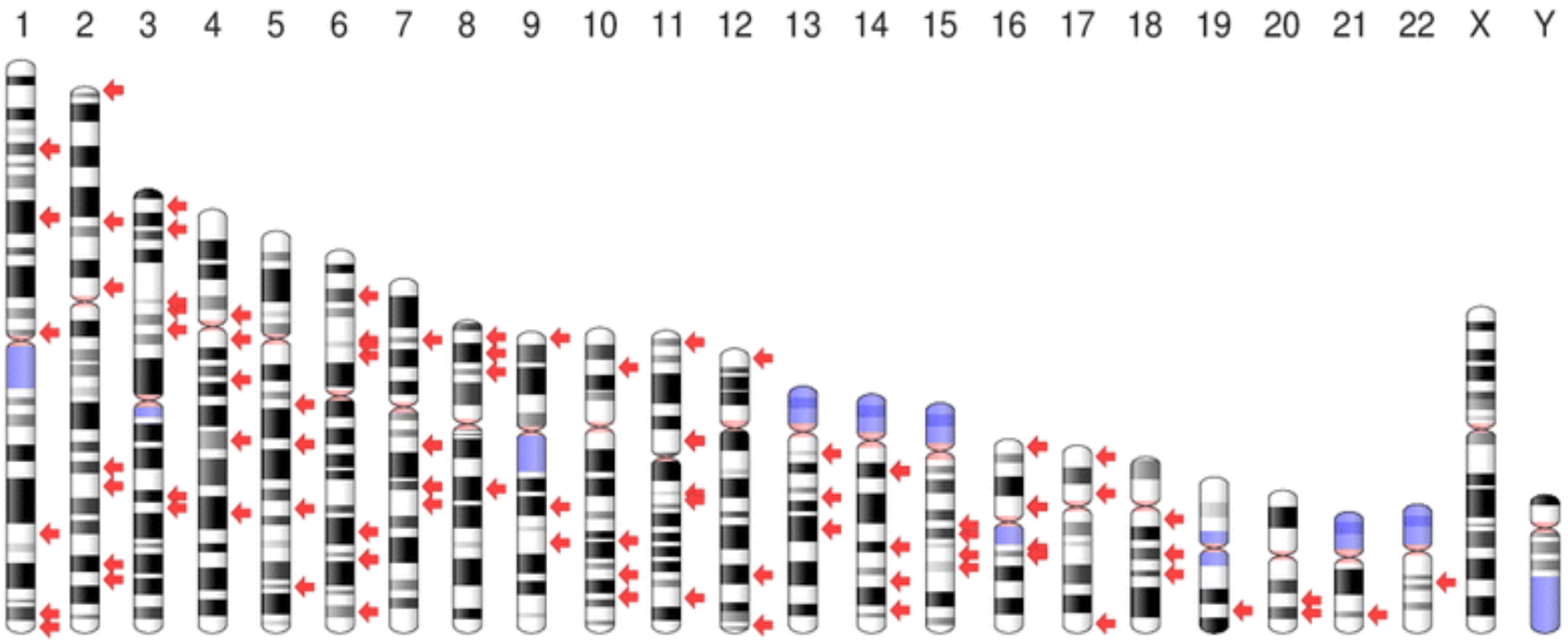


- ***FTO* (fat mass and obesity associated gene)**: Το 1ο γονίδιο που αδιαμφισβήτητα συσχετίστηκε με την παχυσαρκία από τις GWAS και επιβεβαιώθηκε σε διαφορετικούς πληθυσμούς

Moleres et l, Curr Obes Rep 2013;2:23–31

Loos, Best Pract Res Clin Endocrinol Metabol. 2012;26:211–26

Genetics of Obesity

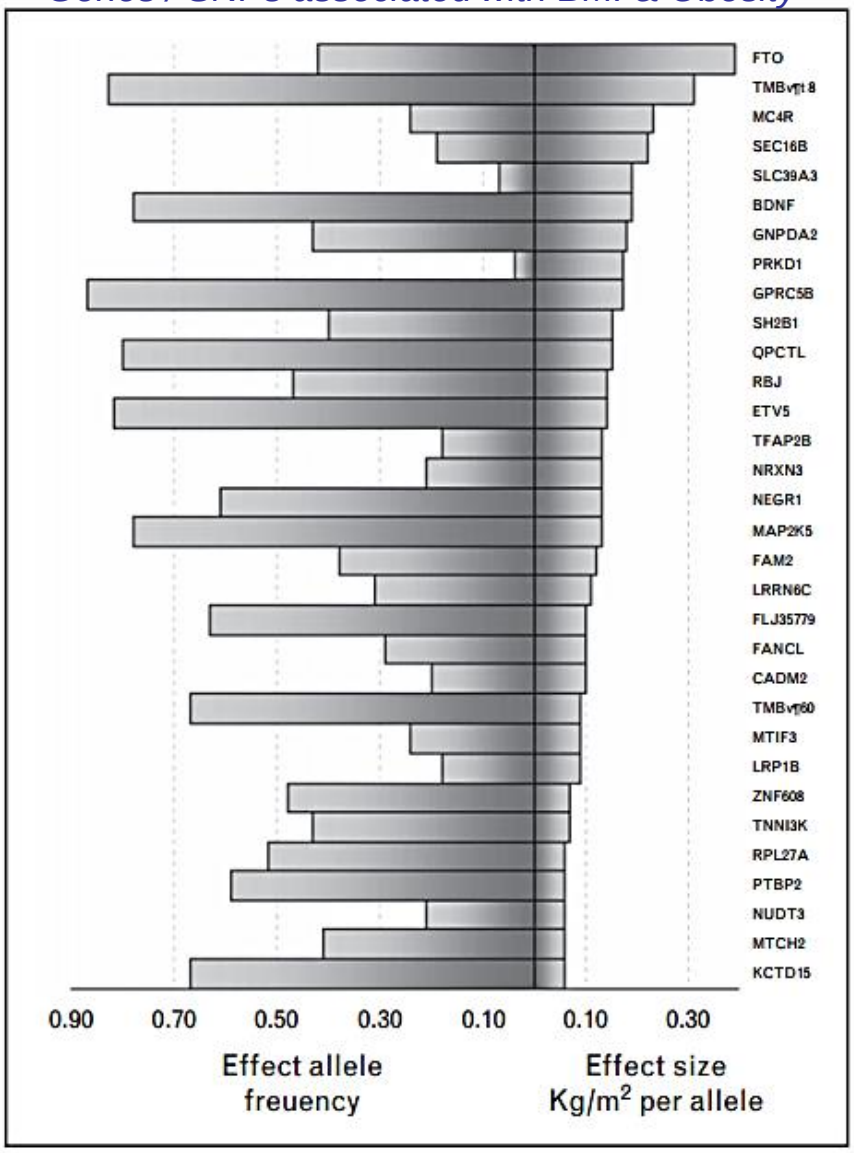


Chromosomal ideogram of human obesity susceptibility genes. The chromosomal loci for 127 obesity susceptibility genes are provided using a chromosomal ideogram and denoted by red arrows

Castillo et al, Genes & Nutr, 2017;12:29

Polygenic Obesity

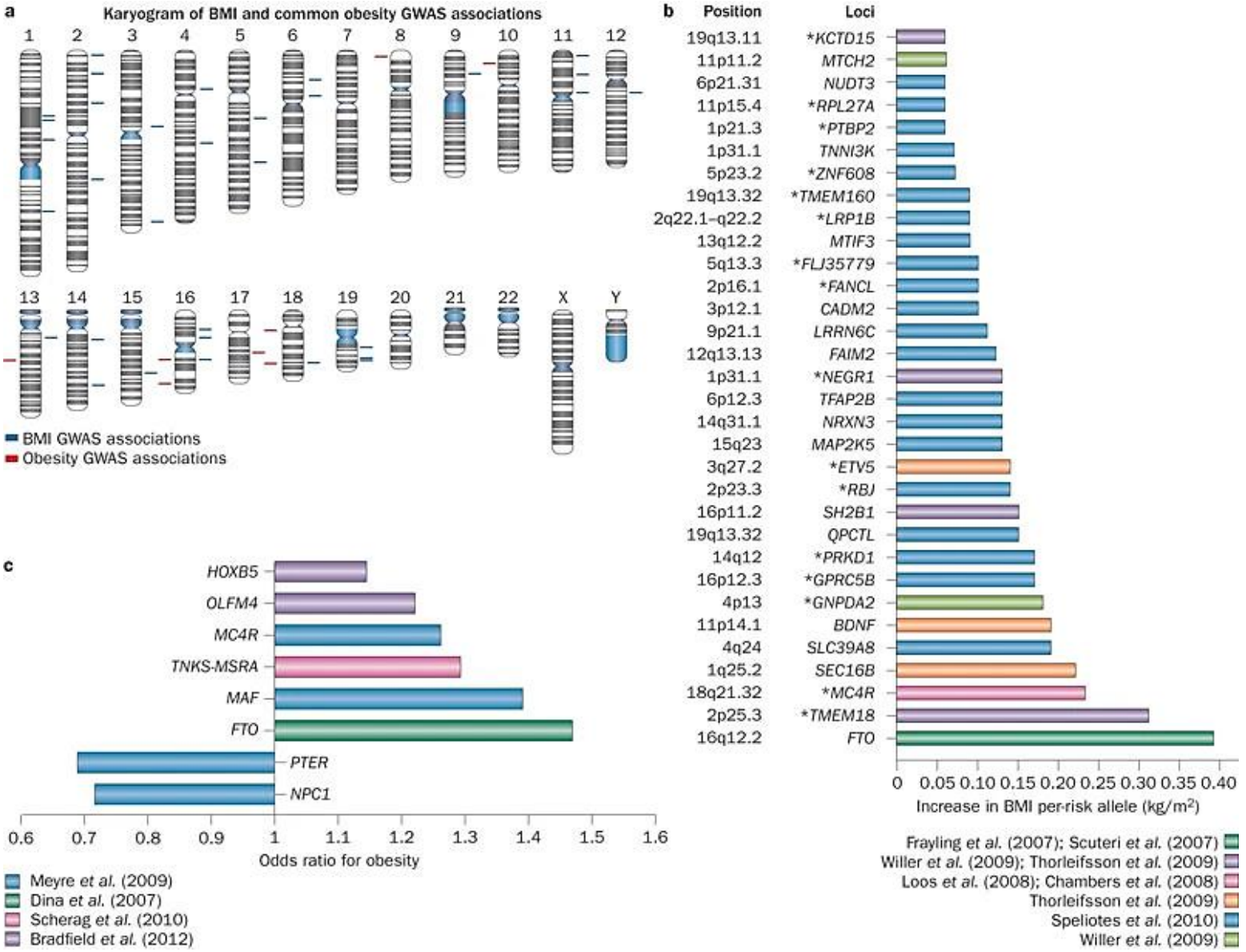
Genes / SNPs associated with BMI & Obesity



Γονίδια που εμπλέκονται σε μονοπάτια που αφορούν:

- **Ρύθμιση ενεργειακής πρόσληψης** (π.χ. *MC3R, MC4R, POMC, LEP, LEPR, FTO*)
- **Μεταβολισμός λίπους & λιπογένεση** (π.χ. *PLIN1, APOA5, LIPC, FABP2*)
- **Θερμογένεση** (π.χ. *ADBRs, UCPs*)
- **Μεταγραφικοί παράγοντες** (π.χ. *PPARG, TCF7L2, CLOCK*)
- **Σύνθεση αντιποκινών, κυτταροκινών** (π.χ. *ADIPOQ, IL-6*)
- **Δράση & σήμανση Ινσουλίνης** (π.χ. *IRS1, INSIG2, GIPR*)

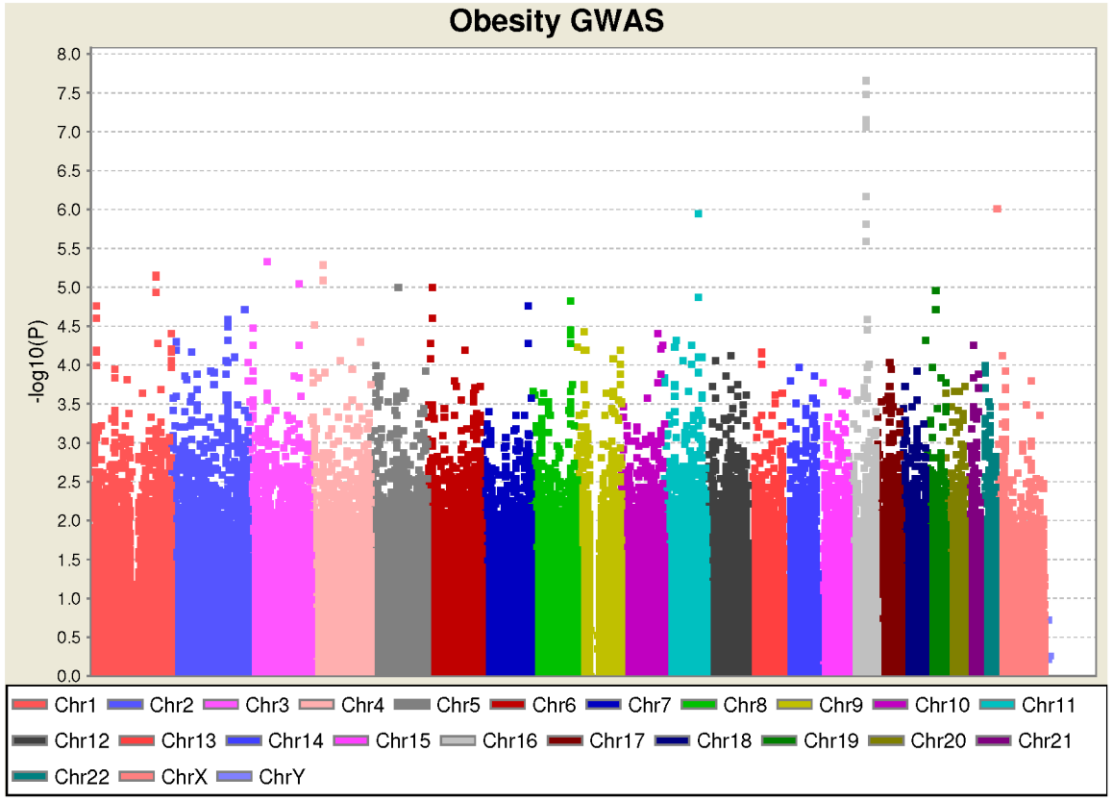
Polygenic Obesity: *Genes / SNPs associated with BMI & Obesity*



Genetics of Obesity

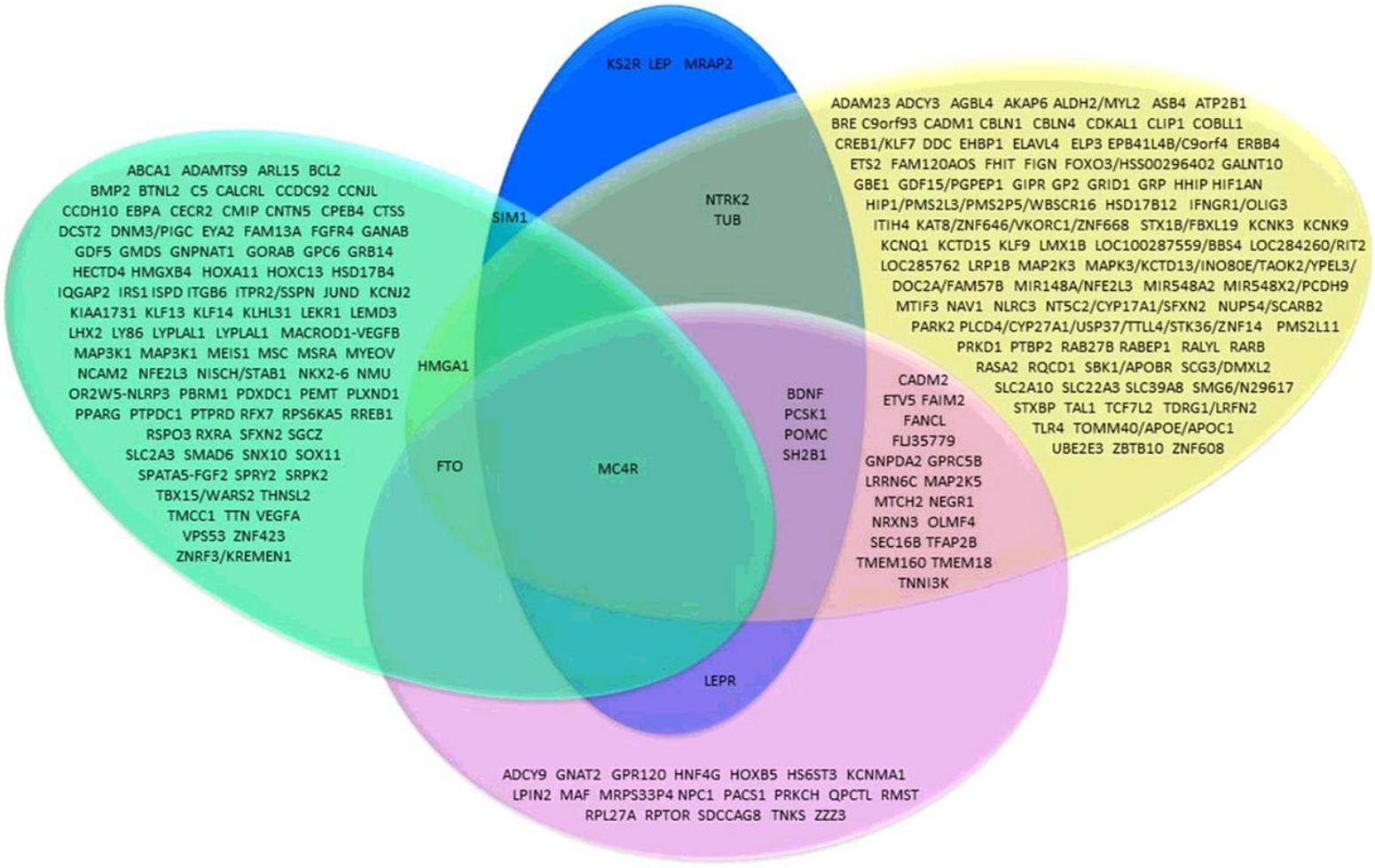
- **Large scale GWAS**:

  > 870 SNPs με ισχυρή συσχέτιση με τον ΔΜΣ



Rohde et al, Metabol Clin Exp, 2018;pii: S0026-0495(18)30225-7

Genetics of Obesity



Venn diagram of genes involved in monogenic, oligogenic and polygenic obesity

Monogenic, oligogenic obesity genes are depicted in blue, polygenic BMI-related genes in yellow, overweight or obesity-related genes in purple and fat distribution-related genes in green.

Pigeyre et al, Clin Sci, 2016;130:943-986

NHGRI celebrates 10th anniversary of the Human Genome Project

Quantitative Advances Since the Human Genome Project (HGP)

	HGP Begins 1990	HGP Ends 2003	10 Years after HGP 2013
Genome Sequencing			
Cost to Generate a Human Genome Sequence	~$1 billion	~$10-50 million	~$3-5 thousand
Time to Generate a Human Genome Sequence	~6-8 years	~3-4 months	~1-2 days
Human Genome Sequences	0	1	Thousands
Genome Sequence Data			
Total DNA Bases in GenBank	~49 million	~31 terabases	~150 terabases
Whole-Genome Shotgun Bases in GenBank	0	~9.6 terabases	~391 terabases
Vertebrate Genome Sequences	0	3	112
Non-Vertebrate, Eukaryotic Genome Sequence	0	14	455
Prokaryotic Genome Sequences	0	167	8760
Human Single-Nucleotide Polymorphisms	~4.4 thousand	~3.4 million	~53.6 million
Human Genetics			
No. Genes with Known Phenotype/ Disease-Causing Mutation	53	1474	2972
No. Phenotypes/Disorders with Known Molecular Basis	61	2264	4847
No. Published Genome-Wide Association Studies (GWAS)	0	0	1542
Replicated Disease-Associated Genetic Variants	0	6	~2900
Genomic Medicine			
Drugs with Pharmacogenomics Information on Label	4	46	106

Since the beginning of the Human Genome Project 23 years ago, genomic data have steadily accumulated, laying the foundation for advances in human health.
Data compiled from various sources by National Human Genome Research Institute.

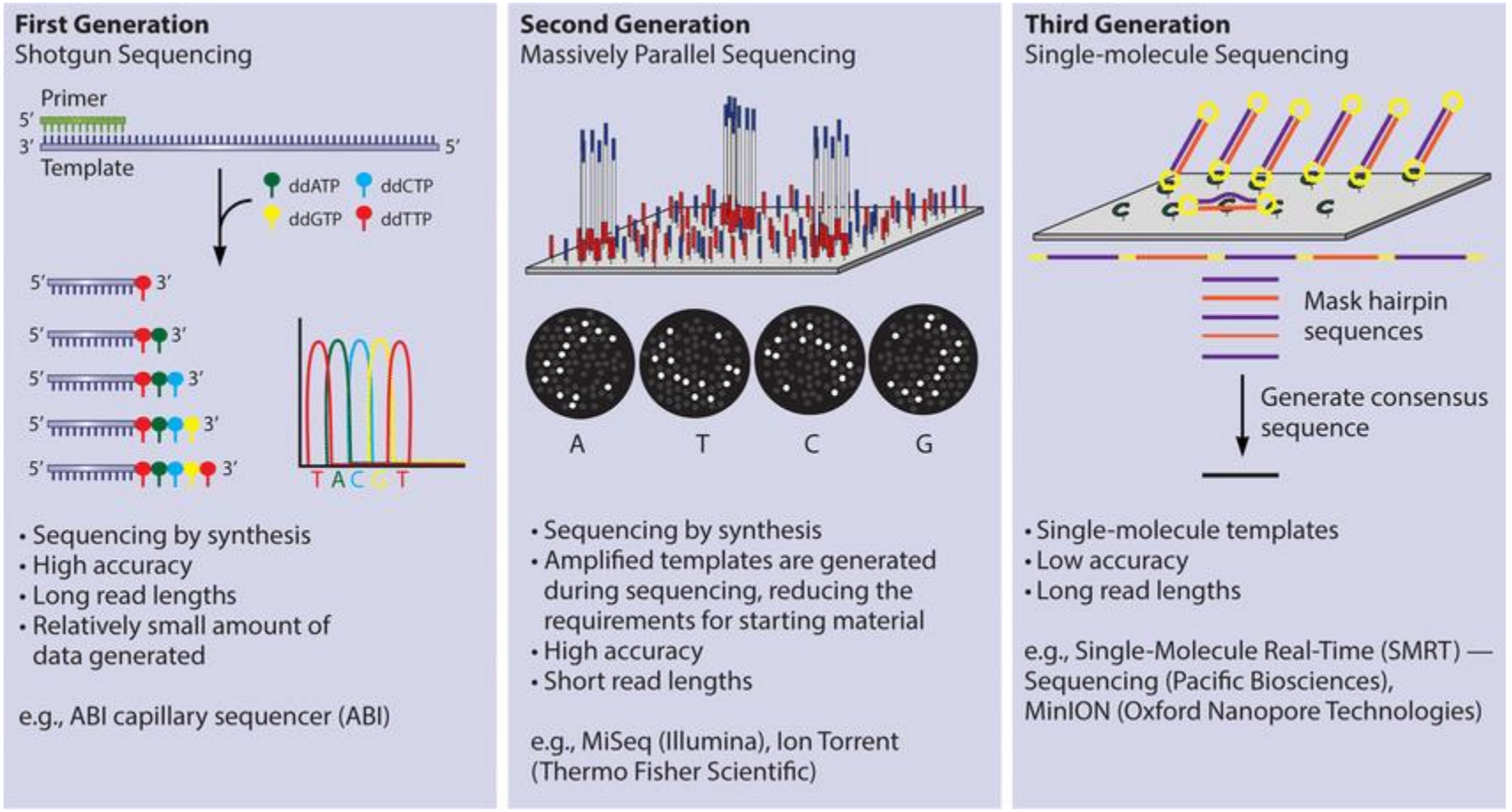
Next generation sequencing (NGS)

- **NGS** *(massively parallel or deep sequencing are related terms)* describe a DNA sequencing technology which has revolutionised genomic research.
- Using NGS an entire human genome can be sequenced within a single day.
- Each of the 3-billion bases in the human genome is sequenced multiple times, providing high depth to deliver accurate data and an insight into unexpected DNA variation.
- NGS can be used to sequence entire genomes or constrained to specific areas of interest, including all 22,000 coding genes (a whole exome) or small numbers of individual genes.

.

Behjati S & Tarpey PS, Arch Dis Child Educ Pract Ed. 2013; 98:236-238

Third-generation sequencing



- **Third-generation sequencing** (also known as **long-read sequencing**) is a class of DNA sequencing methods which produce longer sequence reads, under active development since 2008.

Third-generation sequencing

nature methods

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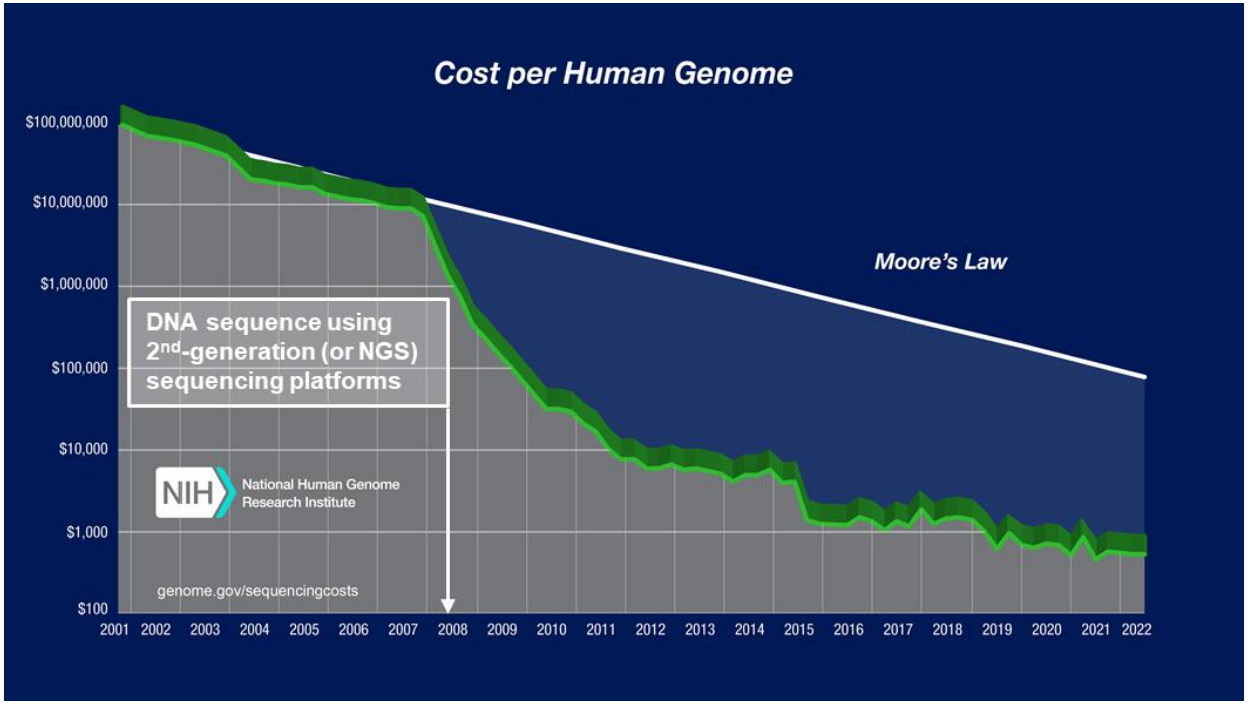
News Feature | Published: 12 January 2023

Method of the year: long-read sequencing

Vivien Marx

- It is expected that these longer read lengths will alleviate numerous computational challenges surrounding genome assembly, transcript reconstruction, and metagenomics among other important areas of modern biology and medicine

Whole Genome Sequencing cost 2023



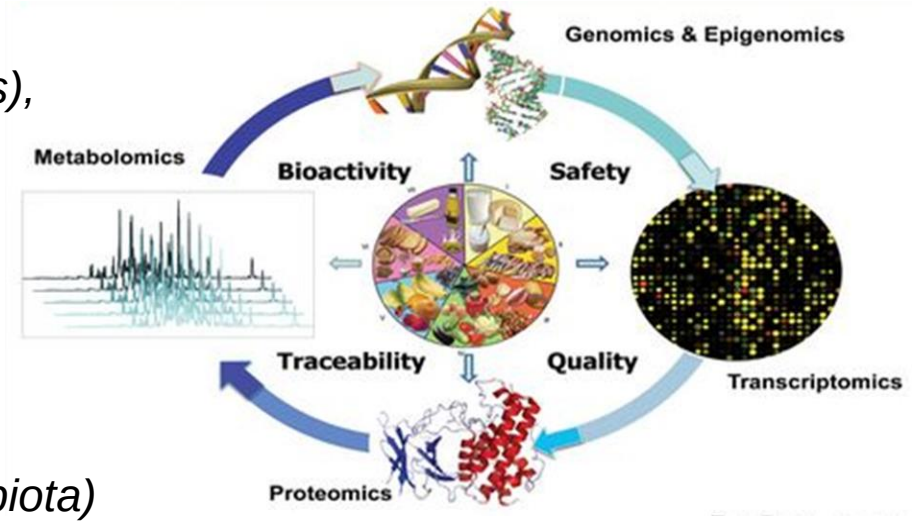
- Sequencing now is much cheaper. And the NGS market is characterized by extreme competition among the key market players. The major market leader Illumina, which controls about 80% of the global DNA sequencing market, unveiled the NovaSeq X series, which will reduce the cost to **$200 per human genome** while providing results at twice the speed. Illumina CEO says that a more powerful model could sequence 20,000 genomes a year. (The current machine can sequence about 7,500 genomes.)
- New companies are also trying to develop tests that cost less. Earlier this year, a startup company, Ultima Genomics, stated that its machine could sequence the genome for **as little as $100**, thereby applying pressure on Illumina.

Πηγή: https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data

The era of …….. ‘omics’

The suffix *‘omics’* means *‘global’* and is used as a modifier for a wide range of endeavors such as:

- **Genomics** *(the comprehensive analysis of genes),*
- **Epigenomics** *(DNA modifications),*
- **Transcriptomics** *(mRNA or transcripts),*
- **Proteomics** *(proteins),*
- **Metabolomics** *(metabolites),*
- **Lipidomics** *(lipids),*
- **Foodomics** *(food),*
- **Microbiomics/Metagenomics** *(microbiota)*



All these techniques can be applied separately or in an integrated manner for a better understanding of health metabolism and disease progression.

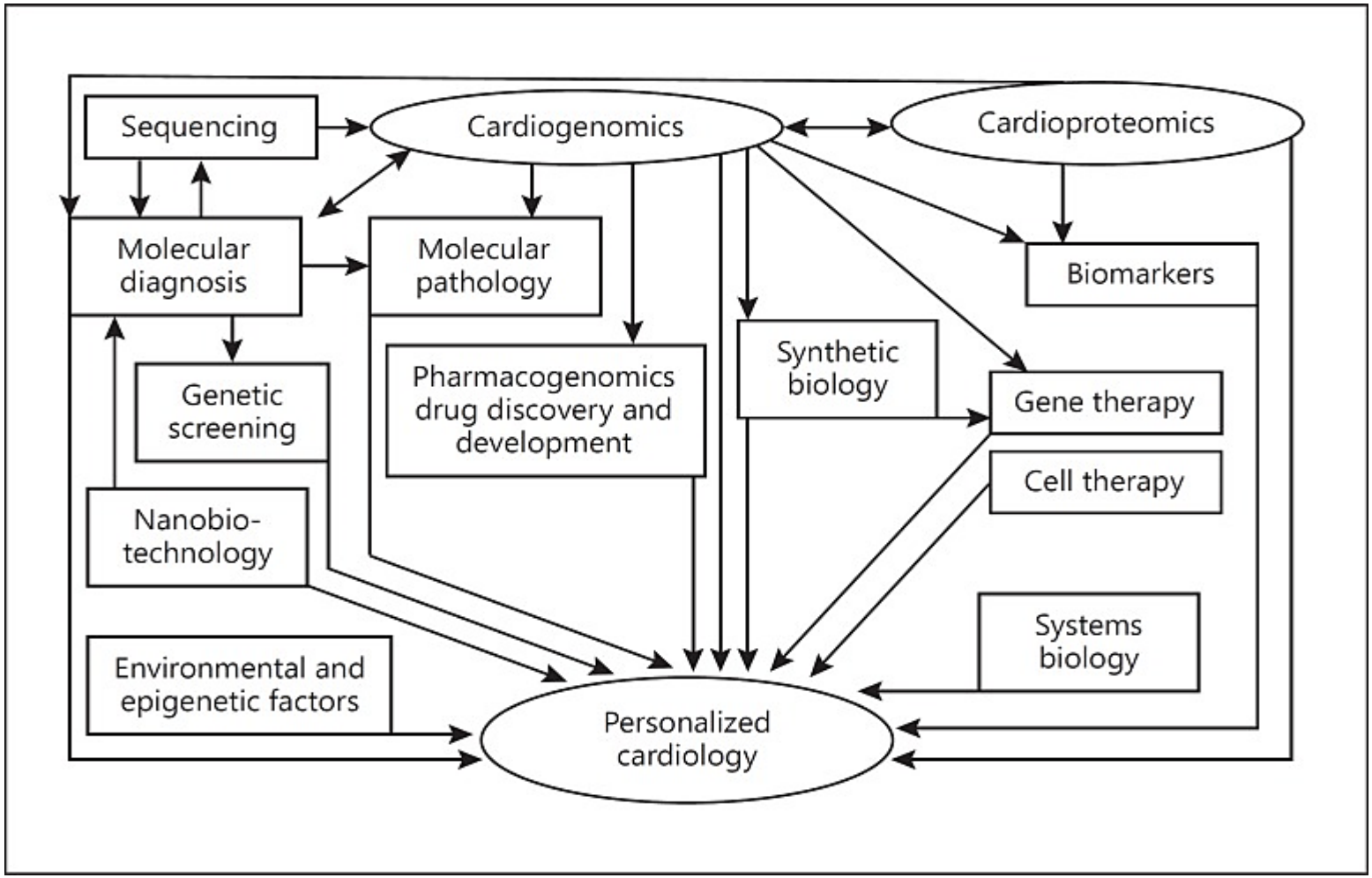
Nutritional genomics

- **Nutritional genomics** is an emerging field that may improve dietary guidelines for chronic disease prevention. It covers both nutrigenomics and nutrigenetics.

- **Nutrigenomics** explores the effects of nutrients or other dietary factors on the gene expression, DNA methylation, proteome & metabolome,

- **Nutrigenetics** is aimed to elucidate whether genetic variations modify the relationships between dietary factors & risk of diseases.
  (Nutrigenetics has the potential to provide scientific evidence for personalized dietary recommendations based on the individual's genetic makeup).

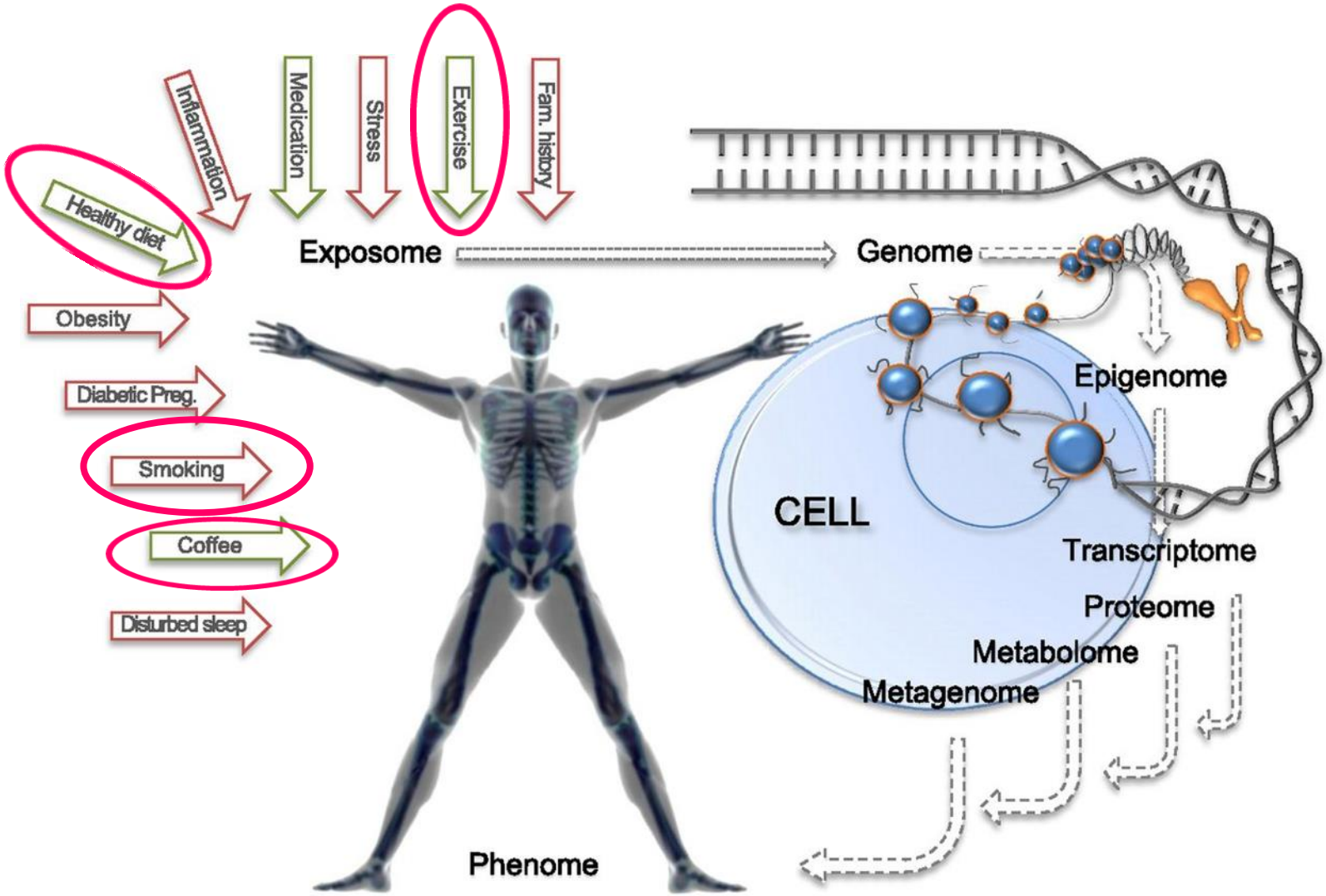
Personalized Cardiology



Integration of technologies for personalized cardiology. Several technologies are integrated for the development of personalized cardiology. These include “omics” such as genomics and proteomics, molecular diagnostics, and biological therapies such as cell and gene therapies. Both genetics and epigenetic factors contribute. Some of the concepts of personalized medicine are like those of systems biology.

Kewal K. J. Med Princ Pract. 2017

Gene – Environment interactions



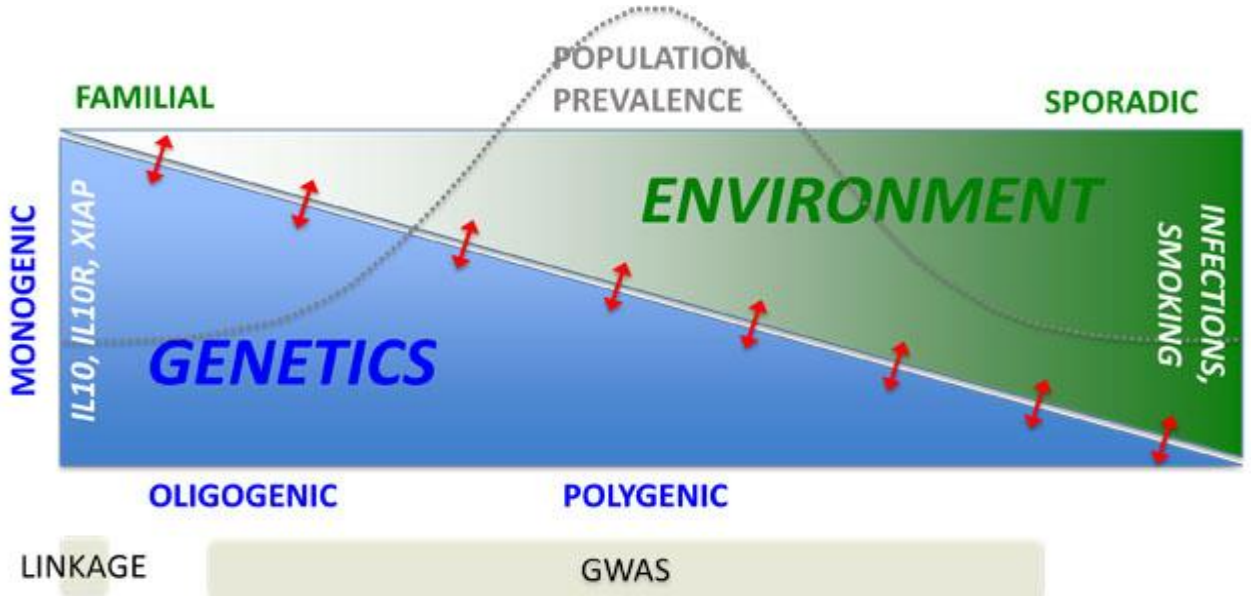
Gene–diet interactions, Obesity & weight loss

- ***Several data have emerged to lend support to gene–diet interaction in determining weight loss & maintenance***
- ***Studies in the area hold great promise to inform future personalized diet interventions on the reduction of obesity and related health problems.***

Qi L. Curr Opin Lipidol 2014, 25:27–34

Gene - Environment interactions (GEI)

- In epidemiology, interaction is defined by estimating whether the degree of risk attributable to the joint effects of a genotype and an environmental factor on an outcome is greater or less than would be expected if these joint effects were additive.
- Alternatively, GEI exists where the risk conveyed by specific genotype depends on one or more environmental exposure levels. This definition is quite helpful in the context of intervention studies where the environmental exposures can be intervened upon, such as diet and physical activity, to offset genetic risk.



Huang & Hu, BMC Medical Genomics 2015

Study designs for testing Gene-Environment interactions

Over the past decades, various study designs have been used to test GEI. Each design has its own advantages and disadvantages, and may be suitable for different situations:

- **Case-control studies**: In population-based case-control studies, incident or prevalent cases in the studied population are ascertained over a certain time period, while the controls are randomly selected from the same source population.

- **Case-only studies**: These studies can be used if the interest is limited to GEI, because the case-only design has the practical advantage that there is no need to collect control samples. This design is based on the assumption that genotypes and environmental exposures are independent of each other, so that the exposures should not differ among different genotypes. The case-only design is more efficient than case-control design, but the independence assumption may not hold.

- **Cohort studies**: The classic prospective cohort study follows subjects over time, comparing the outcome of interest in individuals who are exposed or not exposed at baseline. Because exposure is assessed before the outcome, the cohort design is less susceptible to selection bias and differential recall bias between cases and noncases when compared to a case-control design. However, cohort studies of chronic conditions with low incidence are expensive, and require large sample size and long follow-up.

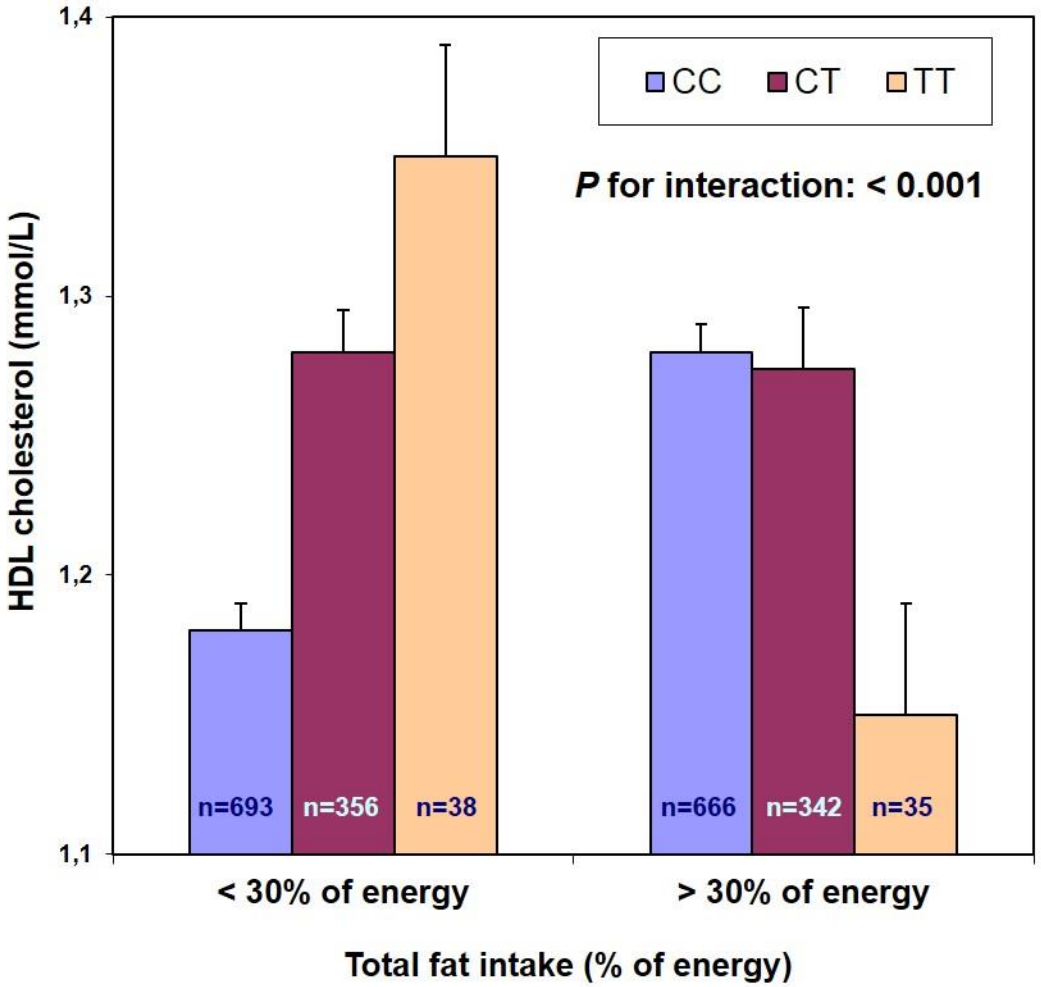
- **Clinical trials**: Randomized controlled trial (RCT) is widely considered to be the most reliable design because of the randomized allocation of the exposures. However, RCT is often infeasible to test the long-term effects of dietary exposures on e.g. obesity or obesity-related chronic diseases due to cost and logistic considerations.

Huang & Hu, BMC Medical Genomics 2015

Gene – Diet interactions

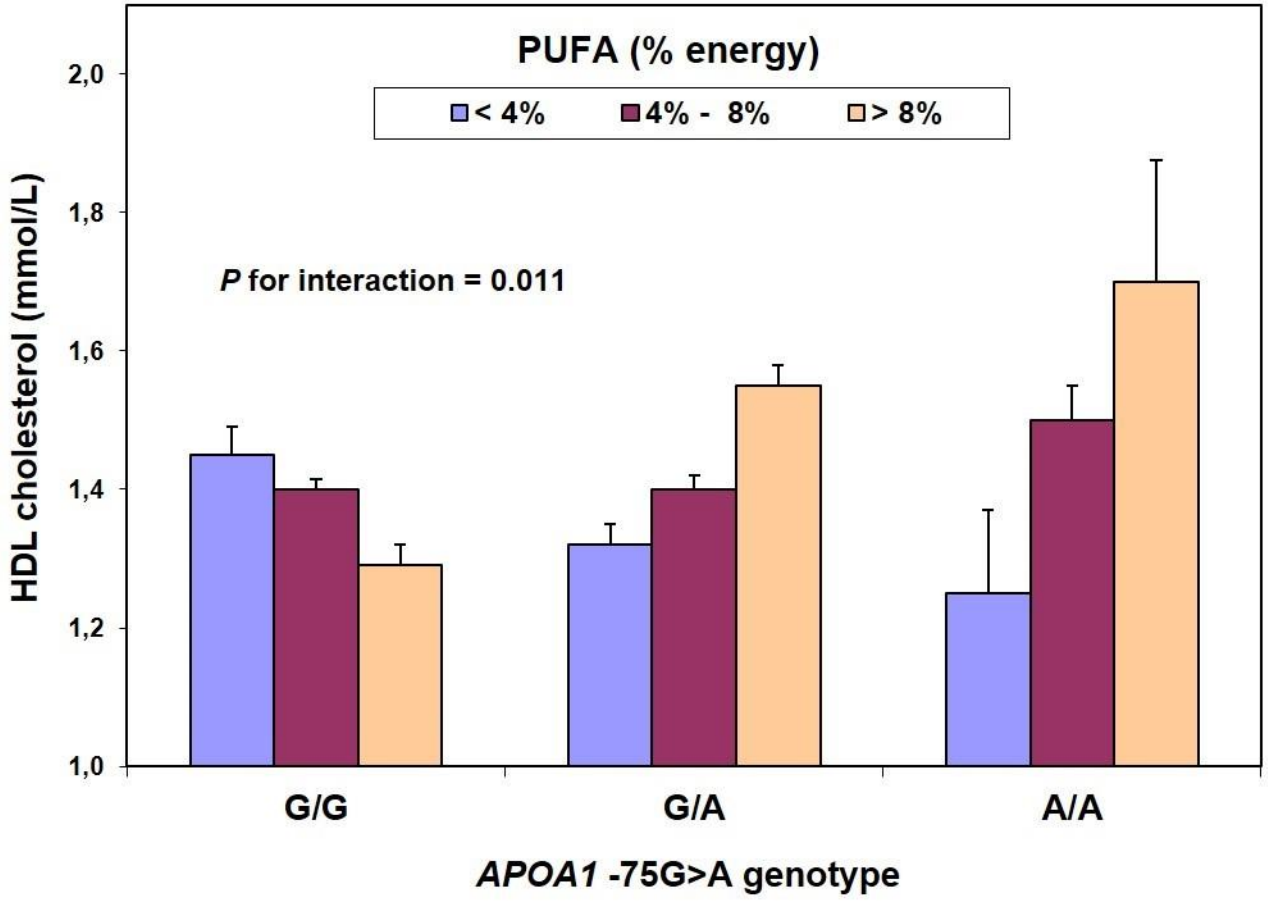
LIPC -514C>T * % λίπους: *επίδραση στην HDL-C*

Ordovas JM et al. *Circulation* 2002



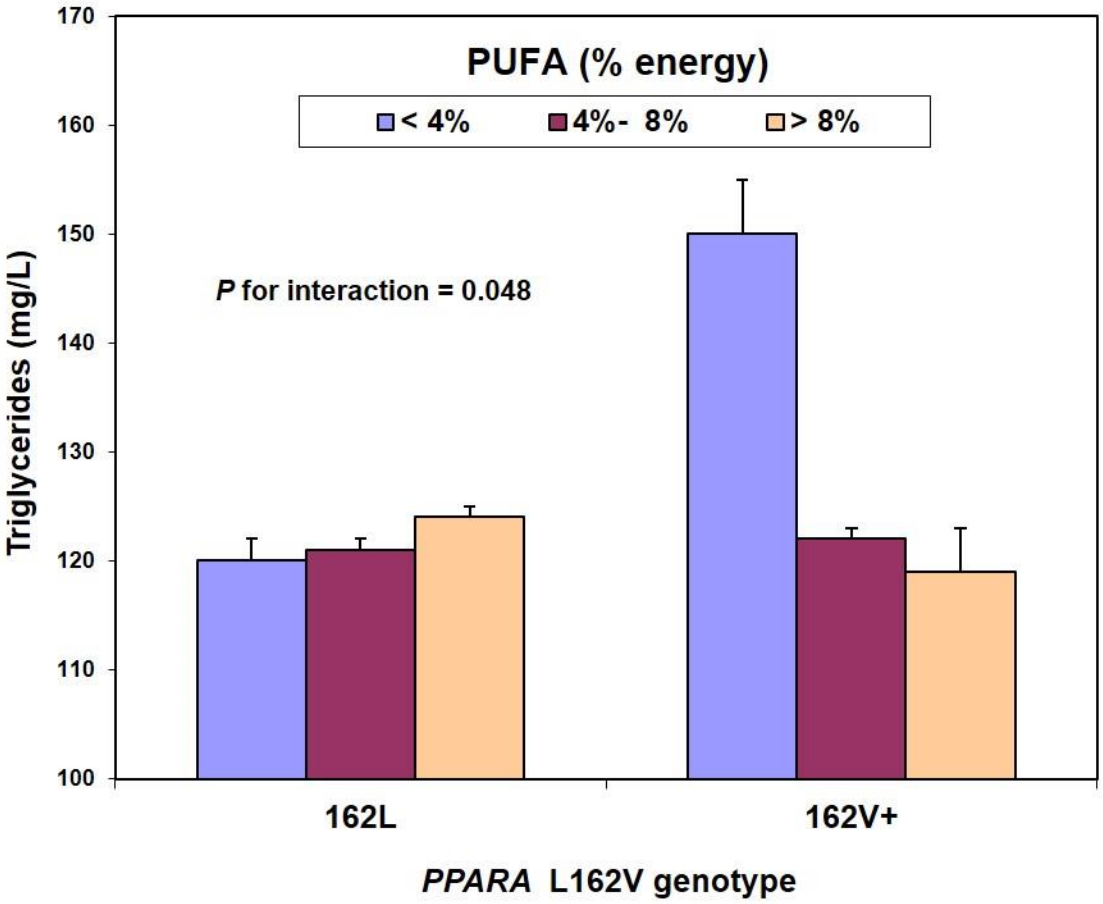
APOA1 -75G>A * PUFAs: *επίδραση στην HDL-C*

Ordovas JM *et al. Am J Clin Nutr* 2002



PPARA L162V * PUFAs: *επίδραση στα TGL*

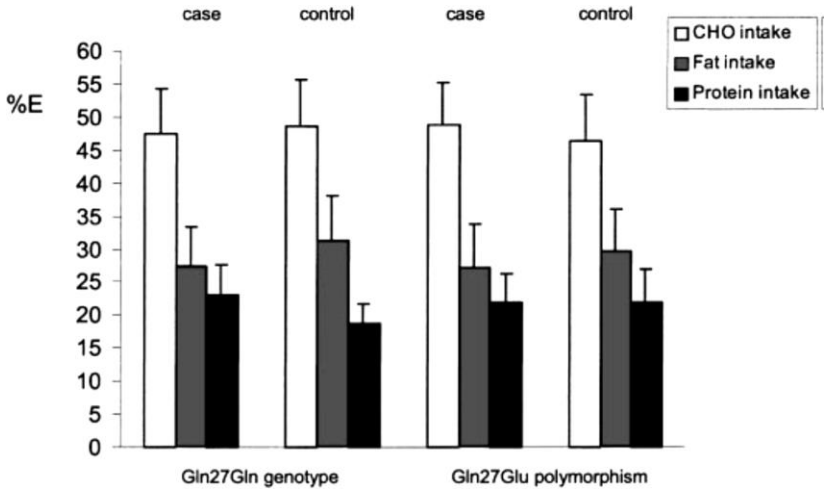
Tai SE et al. *J Nutr* 2005



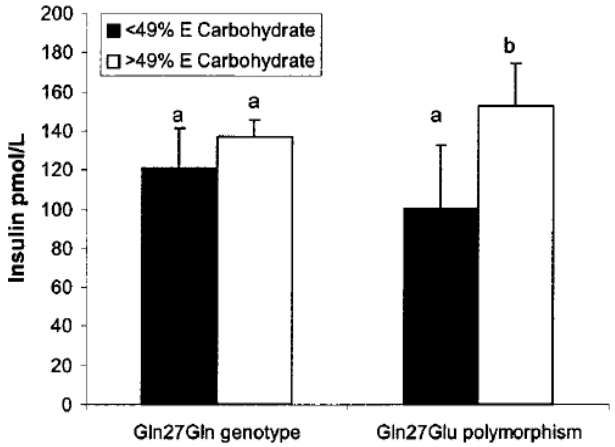
Gene - Diet interactions & Obesity

- **Case-control study** to assess a possible effect modification on obesity risk of the Gln27Glu polymorphism for the β_2-adrenoceptor gene depending on dietary intake.
- 159 cases (BMI>30 kg/m^2) & 154 controls (BMI<25 kg/m^2)
- **ADRB2 genotype modified the effect of CHO consumption on obesity risk. Females with the polymorphism and a higher CHO intake (>49% energy) had a higher obesity risk (OR: 2.56, *P*=0.051; $P_{interaction}$=0.058).**
- Furthermore, a high intake of CHO was associated with higher insulin levels among women carrying the Gln27Glu SNP (P<0.01).

Martinez et al. J Nutr 2003



No differences between cases & controls within genotype for CHO, fat or protein intakes.



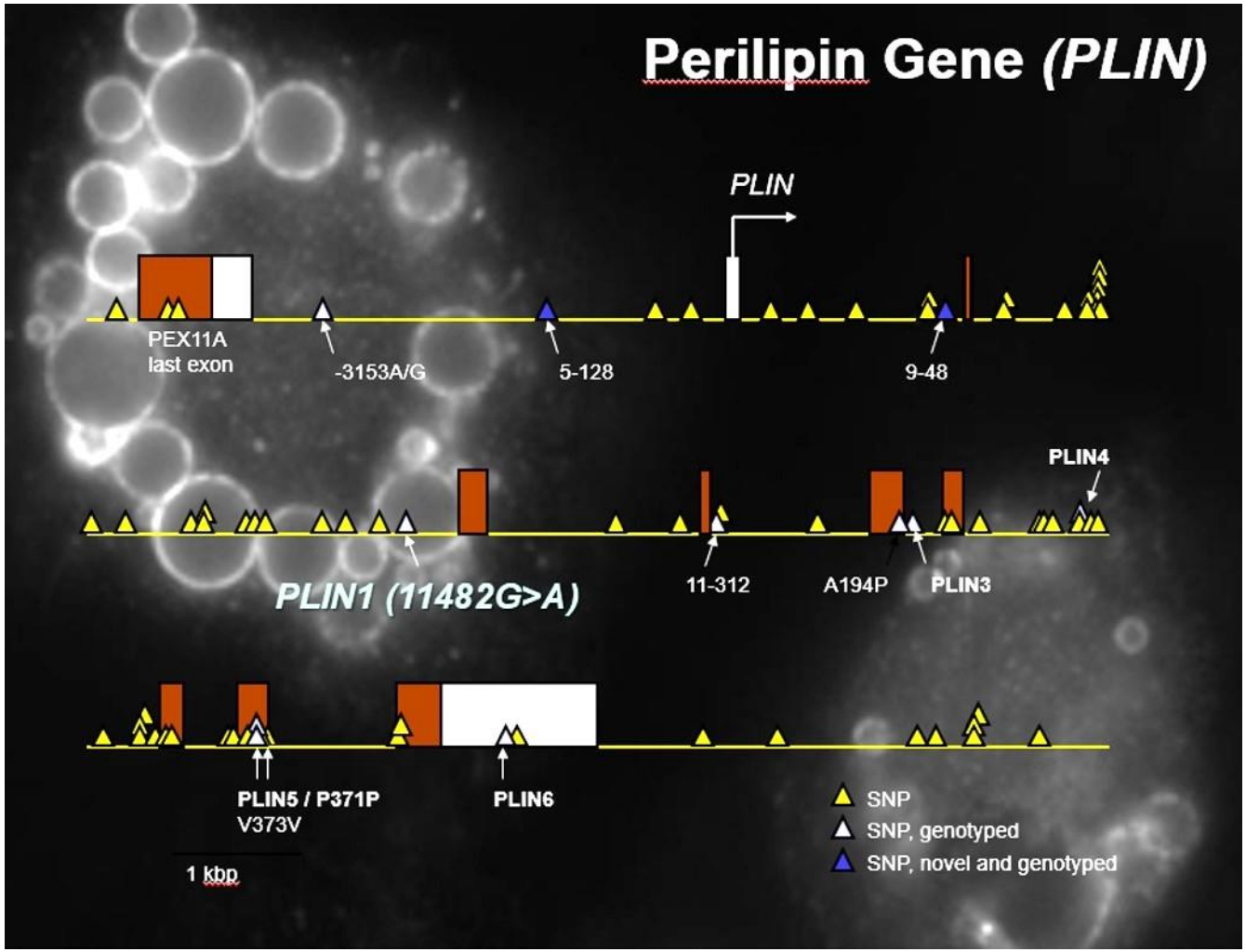
Mean insulin levels according to CHO intake among women categorized by Gln27Glu.

Gene - Diet interactions & Obesity

- **Case-only study** among 549 adult obese women recruited from eight European centres
- A total of 42 SNPs in 26 candidate genes for obesity were genotyped
- Nutritional variables assessed: dietary fiber intake (gr/day), the ratio of dietary PUFAs/SFAs & % of energy derived from fat in the diet (3-day food records)
- Observed an interaction between fiber intake and the LIPC –514 C>T SNP ($p_{\text{for interaction}}$ =0.01).
- Similarly, the ADIPOQ –11377G>C SNP & the PPARG3 –681 C>G SNP were found to modify the association of dietary fat intake and obesity (all $p_{\text{for interaction}}$ <0.05).

Santos et al. Eur J Nutr 2006

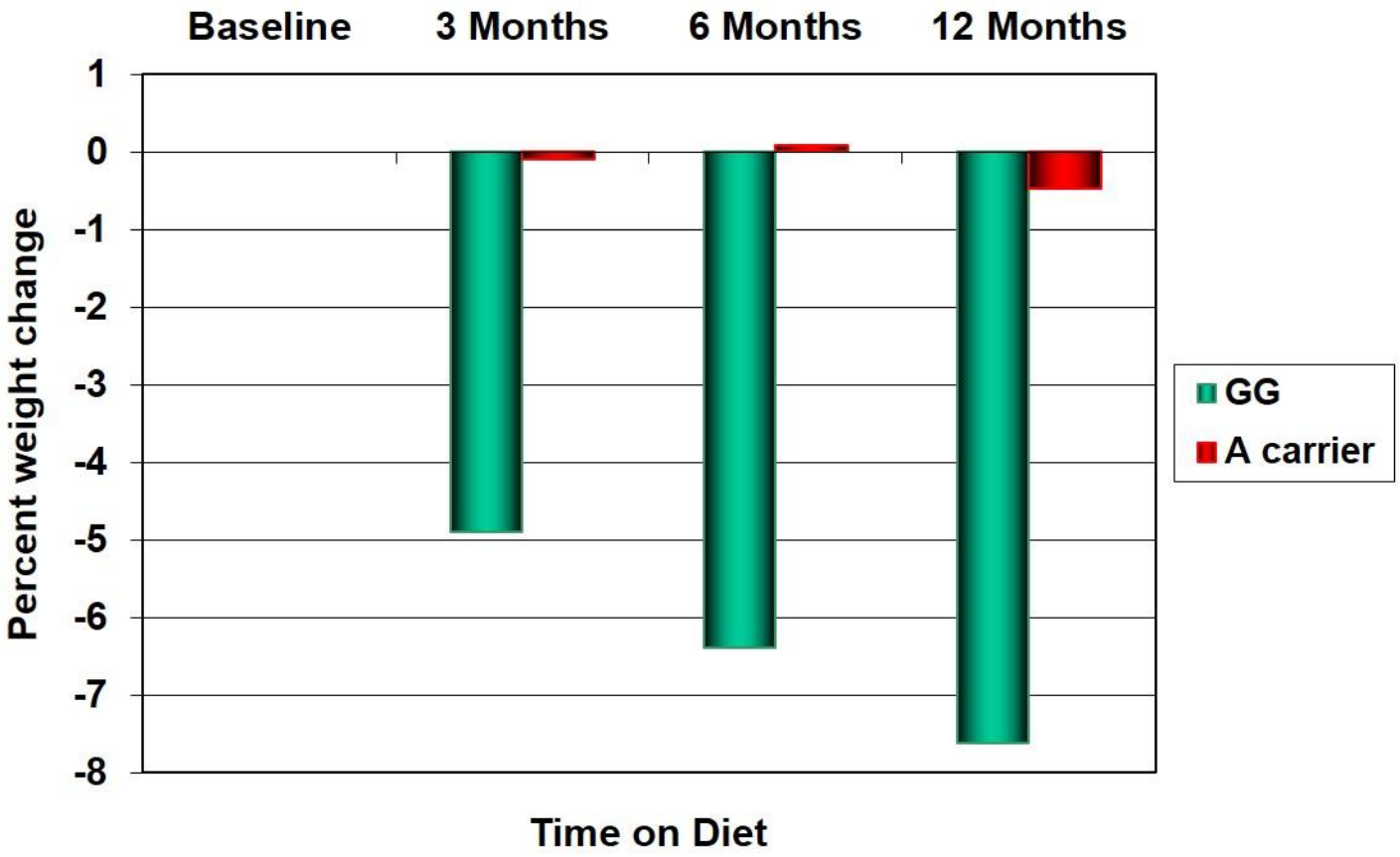
Διατροφογενετική της Παχυσαρκίας



Διατροφογενετική της Παχυσαρκίας

PLIN gene – 11482G>A (*PLIN1*)

……effect on weight loss after a hypocaloric diet

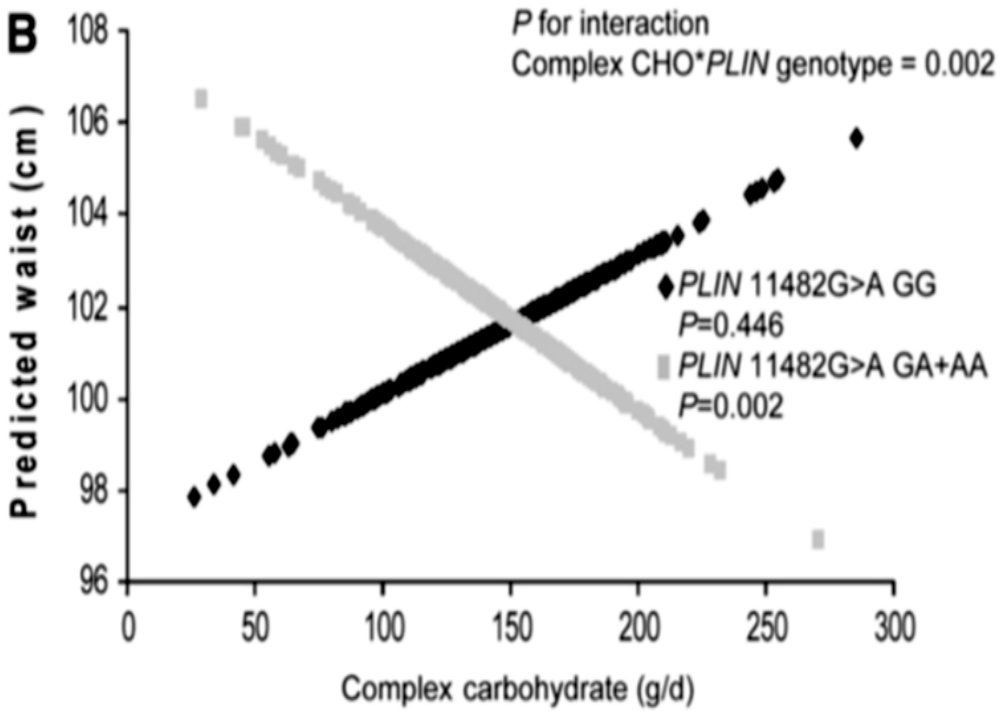


Corella et al, J Clin Endocrinol Metab. 2005

Διατροφογενετική της Παχυσαρκίας

PLIN gene – 11482G>A (*PLIN1*)

- Εξετάστηκε αν τα μακροθρεπτικά συστατικά τροποποιούν τη συσχέτιση του πολυμορφισμού με την παχυσαρκία



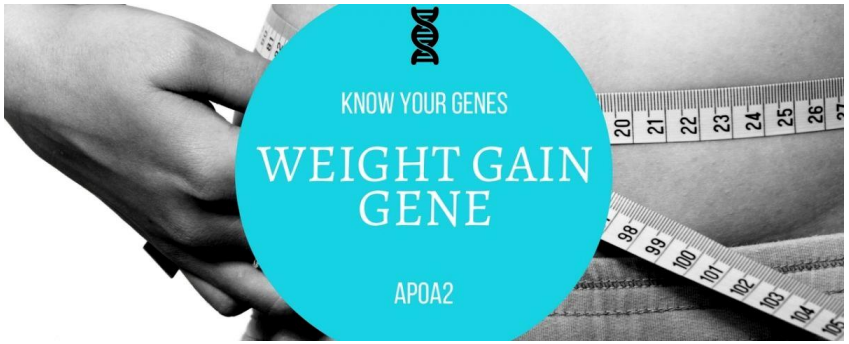
A allele:

- ↓ complex CHO: increased obesity risk
- ↑ complex CHO: protective against obesity

Smith et al, J Nutr 2008;138:1852-8

Διατροφογενετική της Παχυσαρκίας

APOA2 gene – rs5082 (-265T>C)

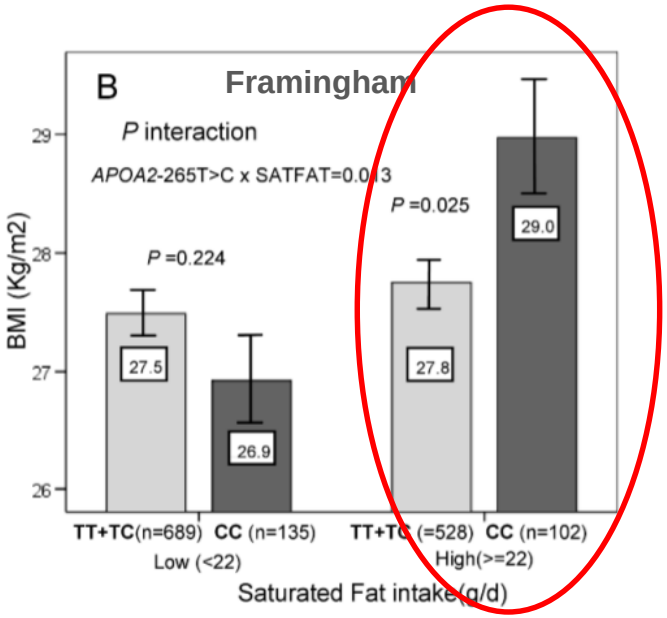


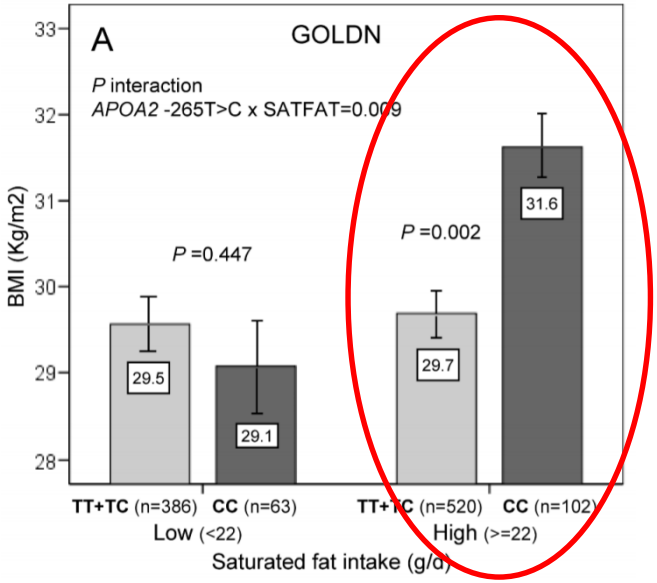
- Εξετάστηκε ο ρόλος του λειτουργικού πολυμορφισμού στην πρόσληψη τροφής & το σωματικό βάρος
- Τρεις ανεξάρτητοι πληθυσμοί
  - Framingham Offspring Study (n=1454 whites)
  - GOLDN Study (n=1078 whites)
  - Boston Puerto Rican Study (n=930 Hispanics of Carribean Origin)

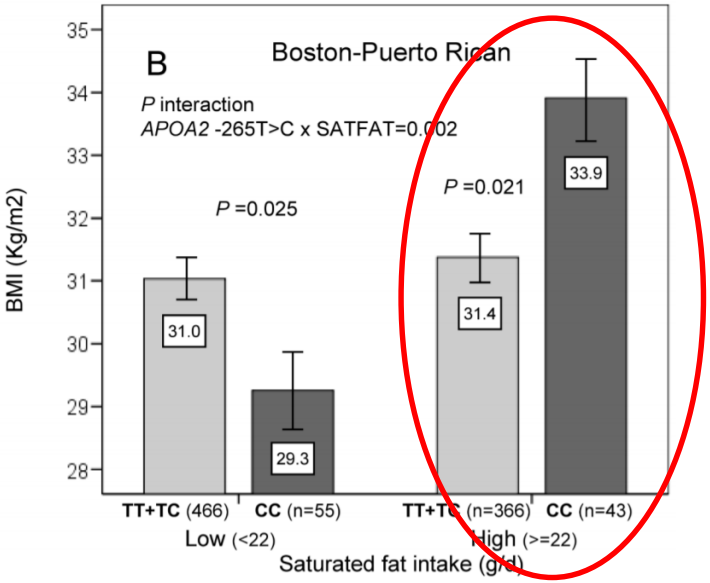
Corella et al, Arch Intern Med. 2009;169:1897–906

Διατροφογενετική της Παχυσαρκίας

APOA2 gene – rs5082 (-265T>C)







Αντίστοιχες αλληλεπιδράσεις και σε Μεσογειακούς & Ασιατικούς πληθυσμούς

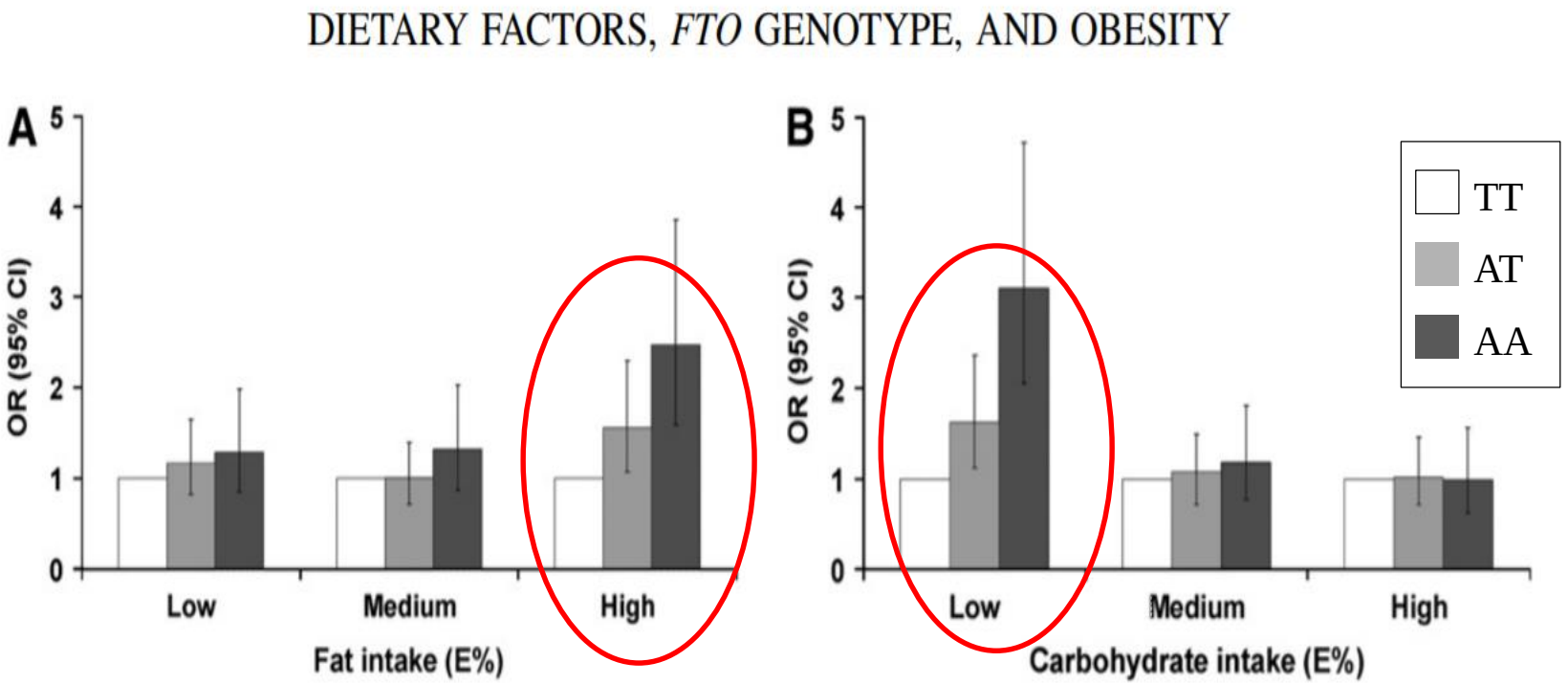
Corella et al, Int J Obes (Lond), 2011;35: 666–675

Corella et al, Arch Intern Med. 2009;169:1897–906

Διατροφογενετική της Παχυσαρκίας

FTO gene – rs9939609

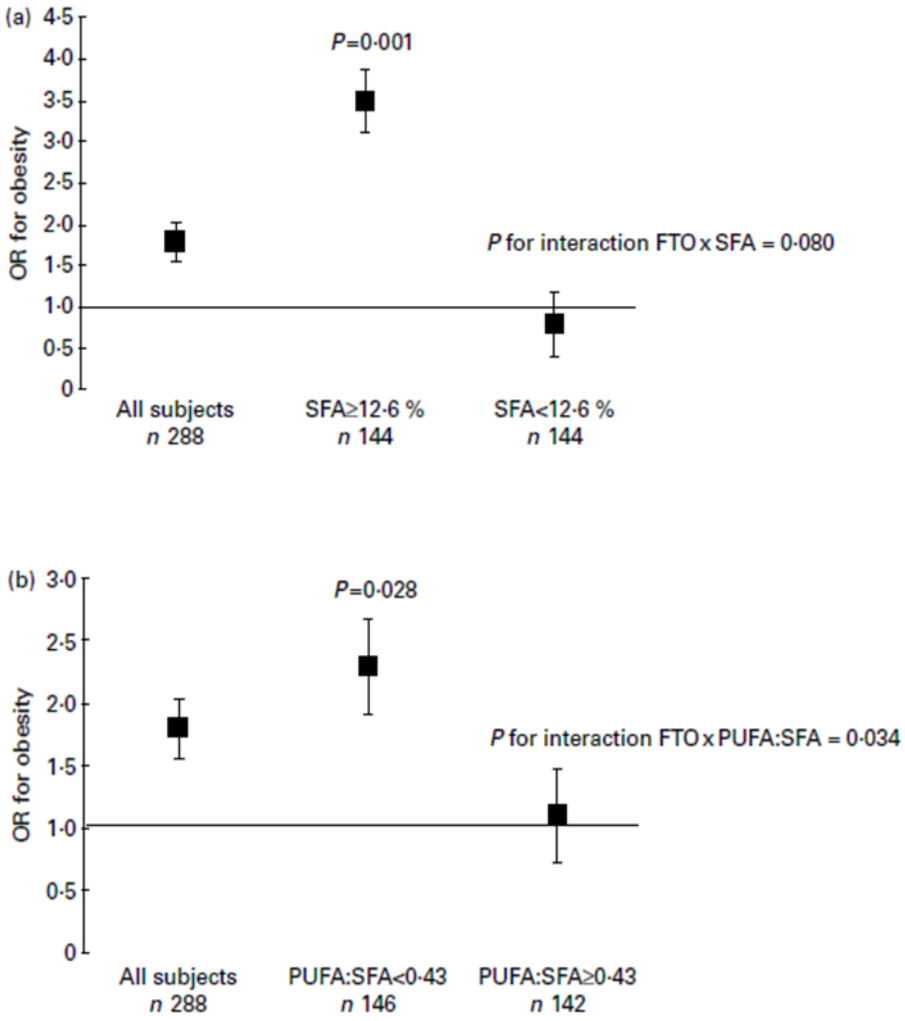
Μελέτη παρατήρησης (n=4839) → **σημαντικές αλληλεπιδράσεις μεταξύ rs9939609 & διαιτητικής πρόσληψης λίπους/υδατανθράκων στον κίνδυνο παχυσαρκίας**



Sonestedt et al, Am J Clin Nutr. 2009;90:1418-1425

Gene - Diet interactions & Obesity

- Spanish **case-control study** among children & adolescents evaluated whether dietary fatty acid intake modified the effect of the FTO rs9939609 (T>A) on risk of obesity.
- A total of 354 Spanish children and adolescents aged 6–18 ys (49% males)
- The risk allele carriers consuming >12.6% SFA (of total energy) had an increased obesity risk compared with TT carriers, but the increased risk was not observed among those with lower saturated fat intake.
- Similarly, A allele carriers with an PUFA:SFA intake ratio <0.43 presented a higher obesity risk than TT subjects.

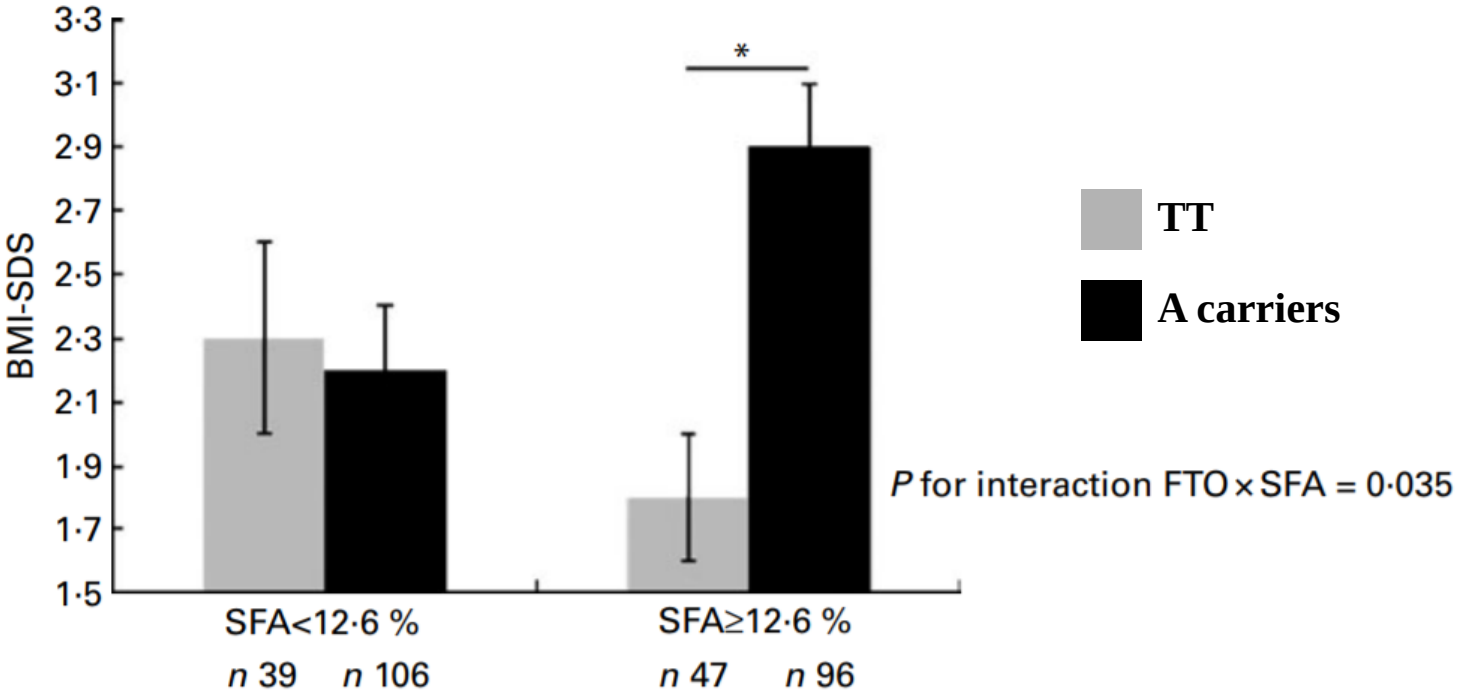


Moleres et al. Br J Nutr 2012

Διατροφογενετική της Παχυσαρκίας

FTO gene – rs9939609

Case control study (n=354) → **το κορεσμένο λίπος διαφοροποίησε την επίδραση του rs9939609 στον BMI & τον κίνδυνο παχυσαρκίας σε παιδιά & εφήβους**

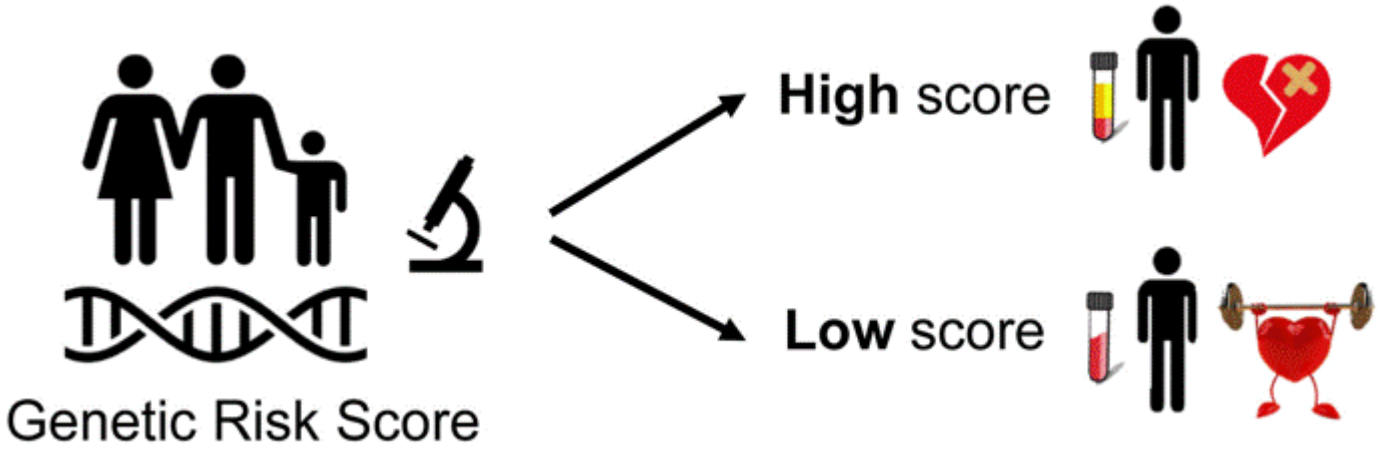


Moleres et al, Br J Nutr 2012;107:533-8

Genetic Risk Scores

- Although individual common polymorphisms have modest predictive capacity, their cumulative impact can be aggregated into a polygenic risk score (**Genetic Risk Score, GRS**)

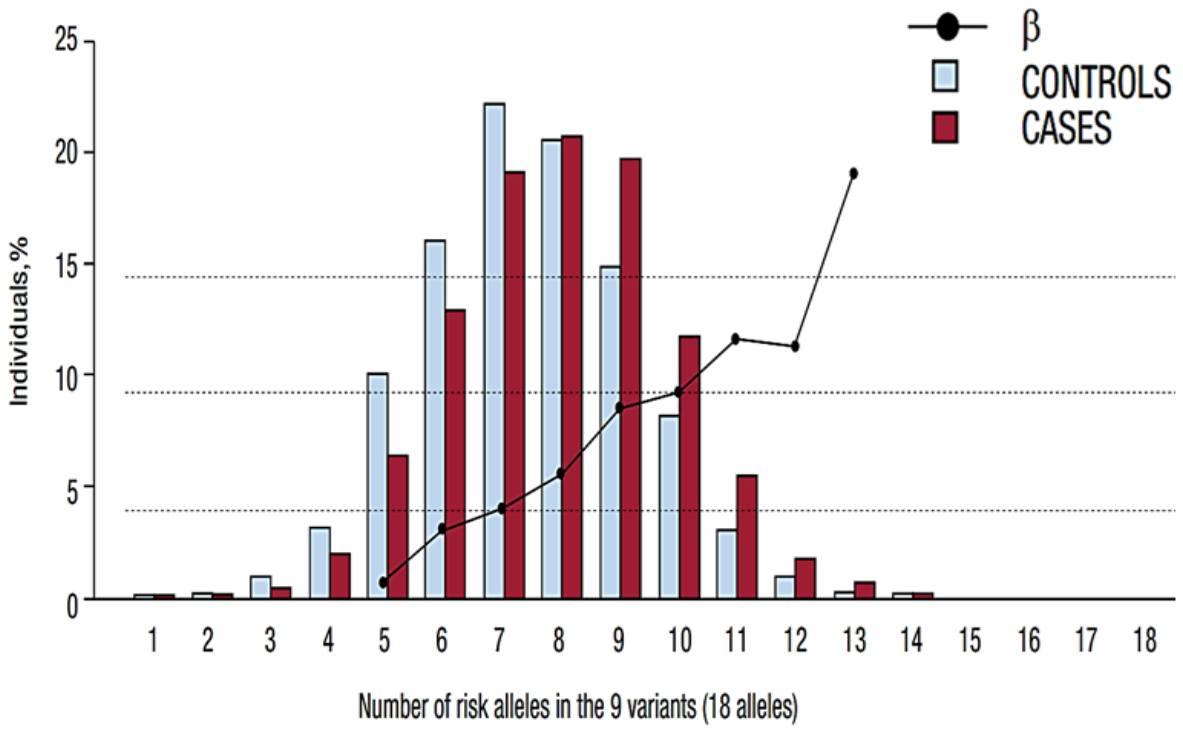
- A **GRS** serves as the best prediction for a trait that can be made when taking into account variation in multiple genetic variants.



Genetic Risk Scores

- Individuals are scored based on how many risk alleles they have for each variant (for example, 0, 1 or 2 copies) included in the GRS

- Weights are generally assigned to each genetic variant according to the strength of their association with disease risk (effect estimate)



Polygenic Risk Scores: *Utility for risk assessment & Treatment decisions*

- Prediction of disease risk is an essential part of preventative medicine, often guiding clinical management. Risk prediction typically includes risk factors such as age, sex, family history of disease and lifestyle (e.g. smoking status)
- Systematic cataloging for e.g. CVD risk alleles enabled the development of **Polygenic risk scores (PRS)** that provide a quantitative metric of an individual's inherited risk based on the cumulative impact of many common SNVs

Human Molecular Genetics, 2019, Vol. 28, No. R2 | **R137**

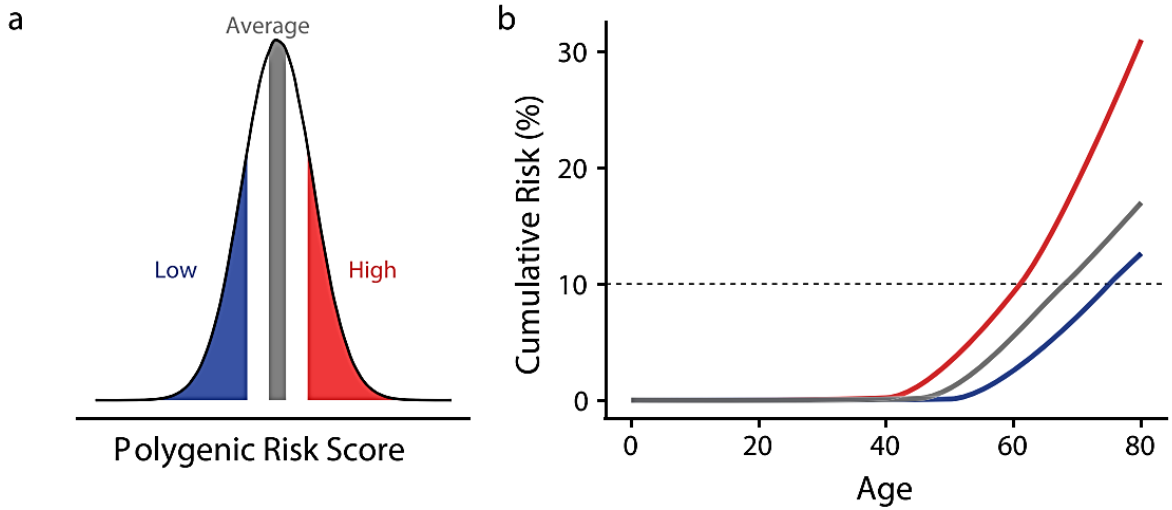


Figure 1. PRS define lifetime risk trajectories. (**a**) Example density plot of a population according to polygenic risk. The distribution is filled and labeled according to the lowest (0–20%; blue), population average (40–60%; grey) and highest (80–100%; red) quintiles of genetic risk. (**b**). Example of a risk trajectory (Kaplan–Meier cumulative risk curve) for the population average (grey) and the highest and lowest quintiles of genetic risk (colored as in a). Representative risk threshold is shown for example.

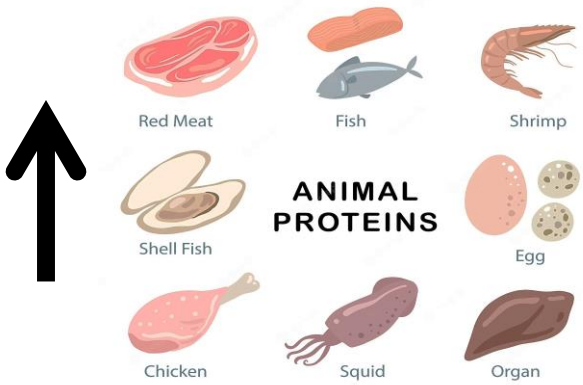
Διατροφογενετική της Παχυσαρκίας

Αλληλεπιδράσεις διατροφής – γενετικών πολυμορφισμών

Genetic Risk Score - GRS

16 πολυμορφισμοί που έχουν συσχετιστεί με παχυσαρκία & διαταραχές λιπιδίων ***(FTO, MC4R, PPARG, MTHFR, PLIN1, GCKR, APOA5, LIPG, LIPC, LPL, CELSR2, APOE, NOS3, CETP, PPARA)***

Άτομα με γενετική προδιάθεση για παχυσαρκία (υψηλό GRS)



↑ Σωματικό λίπος (%)

Goni et al, Genes Nutr 2015;10:1-10

Διατροφογενετική της Παχυσαρκίας

Αλληλεπιδράσεις διατροφής – γενετικών πολυμορφισμών

Genetic Risk Score - GRS

16 πολυμορφισμοί που έχουν συσχετιστεί με παχυσαρκία & διαταραχές λιπιδίων ***(FTO, MC4R, PPARG, MTHFR, PLIN1, GCKR, APOA5, LIPG, LIPC, LPL, CELSR2, APOE, NOS3, CETP, PPARA)***

Άτομα χαμηλού γενετικού κινδύνου για παχυσαρκία (χαμηλό GRS)

↓ Σωματικό λίπος (%)

Goni et al, Genes Nutr 2015;10:1-10

Διατροφογενετική της Παχυσαρκίας

Αλληλεπιδράσεις διατροφής – γενετικών πολυμορφισμών

Genetic Risk Score - GRS

GRS από 32 πολυμορφισμούς που έχουν συσχετιστεί με τον BMI

- Μελέτη σε δείγμα από τρεις μεγάλες μελέτες follow up
  - **Nurses' Health Study (NHS):** 18 χρ., 7000 άτομα
  - **Health Professionals Follow-up Study (HPFS):** 12 χρ., 4500 άτομα
  - **Women's Genome Health Study (WGHS)** : 6 χρ., 22000 άτομα

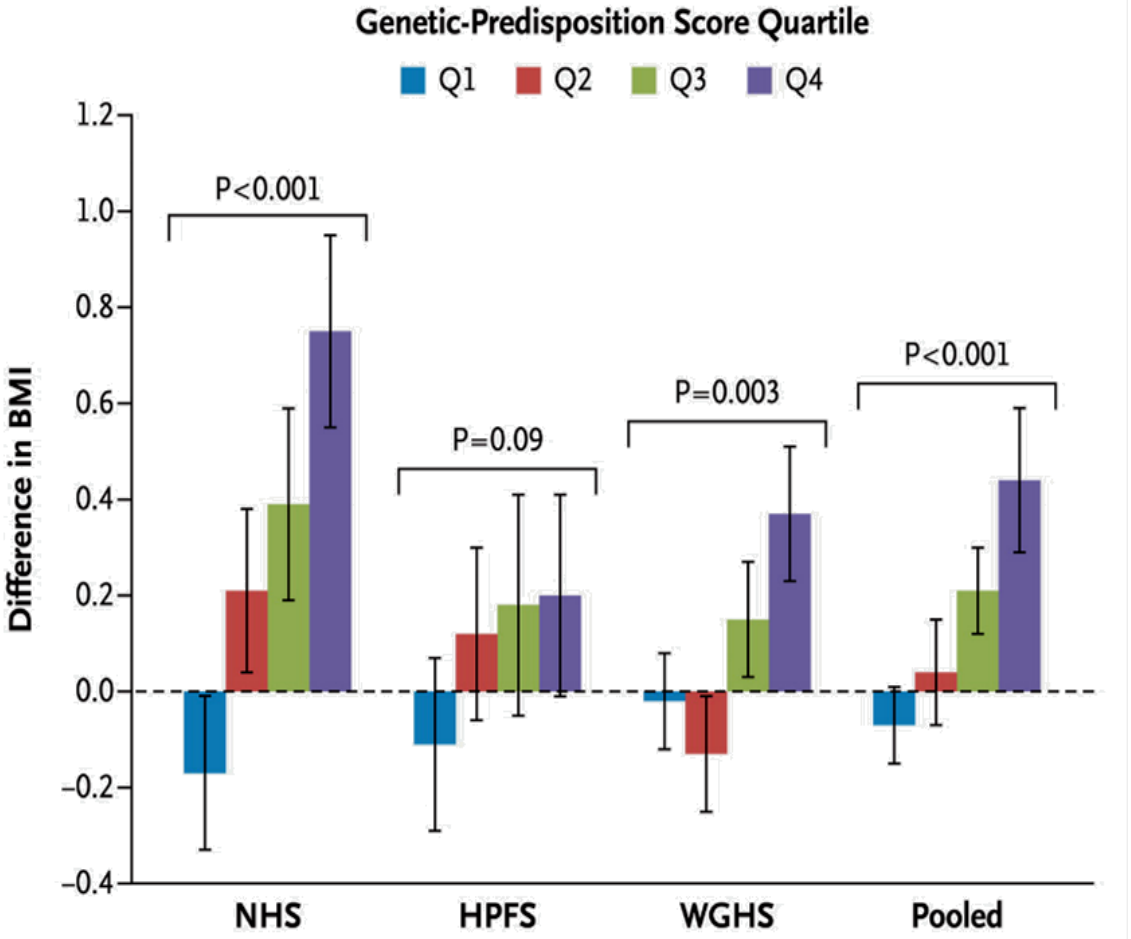
Outcome measure:
Repeated measurement of BMI over follow-up

Πρόσληψη σακχαρούχων ροφημάτων & κίνδυνος παχυσαρκίας ανάλογα με το GRS

Qi et al, N Engl J Med 2012;367:1387-96

Gene - Diet interactions & Obesity

- **Prospective** study (>32,000 men & women from 3 **cohort studies** in USA)
- Genetic risk score: based on 32-BMI associated variants
- Assessment of sugar-sweetened beverage intake (FFQs)
- Outcome measure: Repeated measurement of BMI over follow-up



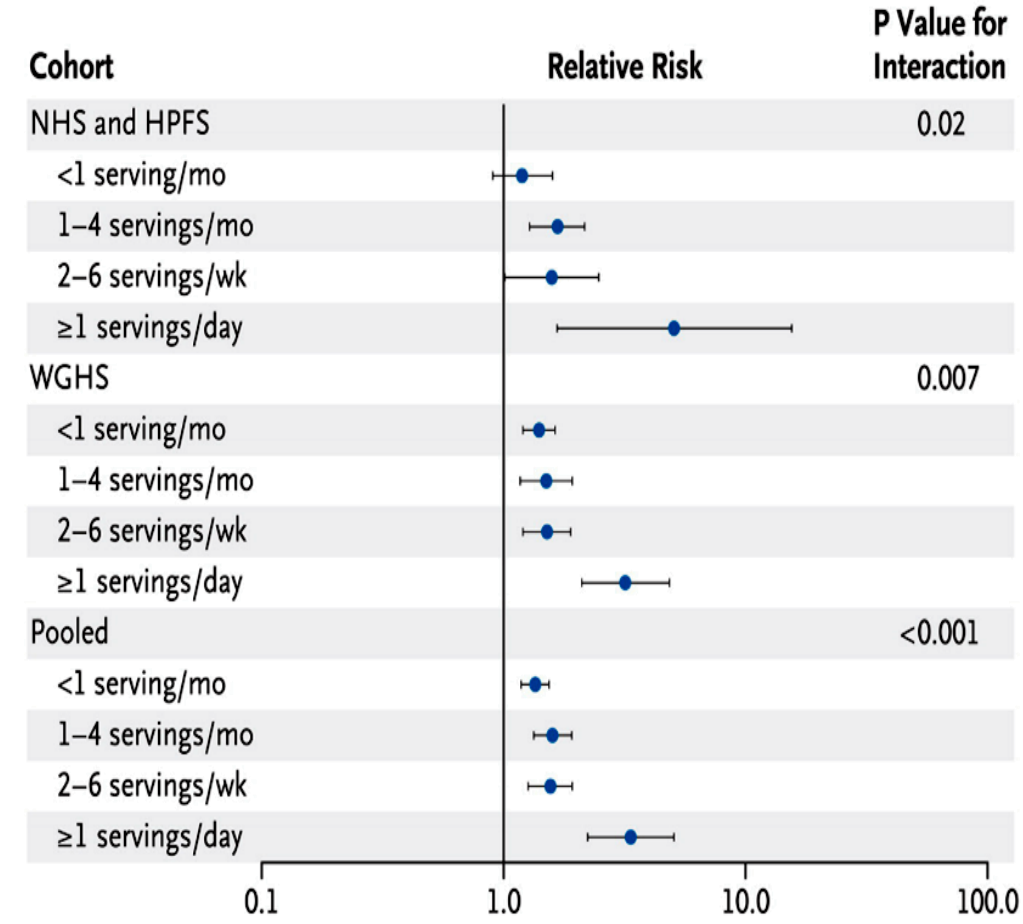
Όσο μεγαλύτερος ο γενετικός κίνδυνος, τόσο πιο έντονη επίδραση στον κίνδυνο παχυσαρκίας έχει η αυξημένη κατανάλωση σακχ. ροφημάτων

Qi et al, N Engl J Med 2012;367:1387-96

Gene - Diet interactions & Obesity

- Genetic association with adiposity was stronger among participants with higher intake of sugar-sweetened beverages than among those with lower intake

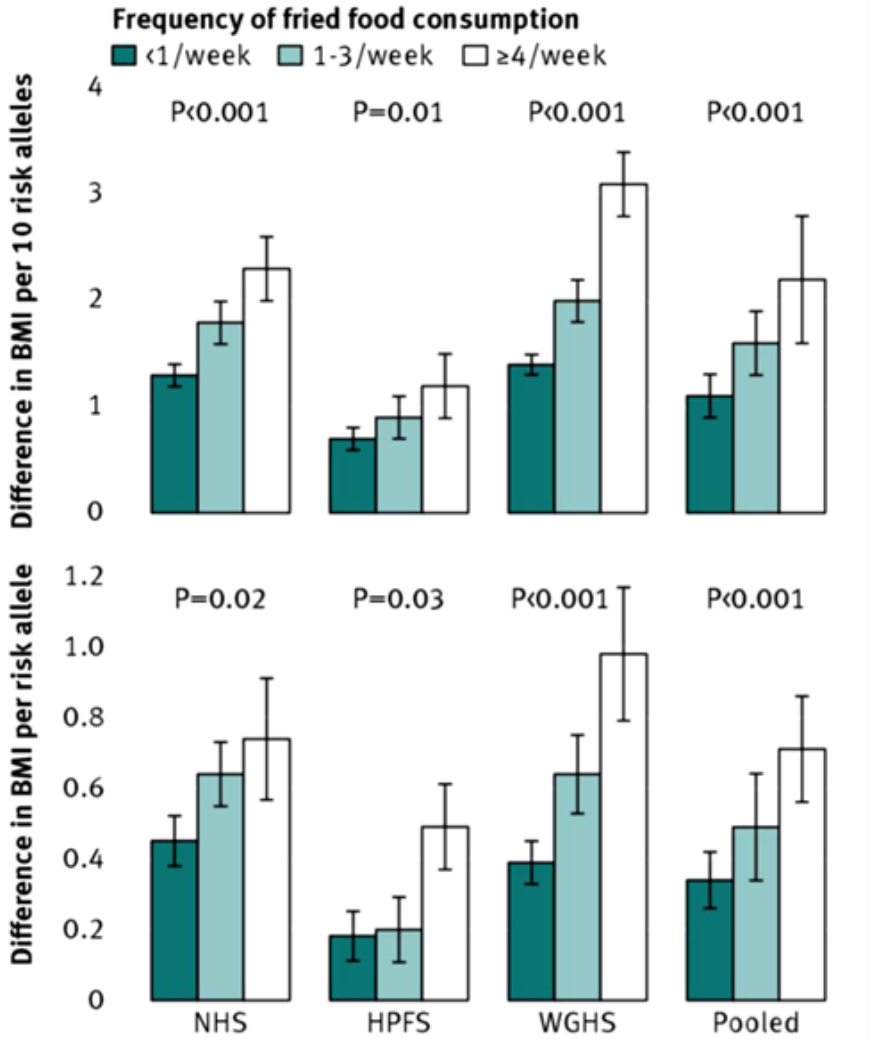
- ***Συμπέρασμα***: *Άτομα με γενετική προδιάθεση για παχυσαρκία πρέπει να αποφεύγουν την κατανάλωση αναψυκτικών τύπου cola*



RR of the development of obesity per increment of 10 risk-alleles, according to intake of sugar-sweetened beverages

Qi et al. *NEJM 2012*

Κατανάλωση τηγανητών τροφίμων & κίνδυνος παχυσαρκίας ανάλογα με το GRS

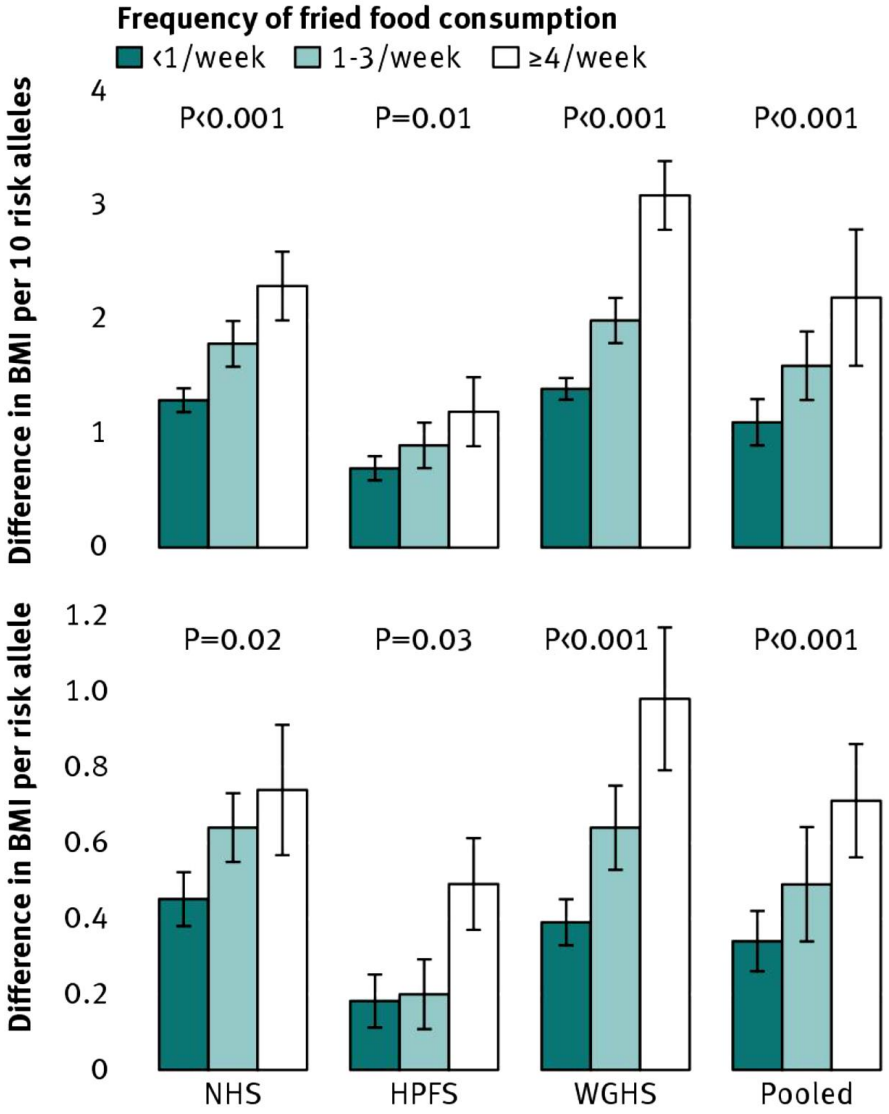


Όσο μεγαλύτερη η κατανάλωση τηγανητών τροφίμων, τόσο εντονότερη η σχέση μεταξύ γενετικού παράγοντα και παχυσαρκίας.

Qi et al, BMJ, 2014;348:g1610

Gene - Diet interactions & Obesity

- Assessment of fried foods & other dietary factors (FFQs)
- In the combined analysis, the differences in BMI per 10 risk alleles were 1.1±0.2, 1.6±0.3 & 2.2±0.6 for fried food consumption <1, 1-3/w & ≥4/w ($p_{interaction}$<0.001)
- These findings suggested that the genetic association with adiposity was strengthened with higher consumption of fried foods.
- ***Συμπέρασμα***: *Άτομα με γενετική προδιάθεση για παχυσαρκία πρέπει να αποφεύγουν την κατανάλωση τηγανητών φαγητών*



Qi et al. *BMJ 2014*

Διατροφογενετική της Παχυσαρκίας

Αλληλεπιδράσεις διατροφής – γενετικών πολυμορφισμών

Genetic Risk Score - GRS

- Genetics of Lipid Lowering Drugs and Diet Network (GOLDN)
- Multi-Ethnic Study of Atherosclerosis (MESA) population

Υψηλότερη κατανάλωση κορεσμένου λίπους

Συσχέτιση με μεγαλύτερο ΔΜΣ στα άτομα με αυξημένη γενετική προδιάθεση για παχυσαρκία **(↑ GRS)**

Casas-Agustench et al, J Acad Nutr Diet, 2014;114:1954-1966

Διατροφογενετική της Παχυσαρκίας

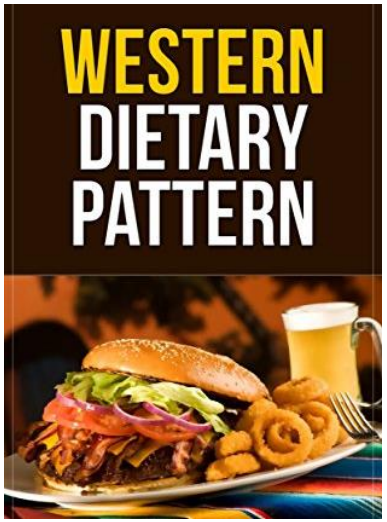
Αλληλεπιδράσεις διατροφής – γενετικών πολυμορφισμών

Σπάνια αλληλόμορφα:

- *MC4R*, rs12970134
- *APOC3*, rs5128
- *APOA1*, rs670, rs5069

+

↑ score



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Αυξημένος κίνδυνος μεταβολικού συνδρόμου (OR=1.71)

Hosseini-Efsahani et al, Br J Nutr, 2014;113:644-653
Ortega-Azorin et al, Cardiovasc Diabetol, 2012;11:137
Hosseini-Efsahani et al, J Nutrigenet Nutrigenomics, 2014;7:105-117

Διατροφογενετική της Παχυσαρκίας

Αλληλεπιδράσεις διατροφής – γενετικών πολυμορφισμών

Συνολικά, αυτά τα αποτελέσματα υποδηλώνουν ότι η συσσώρευση κοινών πολυμορφισμών σε γενετικούς τόπους που είναι γνωστό ότι επηρεάζουν το σωματικό βάρος μπορεί να επηρεάσει την προδιάθεση κάποιου να πάρει βάρος όταν εκτίθεται σε συγκεκριμένους τύπους δίαιτας ή διατροφικό πρότυπο

Toro-Martin et al, Nutrients, 2017;9:913

Διατροφογενετική της Παχυσαρκίας

Επίδραση γενετικής ποικιλομορφίας στη ρύθμιση του βάρους

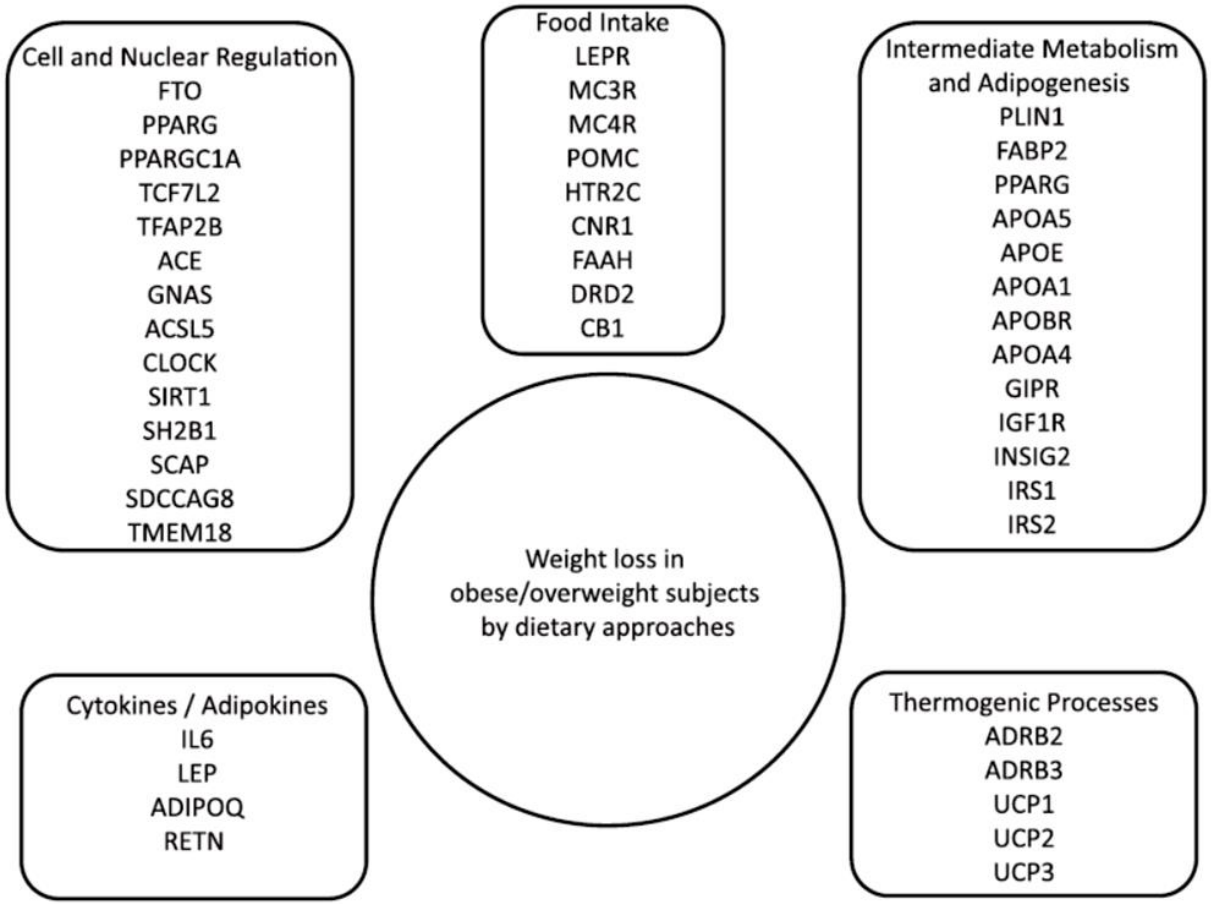


Fig. 2. Genes regulating metabolic functions in which there are polymorphisms that have been related to genetically mediated differences to dietary treatments seeking weight loss.

Martinez et al, Trends Food Sci Tech, 2015;42:97-115

Gene – Diet interactions & Obesity: Clinical Trials

ORIGINAL ARTICLE

FTO Genotype and 2-Year Change in Body Composition and Fat Distribution in Response to Weight-Loss Diets

The POUNDS LOST Trial

Xiaomin Zhang,[1,2] Qibin Qi,[1] Cuilin Zhang,[3] Steven R. Smith,[4] Frank B. Hu,[1,5] Frank M. Sacks,[1,5] George A. Bray,[6] and Lu Qi[1,5]

- FTO rs1558902`(T>A) was genotyped in 742 obese adults who were randomly assigned to one of 4 diets differing in the proportions of fat, protein & CHO.
- Body composition and fat distribution were measured by DXA & computed tomography.
- Found significant modification effects for intervention varying in dietary protein on 2-year changes in FFM, %FM, total adipose tissue mass, visceral adipose tissue mass & superficial adipose tissue mass (all $P_{interactions}<0.05$).

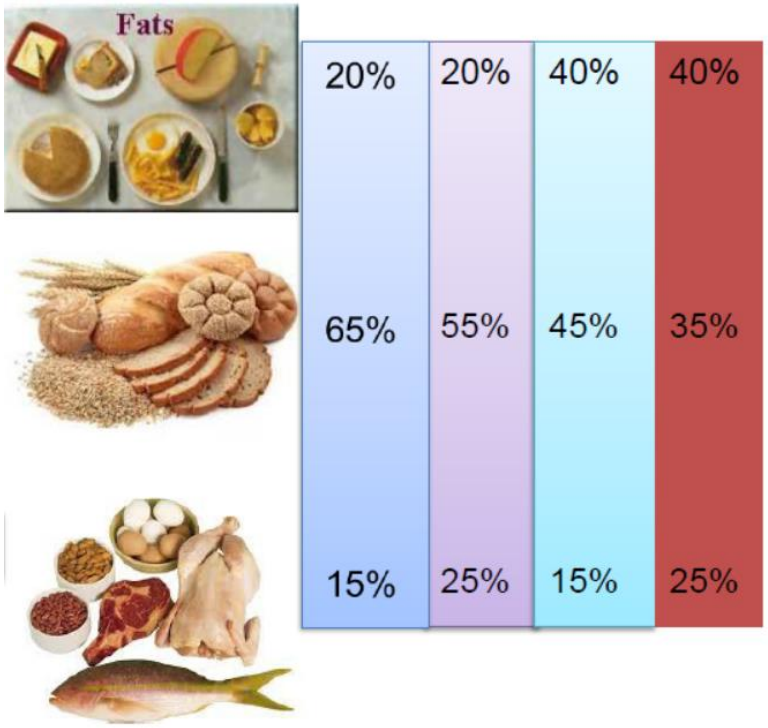
Zhang et al. *Diabetes 2012*

Γονίδια που ρυθμίζουν την πρόσληψη ενέργειας/τροφής

FTO gene – rs1558902

POUNDS LOST trial:

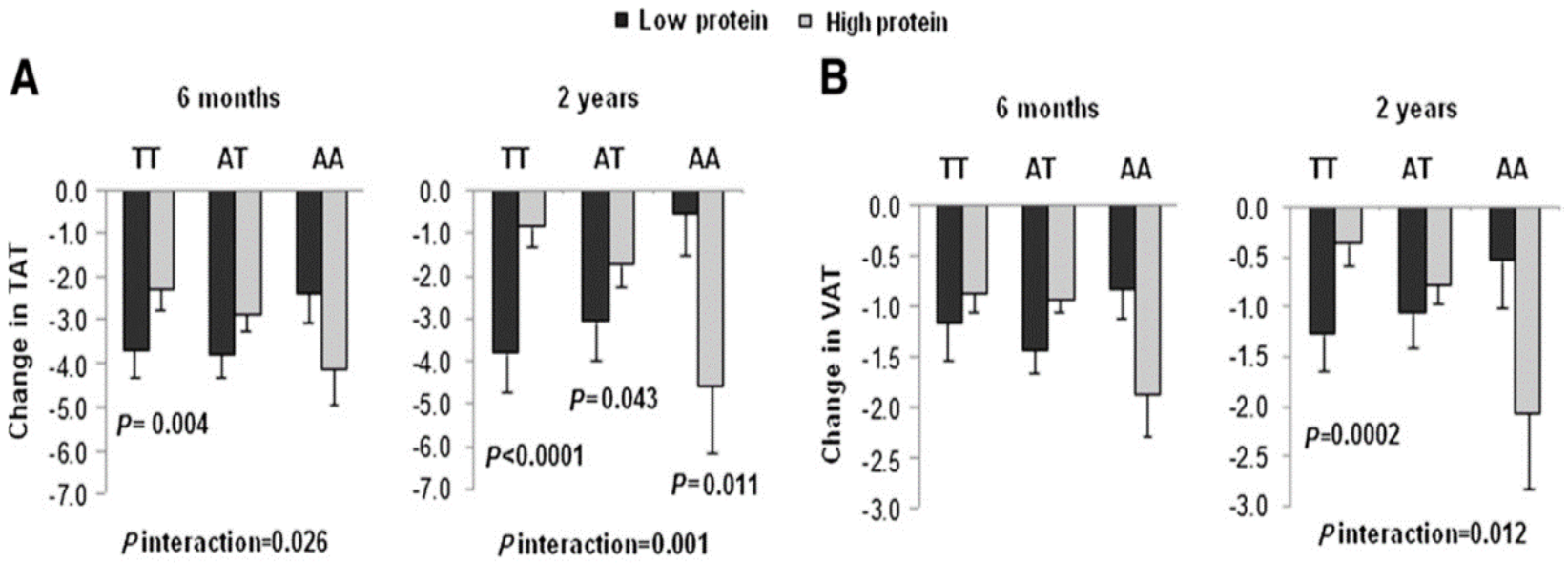
- 2 χρόνια RCT για τη σύγκριση των επιδράσεων στο σωματικό βάρος υποθερμιδικών διαιτών με διαφορετικές συστάσεις μακροθρεπτικών συστατικών
- 811 υπέρβαροι/παχύσαρκοι ενήλικες τοποθετήθηκαν τυχαία στις 4 ομάδες διαιτών με διαφορετική σύσταση



Zhang et al, Diabetes, 2012;61:3005-11

Gene – Diet interactions & Obesity: Clinical Trials

- Carriers of the A-risk allele of the FTO variant rs1558902 had a greater reduction in weight, body composition & fat distribution in response to a high-protein diet, whereas an opposite genetic effect was observed on changes in fat distribution in response to a low-protein diet.



- **Conclusion**: A high-protein diet may be beneficial for weight loss and improvement of body composition and fat distribution in individuals with the risk allele A of the FTO rs1558902 SNP.

Zhang et al. *Diabetes 2012*

Γονίδια που ρυθμίζουν την πρόσληψη ενέργειας/τροφής

FTO gene – rs1558902

Φορείς του Α αλληλομόρφου κινδύνου παρουσίαζαν μεγαλύτερη μείωση του σωματικού βάρους & λίπους όταν ακολουθούσαν δίαιτα υψηλή σε πρωτεΐνη.

Μία δίαιτα υψηλή σε πρωτεΐνη μπορεί να βοηθά στην απώλεια βάρους σε άτομα που φέρουν αυτό το αλληλόμορφο κινδύνου για παχυσαρκία.

TABLE 2
The effects of the *FTO* rs1558902 genotype on weight, body composition, and fat distribution response to dietary protein intervention

	At 6 months			At 24 months		
	β*	SE	*P*	β*	SE	*P*
Low protein†						
Weight, kg	−0.11	0.46	0.807	0.07	0.65	0.914
WC, cm	0.02	0.48	0.971	−0.31	0.69	0.654
Body composition						
Total fat, kg	0.29	0.47	0.544	0.73	0.84	0.381
FFM, kg	0.54	0.25	**0.029**	0.64	0.45	0.150
FM%	−0.01	0.32	0.983	0.36	0.48	0.455
Trunk fat %	0.09	0.43	0.840	0.41	0.61	0.495
Fat distribution						
TAT	0.53	0.47	0.260	2.11	0.65	**0.001**
VAT	−0.01	0.22	0.949	0.35	0.29	0.223
DSAT	0.27	0.20	0.164	0.31	0.24	0.211
SAT	0.61	0.29	**0.040**	1.46	0.42	**0.0004**
High protein‡						
Weight, kg	−0.33	0.43	0.434	−1.51	0.58	**0.010**
WC, cm	0.04	0.46	0.933	−0.68	0.62	0.270
Body composition						
Total fat, kg	−0.80	0.43	0.061	−1.60	0.63	**0.011**
FFM, kg	−0.49	0.23	**0.031**	−0.63	0.30	**0.035**
FM%	−0.46	0.29	0.112	−1.13	0.41	**0.006**
Trunk fat %	−0.54	0.39	0.162	−1.42	0.54	**0.009**
Fat distribution						
TAT	−0.72	0.32	**0.024**	−1.31	0.55	**0.017**
VAT	−0.43	0.13	**0.001**	−0.64	0.24	**0.007**
DSAT	−0.09	0.12	0.425	−0.10	0.20	0.625
SAT	−0.24	0.19	0.215	−0.58	0.31	0.059

Boldface *P* values indicate statistical significance. *β represents change in each trait for each A allele of the *FTO* genotype. Values calculated

Zhang et al, Diabetes, 2012;61:3005-11

Γονίδια που ρυθμίζουν την πρόσληψη ενέργειας/τροφής

FTO gene – rs1558902

- Εξετάστηκε εάν η διαιτητική πρωτεΐνη τροποποιεί τη σχέση μεταξύ του ***FTO* rs1558902** με τον **ΔΜΣ & την περιφέρεια μέσης** σε νεαρούς ενήλικες Ασιάτες.

"These findings suggest that high dietary protein intake may protect against the effects of risk variants in the FTO gene on BMI and waist circumference".

Merrittet al, Genes & Nutr, 2018;13:4

Γονίδια που ρυθμίζουν την πρόσληψη ενέργειας/τροφής

FTO gene – rs9939609

- **Weight loss trial**
  (δίαιτα **υψηλής πρωτεΐνης/χαμηλής σε υδατάνθρακες** συγκριτικά με μια συνήθη υποθερμιδική δίαιτα 1,000 kcal/day)

de Luis al, J Nutrigenet Nutrigenomics, 2015;8:128-36

Γονίδια που ρυθμίζουν την πρόσληψη ενέργειας/τροφής

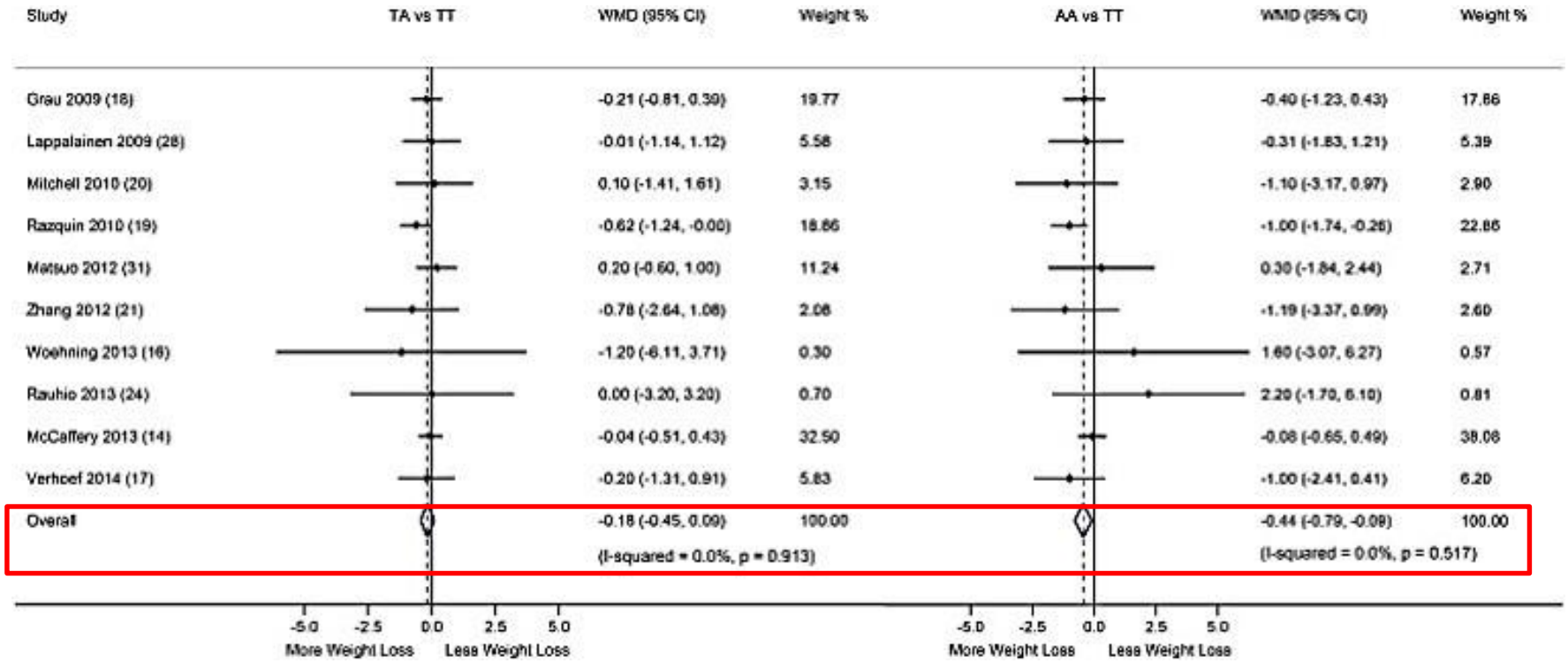
***FTO* gene**

Δίαιτες με υψηλή περιεκτικότητα σε πρωτεΐνη μπορεί να περιορίζουν σημαντικά τη γενετική προδιάθεση για παχυσαρκία που οφείλεται στο γονίδιο *FTO*, βελτιώνοντας έτσι την καρδιαγγειακή υγεία

Γονίδια που ρυθμίζουν την πρόσληψη ενέργειας/τροφής

FTO genotype and weight loss in diet and lifestyle interventions: a systematic review and meta-analysis[1,2]

*Lingwei Xiang,[3] Hongyu Wu,[4] An Pan,[5] Bhakti Patel,[3] Guangda Xiang,[6] Lu Qi,[4,7] Robert C Kaplan,[3] Frank Hu,[4,7] Judith Wylie-Rosett,[3] and Qibin Qi[3]**



Οι ομοζυγώτες για το επικίνδυνο για παχυσαρκία *FTO* rs9939609 αλληλόμορφο ενδέχεται να χάσουν περισσότερο βάρος μέσω παρεμβάσεων διατροφής/τρόπου ζωής από ό,τι οι μη φορείς

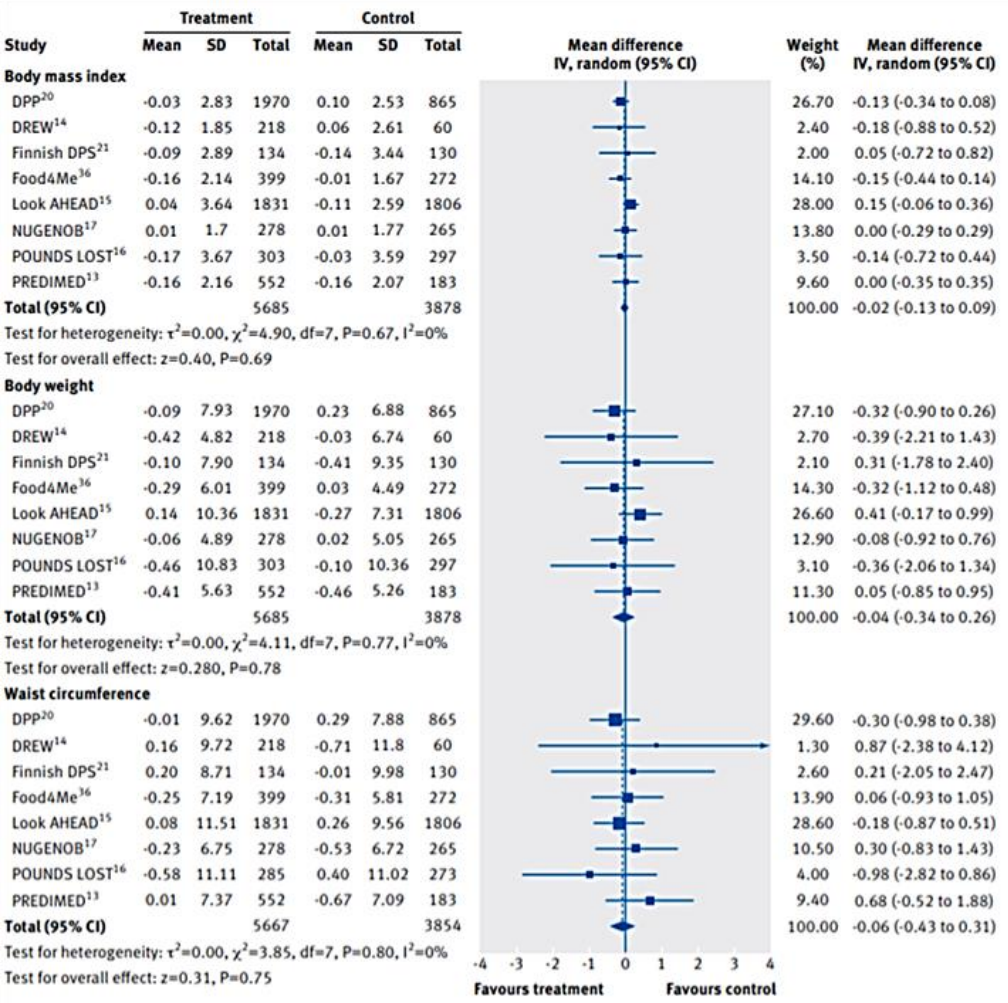
Xiang et al, Am J ClinNutr, 2016;103:1162–70

Γονίδια που ρυθμίζουν την πρόσληψη ενέργειας/τροφής

FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials

Katherine M Livingstone,[1,2] Carlos Celis-Morales,[1,3] George D Papandonatos,[4] Bahar Erar,[4] Jose C Florez,[5,6] Kathleen A Jablonski,[7] Cristina Razquin,[8,9] Amelia Marti,[9,10] Yoriko Heianza,[11] Tao Huang,[11,12] Frank M Sacks,[13] Mathilde Svendstrup,[14,15] Xuemei Sui,[16] Timothy S Church,[17] Tiina Jääskeläinen,[18,19] Jaana Lindström,[20] Jaakko Tuomilehto,[21,22] Matti Uusitupa,[18] Tuomo Rankinen,[23] Wim H M Saris,[24] Torben Hansen,[14] Oluf Pedersen,[14] Arne Astrup,[25] Thorkild I A Sørensen,[14,26] Lu Qi,[11,13] George A Bray,[17] Miguel A Martinez-Gonzalez,[9,10] J Alfredo Martinez,[9,10,27] Paul W Franks,[13,28] Jeanne M McCaffery,[29] Jose Lara,[1,30] John C Mathers[1]

Οι φορείς του *FTO rs9939609* αλληλομόρφου κινδύνου, δεν είχαν μεγαλύτερες βελτιώσεις σε ΔΜΣ, σωματικό βάρος, περιφέρεια μέσης μετά από παρεμβάσεις μείωσης βάρους

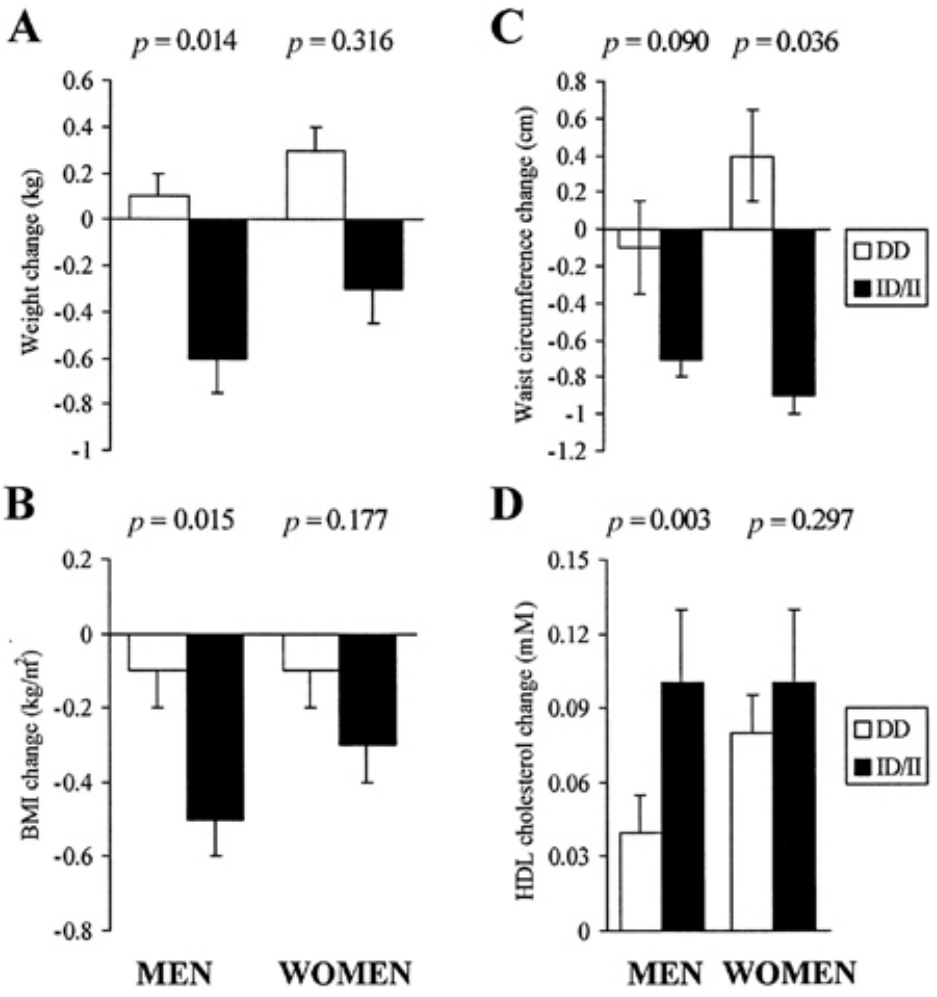


Livingston et al, BMJ 2016;354:i4707

Γονίδια που ρυθμίζουν την πρόσληψη ενέργειας/τροφής

LEPR gene
3'UTR pentanucleotide I/D polymorphism

Οι φορείς του αλληλομόρφου **I** είχαν μεγαλύτερες μειώσεις σε ΔΜΣ, σωματικό βάρος, περιφέρεια μέσης, συγκριτικά με τους **DD** ομοζυγώτες, μετά από παρέμβαση 3 χρόνων για τη μείωση βάρους



Zacharova et al, Obes Res, 2005;13:501-6

Gene - Diet interactions & Obesity

Summary of selected intervention & cohort studies on gene-diet interactions during the past 5-years.

Author	Study design	Genetic markers	Main findings
Qi et al. 2011 [42]	Two years, intervention, n=738	*IRS* rs2943641	*IRS1* genetic variants modified effects of dietary carbohydrate on weight loss
Mattei et al. 2012 [43]	Two years, intervention, n=591	*TCF7L2* rs7903146	Dietary fat intake modified effect of *TCF7L2* genotype on changes in BMI, total fat mass, and trunk fat mass
Qi et al. 2012 [44]	Two years, intervention, n=737	*GIPR* rs2287019	Dietary carbohydrate modified *GIPR* genotype effects on changes in body weight
Xu, et al. 2013 [23]	Two years, intervention, n=734	*PPM1K* rs1440581	Dietary fat modified genetic effects on changes in weight
Alsaleh et al, 2013 [25]	One year, intervention, n=367	*ADIPOQ* rs2241766	A diet high in n-3 polyunsaturated fatty acids modified the effects of rs2241766 on risk of obesity
Knoll et al 2012 [27]	One year, intervention, n=453	*FAAH* rs324420	The *FAAH* rs324420 AA/AC is not associated with weight loss in a 1-year lifestyle intervention for obese children and adolescents
de Luis et al, 2013 [26]	Three months intervention, n=305	*FTO* rs9939609	Metabolic improvement secondary to weight loss was better in A carriers with a low fat hypocaloric diet
Lai et al 2013 [45]	Four weeks intervention, n=88	*Visfatin* rs4730153	*Visfatin* rs4730153 homozygous GG Genotype may affect glucose and lipid metabolism in obese children and adolescents by reducing total triglyceride level and increasing insulin sensitivity to exercise
Qi et al 2012 [8]	Cohorts (NHS, HPFS, WGHS)	BMI-GRS	The genetic association with adiposity was stronger among participants with higher intake of sugar-sweetened beverages than among those with lower intake.
Qi et al 2012 [21]	Cohorts (NHS, HPFS)	BMI-GRS	Sedentary lifestyle may accentuate the predisposition to elevated adiposity, whereas greater leisure time physical activity may attenuate the genetic association.
Qi et al 2014 [6]	Cohorts (NHS, HPFS, WGHS)	BMI-GRS	Participants in the highest risk groups for both fried food and GRS had the highest BMI overall. Eating fried food more than four times a week had twice the effect on BMI for those in the highest third of GRS than those in the lowest third.

GRS: genetic risk score, NHS: the Nurses' Health Study, HPFS: the Health Professionals Follow-up Study, WGHS, the Women's Genome Health Study.
The GRS was calculated on the basis of 32 established BMI-associated variants.

Huang & Hu, BMC Medical Genomics 2015

Gene – Diet interactions & T2DM

- **PREDIMED study**: Case-control study in 7,052 high CVD subjects (3,430 T2DM cases & 3,622 non-diabetics) with no differences in BMI.
- **AIM**: To investigate whether MC4R rs17782313 & FTO rs9939609 associations with T2DM & BMI are modulated by MedDiet.
- Neither of the SNPs was associated with T2DM. However, there were consistent gene-diet interactions with adherence to the MedDiet both for FTO-rs9939609, MC4R-rs17782313 & their aggregate score ($P_{\text{-interaction}}$<0.05). These gene-diet interactions remained significant even after adj. for BMI.
- **Conclusion**: When adherence to the MedDiet was low, the obesity risk alleles were associated with T2DM regardless of BMI.

	Adherence to the Mediterranean diet				
	Low (<9 points)		High (>=9 points)		P^2 interaction
	OR	95% CI	OR	95% CI	Gene x AMD
***FTO* rs9939609** (n=7,052)					0.039
TT	1.00	(reference)	1.00	(reference)	
TA + AA	1.21	(1.03-1.40)	0.97	(0.85-1.13)	
	P^1=0.019		P^1=0.673		
MC4R rs17782313 (n=7,019)					0.009
TT	1.00	(reference)	1.00	(reference)	
TC + CC	1.17	(1.01-1.36)	0.89	(0.78-1.02)	
	P^1=0.035		P^1=0.097		
Aggregate score (*FTO/MC4R*)					0.006
TT and TT (0)	1.00	(reference)	1.00	(reference)	
TA or TC (1)	1.26	(1.05-1.56)	0.89	(0.75-1.07)	
TA and TC or AA or CC (2)	1.29	(1.05-1.59)	0.96	(0.79-1.16)	
Otherwise (3 or 4 variants)	1.45	(1.10-1.93)	0.86	(0.66-1.12)	
	P^1=0.024		P^1=0.532		
*Variant allele effects***					0.012
(Per variant allele: 1,2,3,or 4)	1.12	(1.03-1.21)	0.97	(0.91-1.05)	
	P^1=0.005		P^1=0.475		

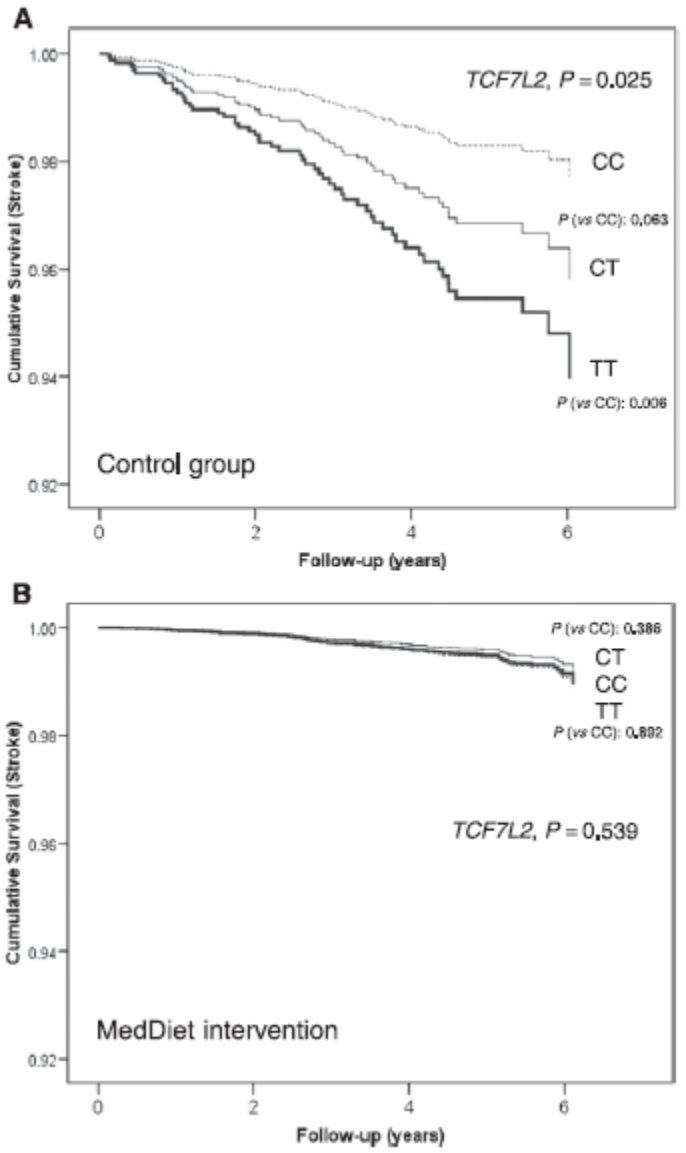
Ortega-Azorín et al. Cardiovascular Diabetology 2012

Gene – Diet interactions & CVD risk factors & Stroke

- **PREDIMED study**: Investigated whether the TCF7L2-rs7903146 (C>T) SNP associations with T2DM, glucose, lipids, & CVD incidence were modulated by MedDiet.

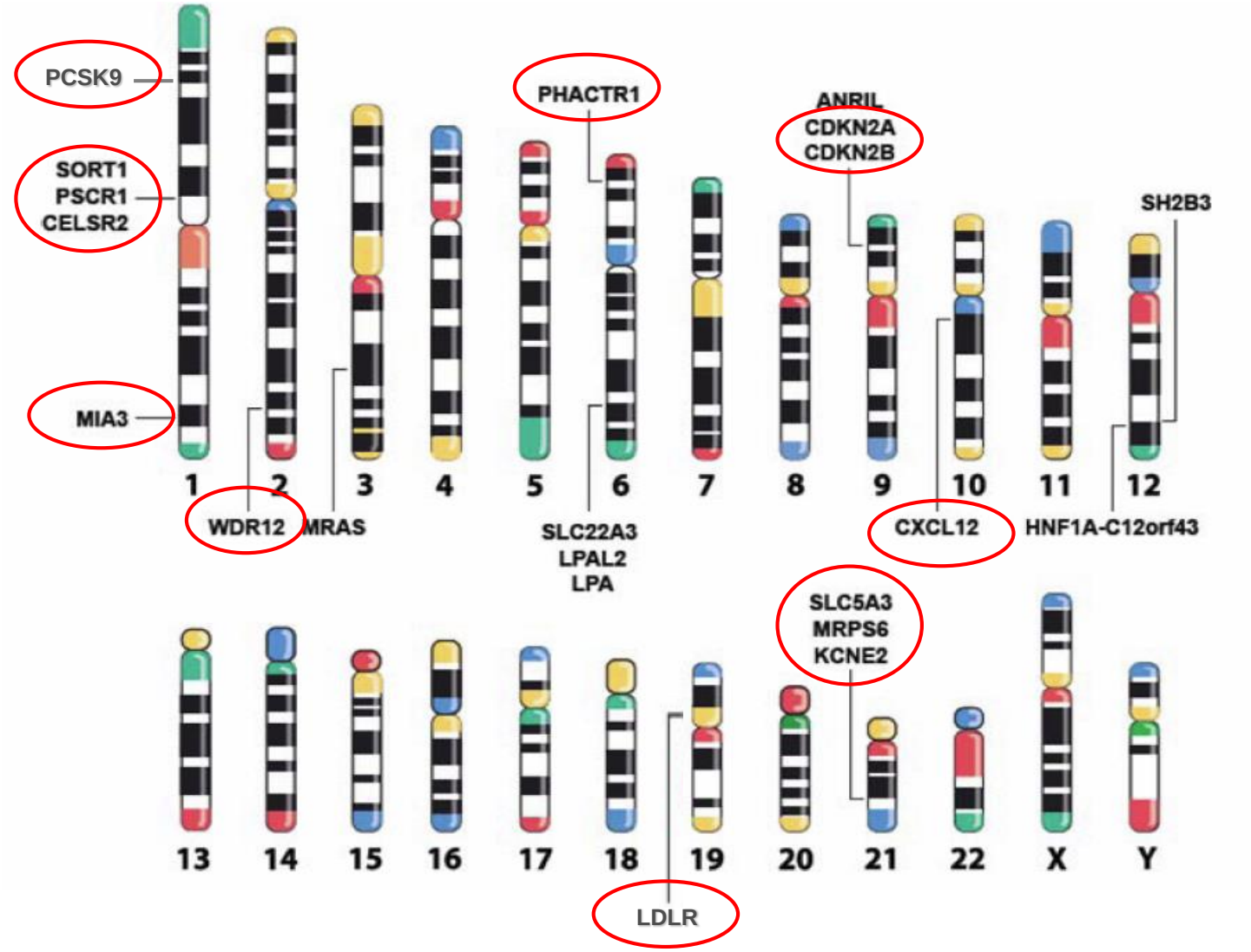
- TCF7L2 was associated with T2DM (TT vs. CC: OR=1.87; 95%CI=1.62-2.17).
- Adherence to MedDiet was found to interact with the TCF7L2 in relation to fasting glucose, TC, LDL & TGL ($P_{interaction}$<0.05). When adherence to MedDiet was low, TT participants had higher fasting glucose & lipids than C allele carriers, but when adherence was high these differences were not apparent.
- TT subjects had a higher stroke incidence in the control group compared with CC, whereas the dietary intervention with MedDiet was associated with reduced stroke incidence in TT but not CC homozygotes.

- **Conclusion**: MedDiet may not only reduce increased fasting glucose & lipids in TT individuals, but also stroke incidence.



Corella et al. Diabetes Care 2013

ΕΠΙΚ-ΕΛΛΑΣ: Γονίδια/SNPs & Καρδιαγγειακός κίνδυνος



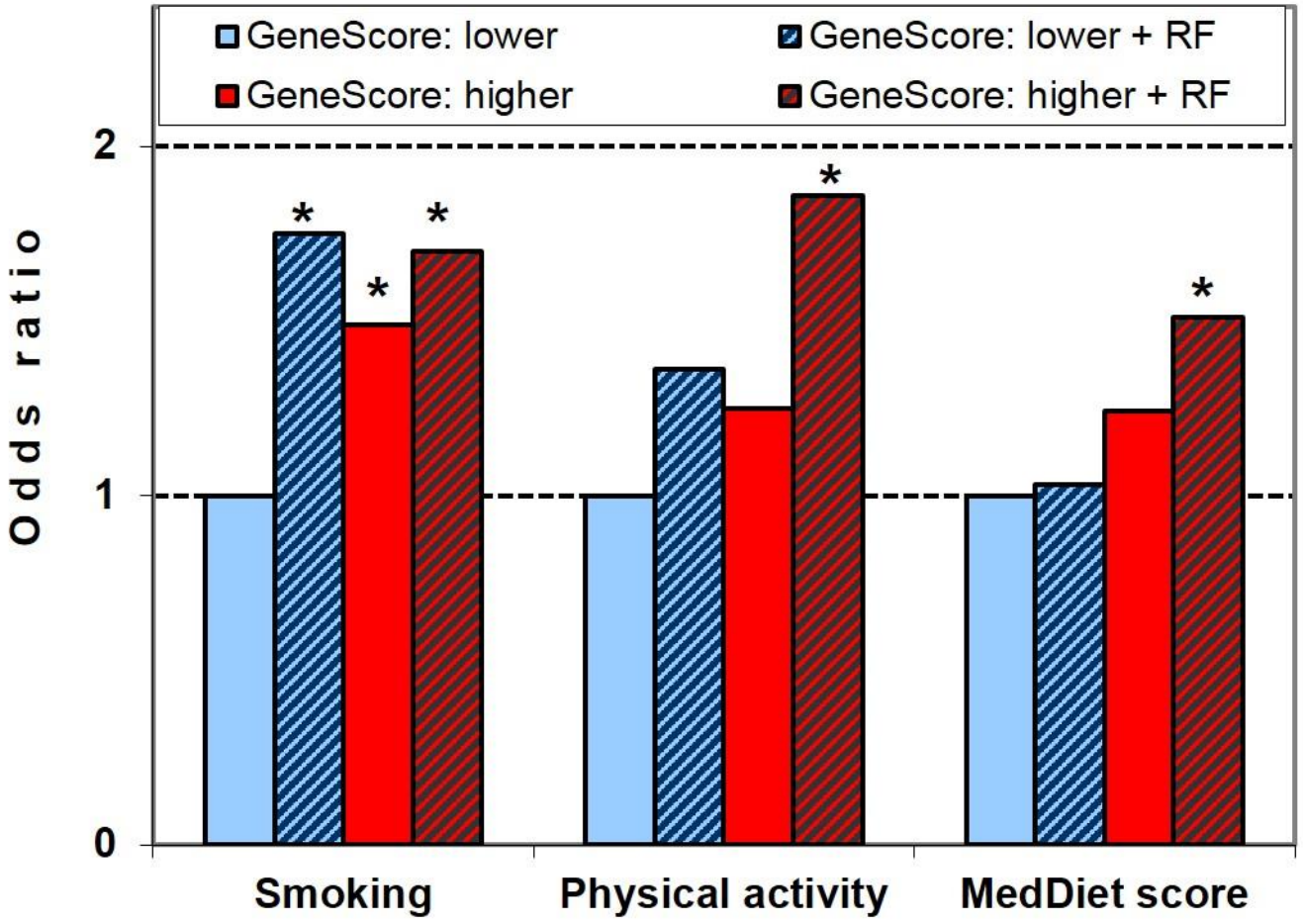
ΕΠΙΚ-ΕΛΛΑΣ: Συσχέτιση γενετικού σκορ & καρδιαγγειακού κινδύνου

Yiannakouris et al. *Atherosclerosis 2012*

	Genetic risk Score quintile					*p-value* for trend
	1st (ref)	2nd	3rd	4th	5th	
Genetic risk Score values	<10.57	10.57-11.79	11.80-12.93	12.94-14.13	>14.13	
Coronary Heart Disease						
Cases/Controls, (n)	77 / 273	88 / 280	98 / 258	108 / 281	123 / 253	
OR (95%CI)	1.00	1.10 (0.78-1.57)	1.36 (0.96-1.92)	1.37 (0.98-1.92)	1.74 1.25-2.43)	0.0004
Stroke						
Cases/Controls, (n)	51 / 273	71 / 280	63 / 258	73 / 281	62 / 253	
OR (95%CI)	1.00	1.37 (0.91-2.05)	1.28 (0.85-1.93)	1.39 (0.93-2.08)	1.36 (0.90-2.06)	0.188

ΕΠΙΚ-ΕΛΛΑΣ: Συσχέτιση Γενετικού & Μεσογειακού σκορ με τον καρδιαγγειακό κίνδυνο

Yiannakouris et al. *BMJ Open 2014*



Gene – Diet interaction & CVD

Genetic susceptibility to dyslipidemia and incidence of cardiovascular disease depending on a diet quality index in the Malmö Diet and Cancer cohort.

- 24,799 participants (62 % women, age 44-74 years) from the Malmö Diet and Cancer cohort. During a mean follow-up time of 15 years, 3068 incident CVD cases (1814 coronary and 1254 ischemic stroke) were identified.
- Genetic risk scores (GRSs) were constructed by combining 80 validated genetic variants associated with higher TG and LDL-C or lower HDL-C.
- The participants' dietary intake, assessed by a modified diet history method, was ranked according to a diet quality index that included six dietary components: saturated fat, polyunsaturated fat, fish, fiber, fruit and vegetables, and sucrose.

Hellstrand et al. Genes Nutr. 2016

Gene – Diet interaction & CVD

- The GRSLDL-C (P = 5 × 10(-6)) and GRSHDL-C (P = 0.02) but not GRSTG (P = 0.08) were significantly associated with CVD risk. No significant interaction between the GRSs and diet quality was observed on CVD risk (P > 0.39).
- A high compared to a low diet quality attenuated the association between GRSLDL-C and the risk of incident ischemic stroke (P interaction = 0.01).

Table 2 HR in strata of diet quality index on incident CVD, coronary event, and ischemic stroke

	Diet quality index			*P* interaction[a]
	Low	Medium	High	
	n = 3360	*n* = 15,538	*n* = 2833	
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	
Total CVD	530 cases	2186 cases	352 cases	
$GRS_{LDL\text{-}C}$	1.11 (1.02–1.21)	1.09 (1.04–1.14)	1.07 (0.96–1.19)	0.39 (0.86)[b]
$GRS_{HDL\text{-}C}$	1.08 (0.99–1.18)	1.03 (0.99–1.07)	1.10 (0.99–1.22)	0.85 (0.58)
GRS_{TG}	1.02 (0.93–1.11)	1.03 (0.99–1.08)	1.05 (0.95–1.17)	0.86 (0.20)
Coronary event	Cases *n* = 313	Cases *n* = 1285	Cases *n* = 216	
$GRS_{LDL\text{-}C}$	1.13 (1.01–1.26)	1.08 (1.02–1.14)	1.15 (1.01–1.32)	0.33 (0.08)
$GRS_{HDL\text{-}C}$	1.02 (0.91–1.14)	1.03 (0.97–1.08)	1.11 (0.97–1.27)	0.35 (0.78)
GRS_{TG}	1.06 (0.95–1.19)	1.06 (1.01–1.12)	1.09 (0.95–1.25)	0.78 (0.23)
Ischemic stroke	Cases *n* = 217	Cases *n* = 901	Cases *n* = 136	
$GRS_{LDL\text{-}C}$	1.08 (0.95–1.24)	1.10 (1.03–1.17)	0.93 (0.79–1.10)	0.01 (0.07)
$GRS_{HDL\text{-}C}$	1.16 (1.02–1.33)	1.04 (0.97–1.11)	1.07 (0.91–1.26)	0.18 (0.21)
GRS_{TG}	0.96 (0.84–1.10)	0.99 (0.93–1.06)	0.99 (0.83–1.17)	0.98 (0.59)

Cox proportional hazard regression was used to calculate HRs (95 % CI) per 1 SD increase of the GRSs, $P < 0.05$, adjusted for age and sex among 24,799 participants in the Malmö Diet and Cancer cohort

[a] *P* interactions (GRSs × diet quality index as continuous variables) adjusted for age, sex, BMI, diet assessment method version, season, total energy intake, alcohol habits, leisure time physical activity, educational level, and smoking habits

[b] *P* values in parentheses are sensitivity analyses excluding those reporting dietary changes in the past and potential energy misreporters, *n* = 16,030

Hellstrand et al. Genes Nutr. 2016

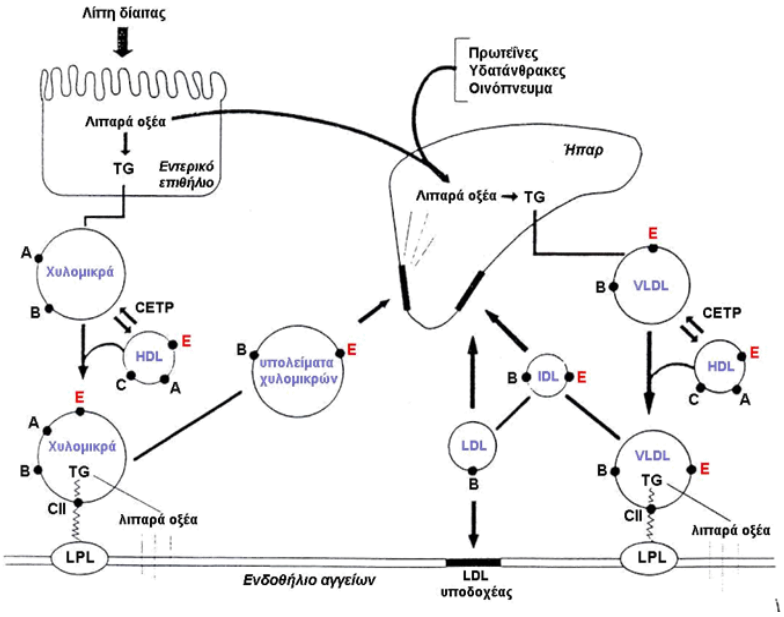
Gene-diet interactions and CVD: a systematic review of observational and clinical trials

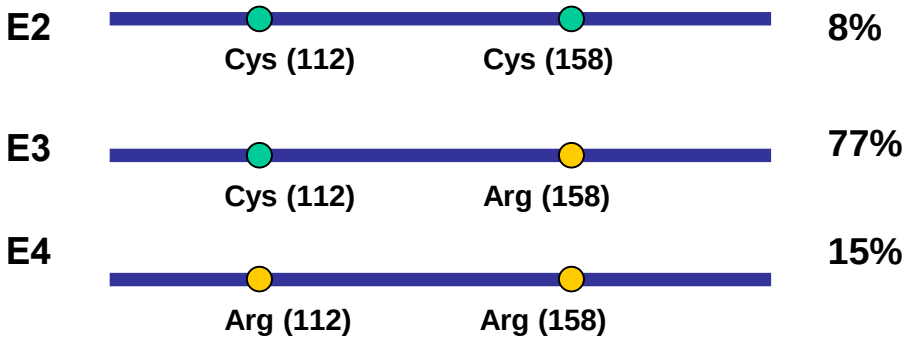
Fig. 3 Findings for interaction between genetic variants and diet in relation to coronary heart diseases. W = women, M = men, B = Both (Men and women)

Roa-Díaz et al. BMC Cardiovascular Disorders (2022) 22:377

Gene – Alcohol interactions

APOE γονίδιο & λιπίδια πλάσματος



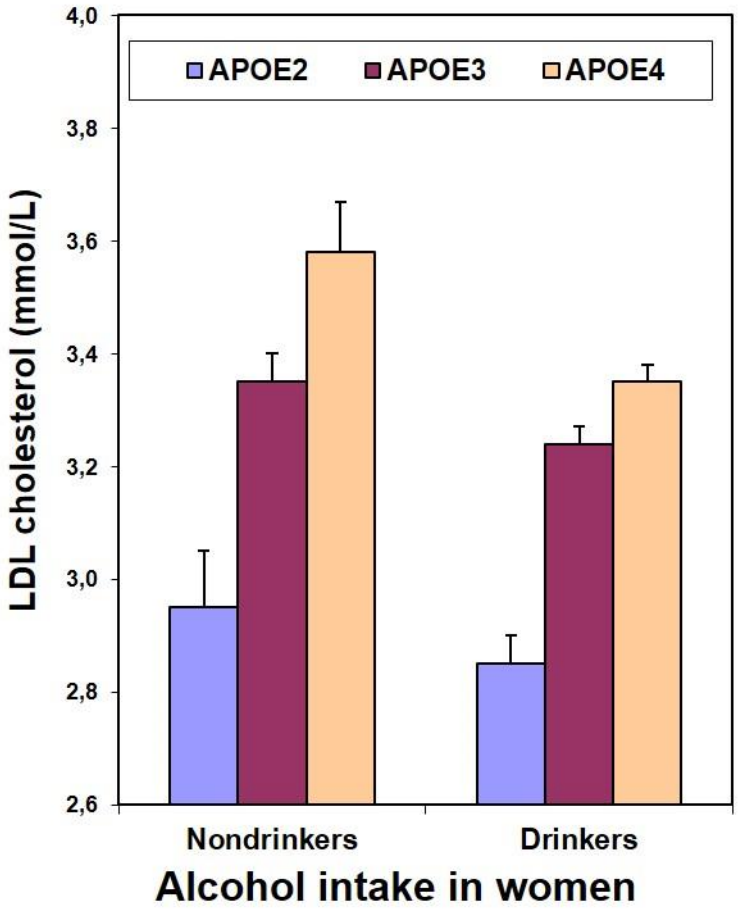


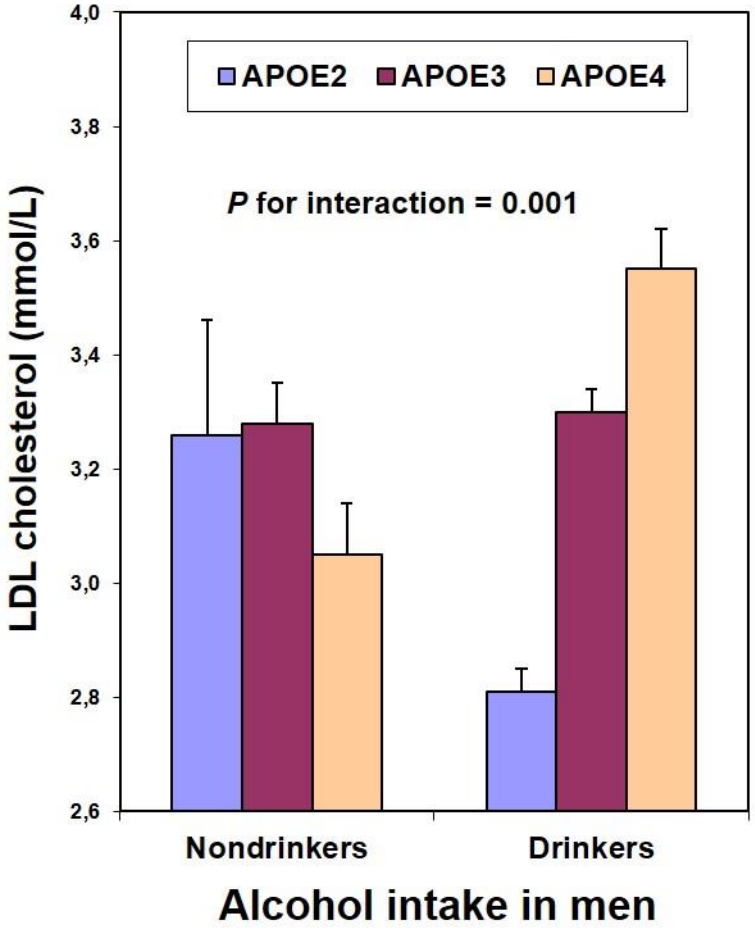
Συγκριτικά με άτομα με γονότυπο *APOE* 3/3:

E2+ : ↓ TC, ↓ LDL-C **E4+ : ↑ TC, ↑ LDL-C, ↓ HDL-C**

Gene (APOE) – Alcohol interactions & Lipid levels

Corella D et al. *Am J Clin Nutr* 2001





Κατανάλωση αλκοόλ:

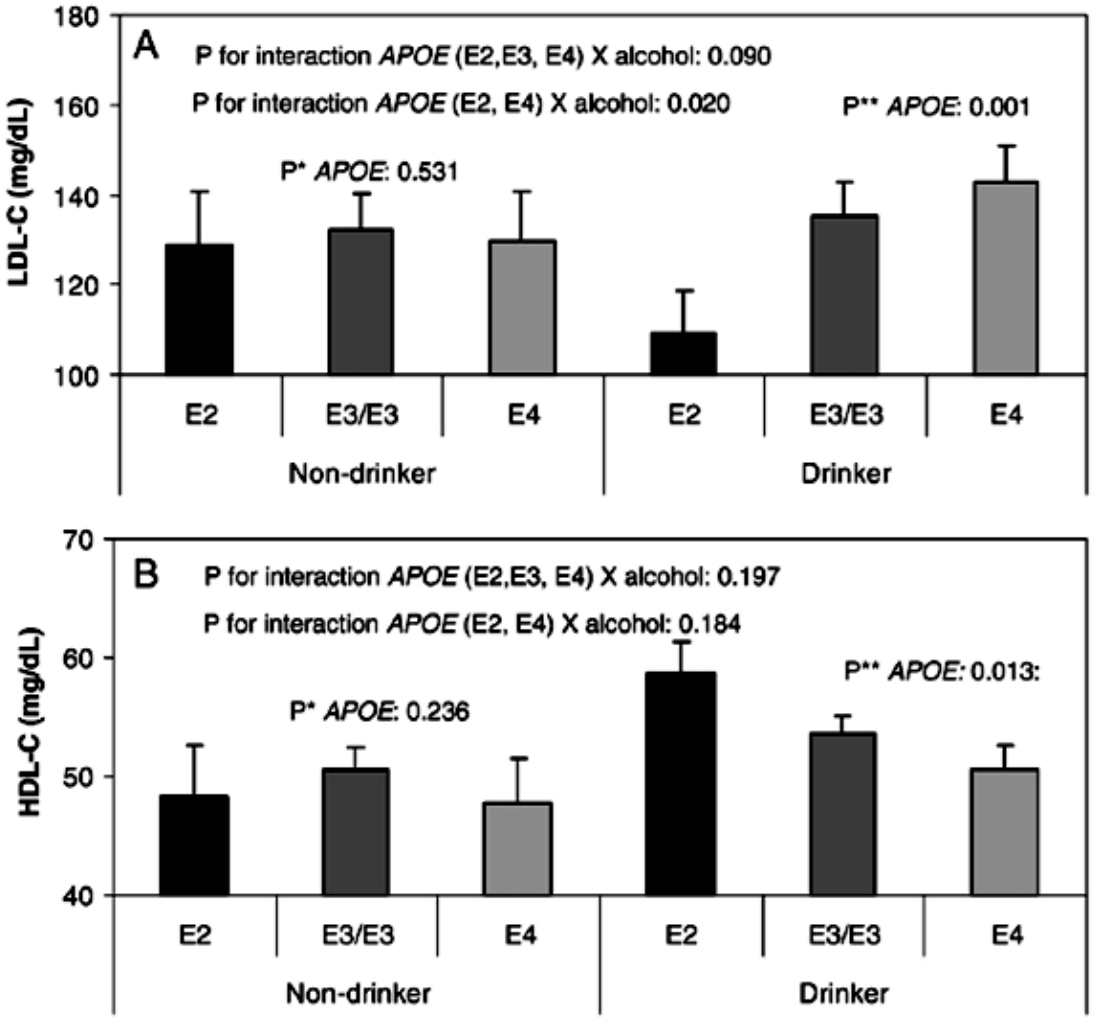
	Μέτρια	***Υψηλή***
Άνδρες:	**< 26.4 gr/ημέρα**	**≥ 26.4 gr/ημέρα**
Γυναίκες:	**< 13.2 gr/ημέρα**	**≥ 13.2 gr/ημέρα**

Plasma LDL-cholesterol concentrations by *APOE* allele type, stratified by alcohol intake

		Men			
APOE allele type	*n*	All men (*n* = 1014)	No intake (*n* = 197)	Moderate intake (*n* = 602)	High intake (*n* = 215)
			mmol/L		
E2	125	2.92 ± 0.86	3.28 ± 1.06	2.88 ± 0.82 *	2.68 ± 0.67*
E3	691	3.37 ± 0.77	3.30 ± 0.79	3.40 ± 0.78	3.35 ± 0.71
E4	198	3.43 ± 0.83 *	3.09 ± 0.80	3.56 ± 0.77 *	3.49 ± 0.92*
All allele types	1014	3.33 ± 0.80	3.21 ± 0.83	3.35 ± 0.81	3.33 ± 0.78

Gene (APOE) – Alcohol interactions & Lipid levels

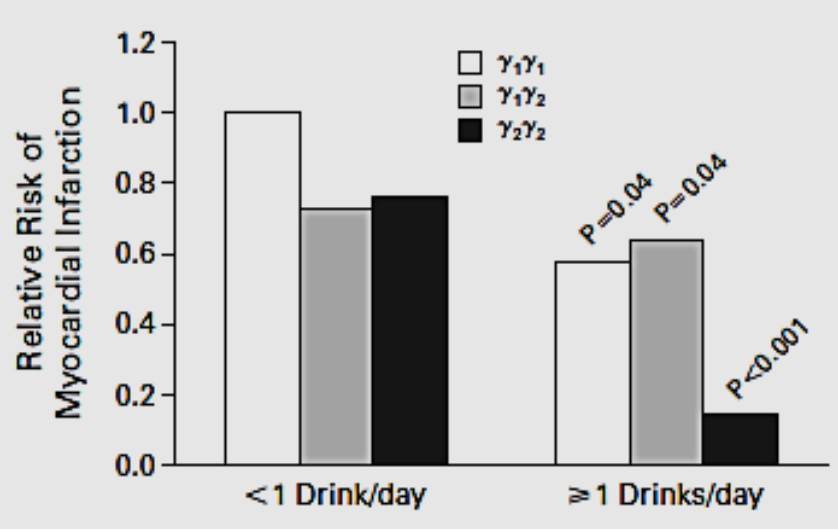
Corella D et al. *J Nutr Biochem* 2010

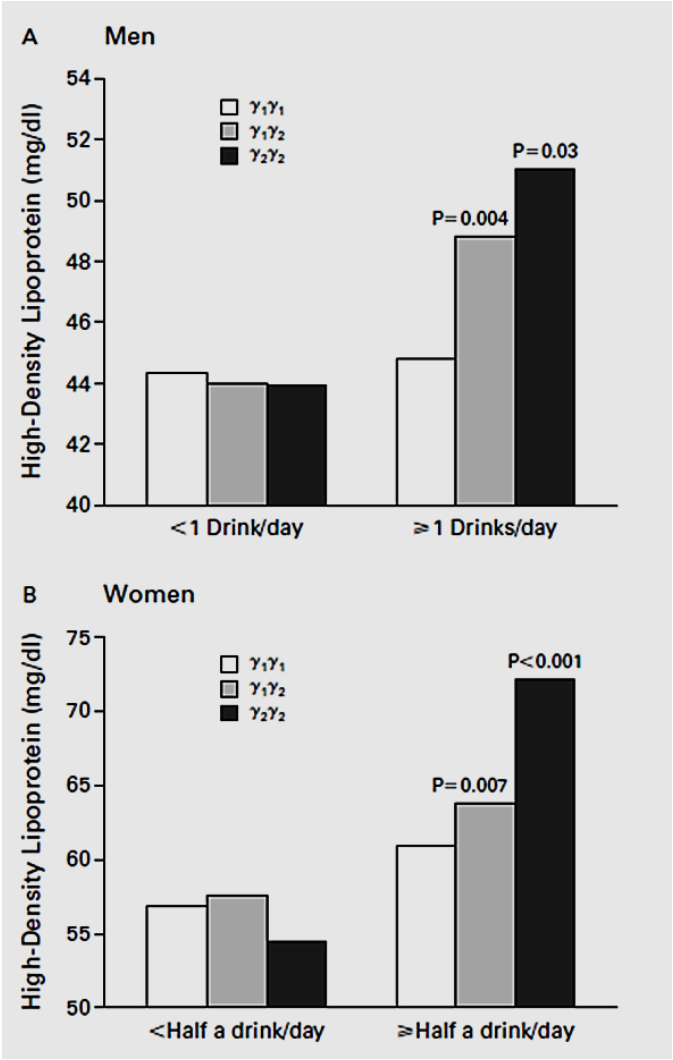


Gene – Alcohol interactions & risk of MI

Hines et al. *NEJM* 2001

- SNP (γ_1/γ_2) in the gene for alcohol dehydrogenase type 3 (ADH3) alters the rate of alcohol metabolism.
- Nested case-control study from the prospective Physicians' Health Study: Investigated the relation among the ADH3 polymorphism, the level of alcohol consumption & the risk of MI.
- **Conclusion**: Moderate drinkers who are homozygous for the slow-oxidizing ADH3 allele (γ_2/γ_2) have higher HDL levels & a substantially decreased risk of MI.



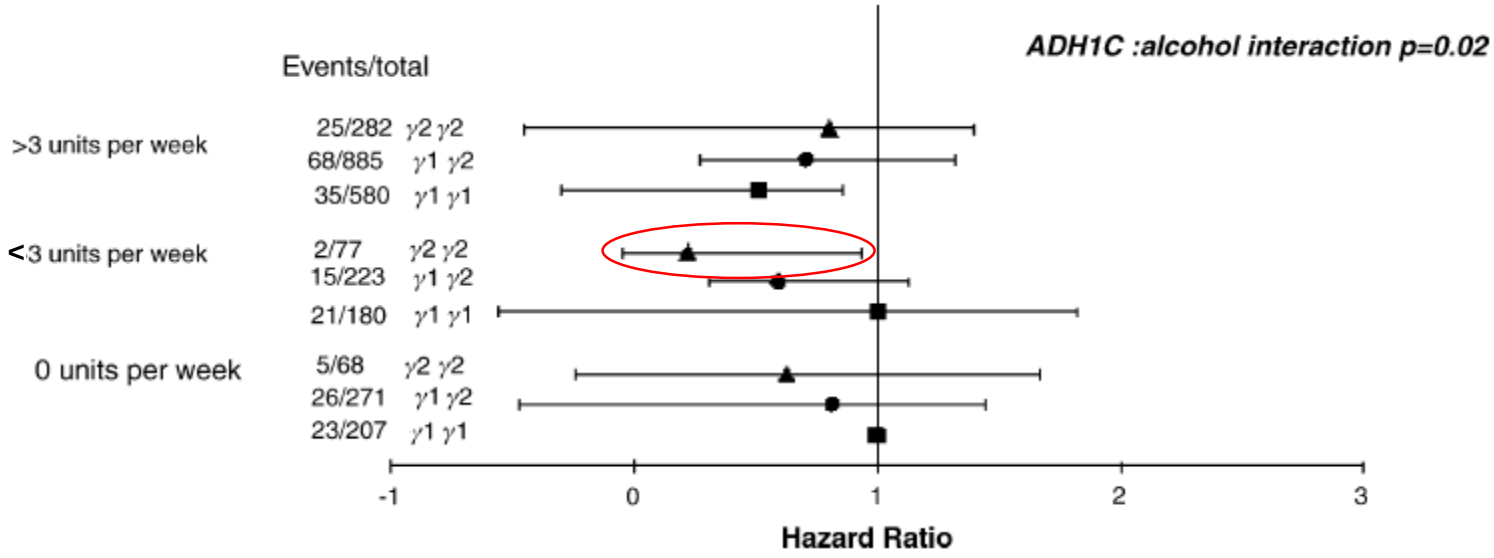


Gene – Alcohol interactions & risk of MI

- This relationship of SNP (γ_1/γ_2) in ADH3 (or ADH1C) was examined in a sample of middle-aged (50–61 years) men (total of 2773 with 220 CHD events) participating in the prospective Second Northwick Park Heart Study (NPHS II).

- Significant alcohol-genotype interaction on CHD risk was observed (p=0.02), with γ_2/γ_2 homozygotes, who were modest drinkers, displaying 78% CHD risk reduction compared to γ_1/γ_1 homozygotes (HR=0.22, 95%CI=0.05-0.94).

- **Conclusion**: ADH1C genotype modifies the relationship between alcohol consumption and CHD risk but at lower levels than previously reported.



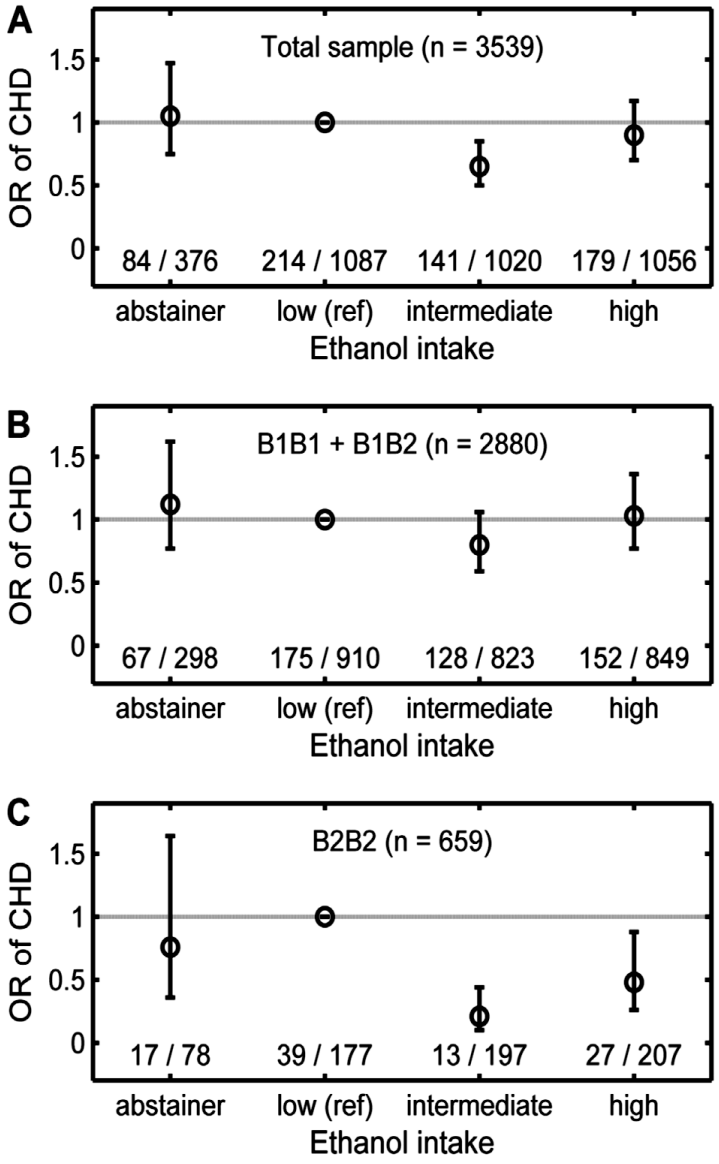
Younis et al. *Atherosclerosis 2005*

Gene – Alcohol interactions & risk of CHD

- **INTERGENE case-control study**: Examined the potential modification of the association between alcohol consumption and CHD by the CETP TaqIB (rs708272) SNP in a sample including both men & women (618 CHD patients & 2921 controls, 19% homozygous for the CETP TaqIB B2 allele).

- The strongest protective association was seen in the CETP TaqIB B2/B2 for intermediate vs. low ethanol intake (OR:0.21; 95%CI: 0.10-0.44) ($p_{interaction}$=0.008)
- Similar effect size in men & women though significant only in men (p=0.01).

- **Conclusion**: The common attitude today is that moderate alcohol intake will decrease everyone's risk of CHD. The present study suggests that this message may be too general and should be assessed in light of the weak overall effect of alcohol on CHD in the general population and the emerging knowledge about genetic susceptibility.



Mehlig et al. *Alcohol 2014*

Gene – Coffee interactions

Gene – Coffee interactions & risk of MI

- The association between coffee intake & risk of myocardial infarction (MI) remains controversial.

- Coffee is a major source of caffeine, which is metabolized by the polymorphic cytochrome P450 1A2 (CYP1A2) enzyme. Individuals who are homozygous for the CYP1A2*1A allele are “rapid” caffeine metabolizers, whereas carriers of the variant CYP1A2*1F are “slow” caffeine metabolizers.

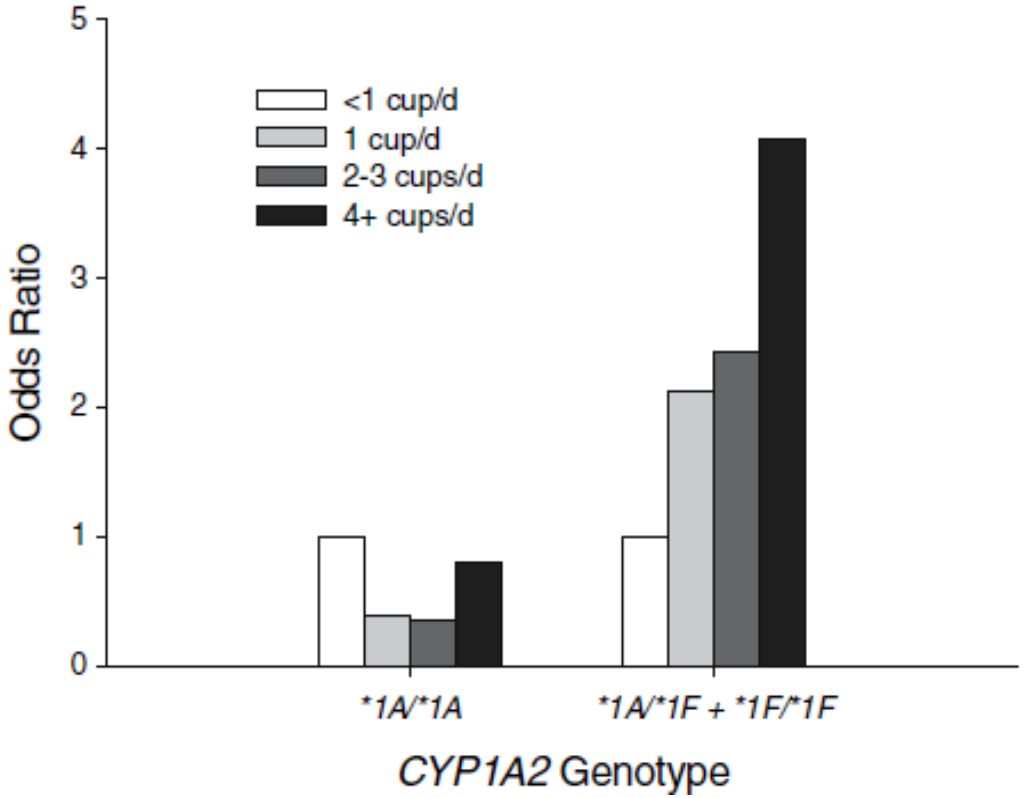
- **AIM**: To determine whether CYP1A2 genotype modifies the association between coffee consumption & risk of acute nonfatal MI.

- Cases (n=2014) with a first acute nonfatal MI & population-based controls (n=2014) living in Costa Rica. Caffeinated coffee intake was assessed via FFQ.

Cornelis et al. JAMA 2006

Gene – Coffee interactions & risk of MI

El-Sohemy et al. Genes Nutr 2007



Coffee intake & risk of MI by CYP1A2 genotype among subjects less than 50 years of age. Adjusted for age, sex, area of residence, smoking (never, past, 1-19 cigarettes/day, ≥20 cigarettes/day), WHR, income, physical activity, history of diabetes, history of hypertension & TEI, SFA intake, PYFAs, trans fat, sucrose & alcohol.

- **CONCLUSION**: Intake of coffee was associated with an increased risk of nonfatal MI only among individuals with slow caffeine metabolism, suggesting that caffeine plays a role in this association.

Gene – Coffee interactions & risk of MI

Table 3. Coffee Intake and Relative Risk of Myocardial Infarction by CYP1A2 Genotype, Smoking Status, and Age Category

Coffee Intake, Cups/d	No. (%)		OR (95% CI)	
	Cases	Controls	Model 1	Model 2
Smoking Status*				
Nonsmokers				
*1A/*1A	n = 532	n = 745		
<1	75 (14)	101 (14)	1.00	1.00
1	84 (16)	135 (18)	0.84 (0.56-1.25)	0.73 (0.47-1.14)
2-3	312 (59)	436 (58)	0.95 (0.68-1.33)	0.75 (0.52-1.07)
≥4	61 (11)	73 (10)	1.13 (0.71-1.77)	1.02 (0.62-1.67)
*1A/*1F + *1F/*1F	n = 677	n = 844		
<1	85 (13)	136 (16)	1.00	1.00
1	97 (14)	158 (18)	0.96 (0.66-1.40)	1.01 (0.67-1.51)
2-3	399 (59)	467 (55)	1.32 (0.97-1.79)	1.27 (0.91-1.76)
≥4	98 (14)	83 (10)	1.93 (1.29-2.88)	1.72 (1.11-2.67)
Smokers				
*1A/*1A	n = 368	n = 187		
<1	19 (5)	12 (6)	1.00	1.00
1	33 (9)	23 (12)	0.90 (0.36-2.23)	0.87 (0.30-2.51)
2-3	198 (54)	102 (55)	1.23 (0.57-2.64)	1.11 (0.45-2.76)
≥4	118 (32)	50 (27)	1.59 (0.71-3.54)	1.22 (0.47-3.18)
*1A/*1F + *1F/*1F	n = 437	n = 238		
<1	25 (6)	20 (8)	1.00	1.00
1	20 (5)	22 (9)	0.65 (0.27-1.54)	0.90 (0.33-2.50)
2-3	237 (54)	128 (54)	1.42 (0.75-2.70)	1.77 (0.83-3.76)
≥4	155 (35)	68 (29)	1.83 (0.94-3.56)	1.79 (0.80-3.98)

(P=0.04 for geneXcoffee interaction in all subjects)

Cornelis et al. JAMA 2006

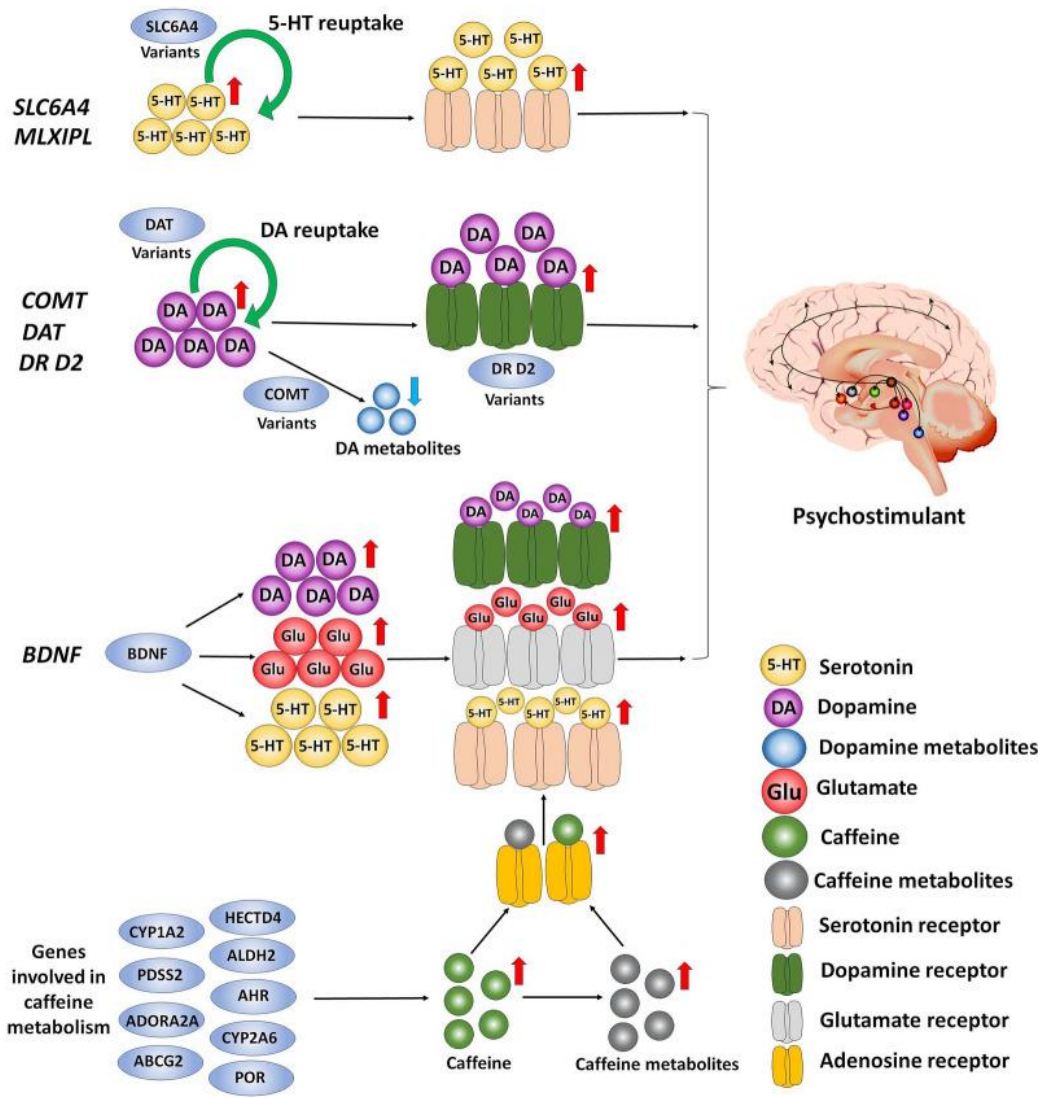
GWAs of coffee consumption

Published in final edited form as:
Mol Psychiatry. 2015 May ; 20(5): 647–656. doi:10.1038/mp.2014.107.

Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption

Several genes are involved with caffeine metabolism such as CYP1A2, ADORA2A, AHR, POR, ABCG2, CYP2A6, PDSS2 and ALDH2.

Genes associated with caffeine reward include BDNF, SLC6A4, GCKR, MLXIPL and dopaminergic genes such as DRD2 and DAT1



Coffee consumption & risk of OSA

Low et al. Journal of Translational Medicine (2024) 22:961
https://doi.org/10.1186/s12967-024-05737-z

Journal of Translational Medicine

REVIEW Open Access

Genetic susceptibility to caffeine intake and metabolism: a systematic review

Jazreel Ju-Li Low[1,2], Brendan Jen-Wei Tan[1], Ling-Xiao Yi[2], Zhi-Dong Zhou[1,2] and Eng-King Tan[1,2*]

Abstract

Background Coffee and tea consumption account for most caffeine intake and 2–3 billion cups are taken daily around the world. Caffeine dependence is a widespread but under recognized problem.

Objectives To conduct a systematic review on the genetic susceptibility factors affecting caffeine metabolism and caffeine reward and their association with caffeine intake.

Methodology We conducted PubMed and Embase searches using the terms "caffeine", "reward", "gene", "polymorphism", "addiction", "dependence" and "habit" from inception till 2024. The demographics, genetic and clinical data from included studies were extracted and analyzed. Only case-control studies on habitual caffeine drinkers with at least 100 in each arm were included.

Results A total of 2552 studies were screened and 26 studies involving 1,851,428 individuals were included. Several genes that were involved with caffeine metabolism such as CYP1A2, ADORA2A, AHR, POR, ABCG2, CYP2A6, PDSS2 and HECTD4 rs2074356 (A allele specific to East Asians and monomorphic in Europeans, Africans and Americans) were associated with habitual caffeine consumption with effect size difference of 3% to 32% in number of cups of caffeinated drink per day per effect allele. In addition, ALDH2 was linked to the Japanese population. Genes associated with caffeine reward included BDNF, SLC6A4, GCKR, MLXIPL and dopaminergic genes such as DRD2 and DAT1 which had around 2–5% effect size difference in number of cups of caffeinated drink for each allele per day.

Conclusion Several genes that were involved in caffeine metabolism and reward were associated with up to 30% effect size difference in number of cups of caffeinated drink per day, and some associations were specific to certain ethnicities. Identification of at-risk caffeine dependence individuals can lead to early diagnosis and stratification of at-risk vulnerable individuals such as pregnant women and children, and can potentially lead to development of drug targets for dependence to caffeine.

Gene – Coffee interactions & risk of MI

International Journal of Epidemiology, 2015, 1–15
doi: 10.1093/ije/dyw325
Original article

Original article

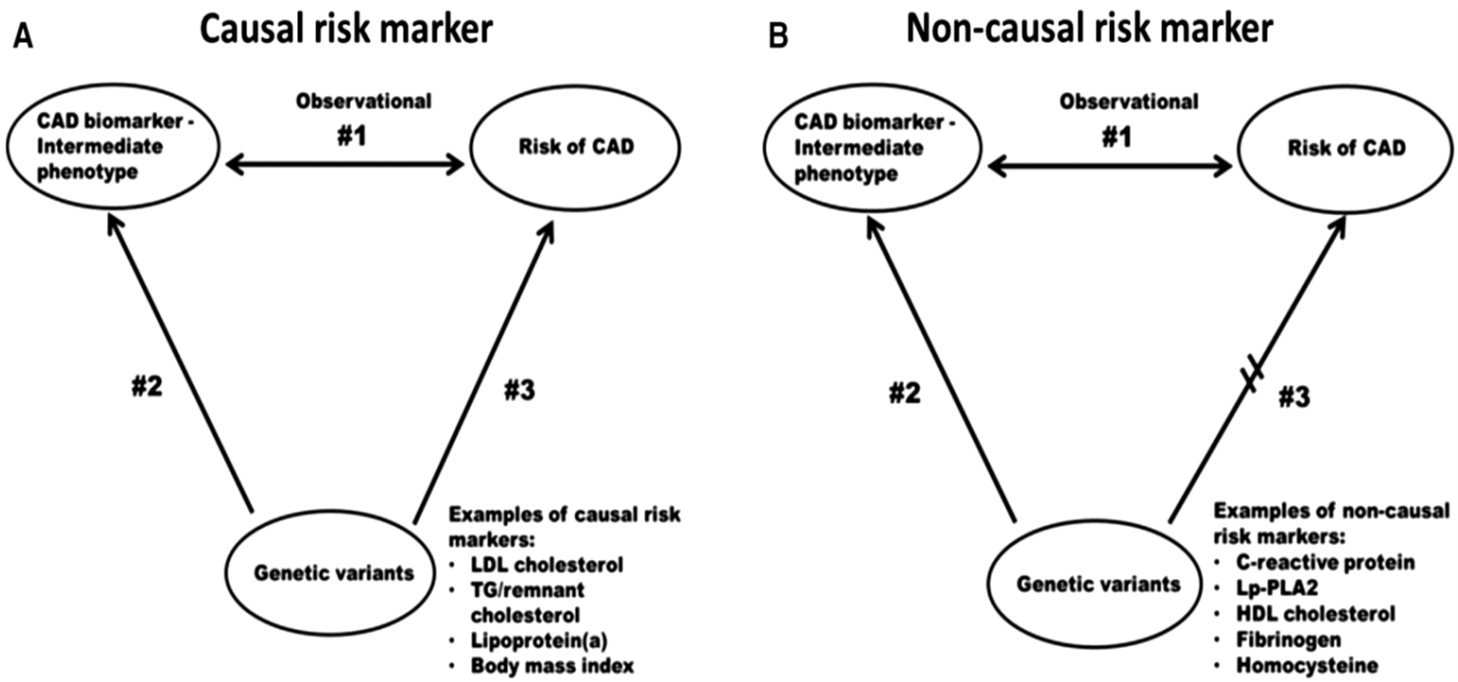
Coffee intake, cardiovascular disease and all-cause mortality: observational and Mendelian randomization analyses in 95 000–223 000 individuals

Ask Tybjærg Nordestgaard[1,2] and Børge Grønne Nordestgaard[1,2,3]*

- **CONCLUSIONS**: Observationally, coffee intake was associated with U-shaped lower risk of CVD and all-cause mortality. However, genetic coffee intake was NOT associated with risk of CVD or all-cause mortality and does therefore NOT support the hypothesis that coffee intake influences risk of CVD and all-cause mortality.

Mendelian Randomazation

- **Methodology is based on the tenet that if a biomarker has a causal association with disease, the genetic determinants of the biomarker will also associate with disease risk.**



***A**, If evidence #1 to #3 are all documented robustly, the interpretation is that the data are compatible with a causal relationship. **B**, If evidence #1 and #2 are documented robustly, but the genetic determinants of the biomarker do not associate with disease risk, the interpretation is that the association is noncausal. Using MR, major advances have been made in determining the causal associations between plasma levels of Lpa, LDL-C,TG (as a marker of remnant cholesterol), and body mass index (as a surrogate for obesity) with risk of CAD. In contrast, CRP, Lp-PLA2, HDL-C, fibrinogen, and homocysteine, despite being robust risk markers, have not been shown to be causal.*

McPherson & Tybjaerg-Hansen, Circulation Res 2016

Coffee consumption & risk of CVD

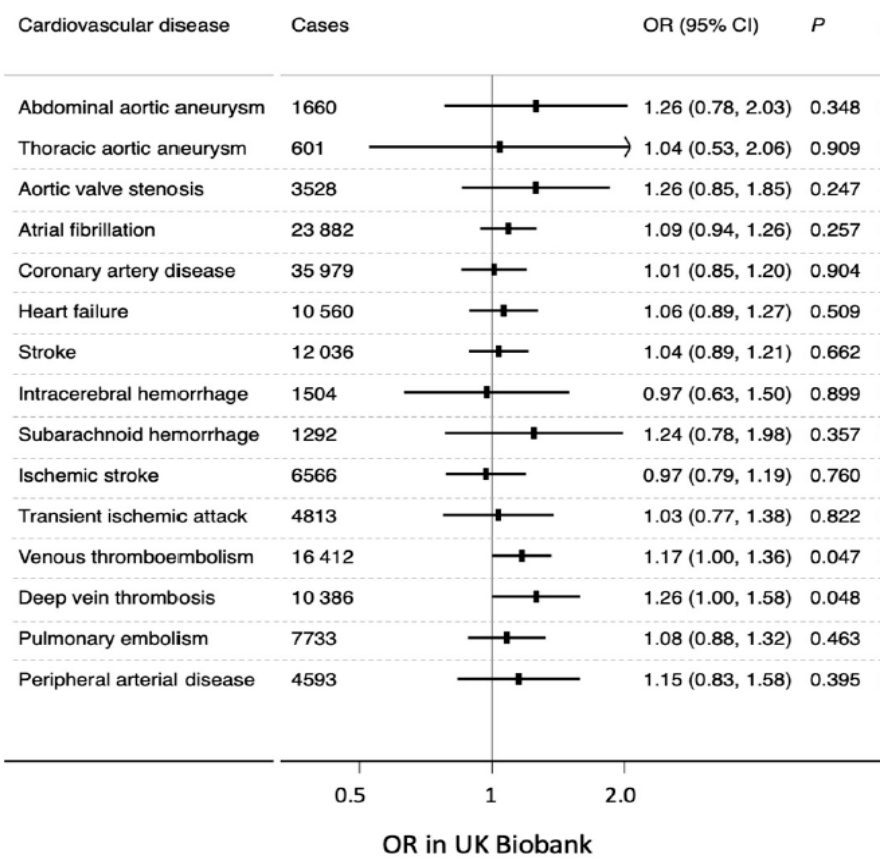
nutrients

MDPI

Article

Coffee Consumption and Cardiovascular Diseases: A Mendelian Randomization Study

Shuai Yuan [1], Paul Carter [2], Amy M. Mason [3,4], Stephen Burgess [3,5] and Susanna C. Larsson [1,6,*]



Nutrients 2021, 13, 2218.
https://doi.org/10.3390/nu13072218

- **CONCLUSION**: This Mendelian randomization study showed limited evidence that coffee consumption affects the risk of developing cardiovascular disease, suggesting that previous observational studies may have been confounded.

Coffee consumption & risk of OSA

European Journal of Nutrition (2023) 62:3423–3431
https://doi.org/10.1007/s00394-023-03239-0

ORIGINAL CONTRIBUTION

Check for updates

Genetic association between coffee/caffeine consumption and the risk of obstructive sleep apnea in the European population: a two-sample Mendelian randomization study

Ming-Gang Deng[1,2] · Fang Liu[3] · Kai Wang[4] · Yuehui Liang[3] · Jia-Qi Nie[5] · Chen Chai[6]

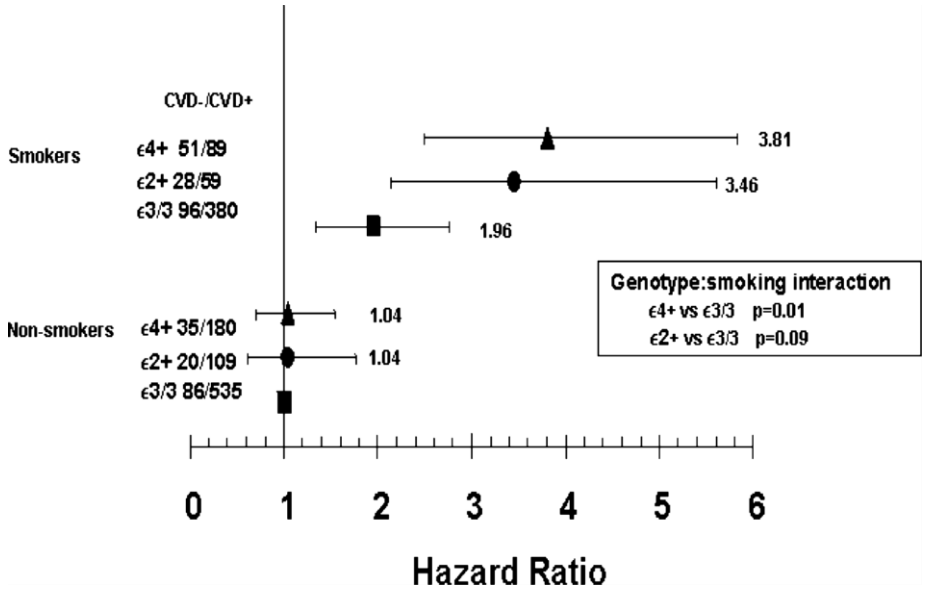
Received: 17 November 2022 / Accepted: 16 August 2023 / Published online: 5 September 2023

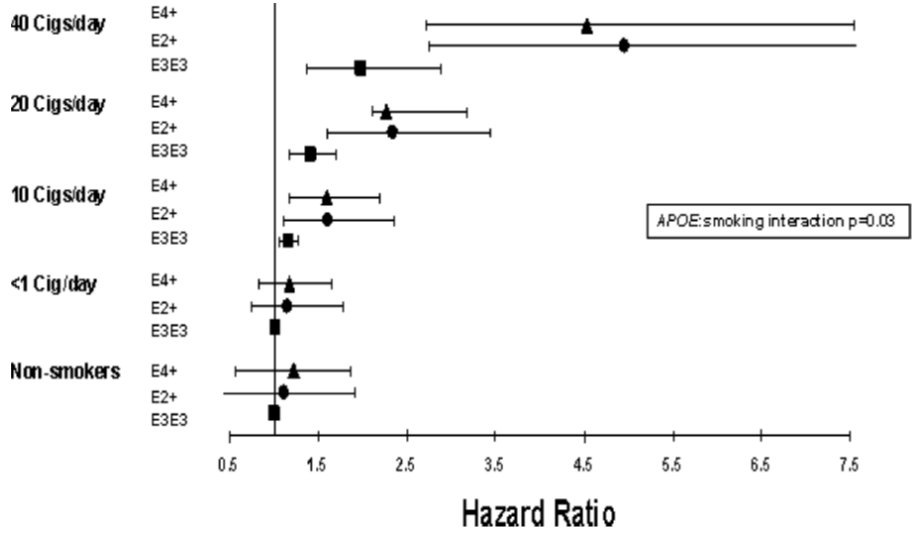
- **CONCLUSION**: ….found NO association between coffee/caffeine consumption and the risk of OSA.

Gene – Smoking interactions

Gene – Smoking interactions & CVD risk

- **Framingham Offspring study**: Data from 1668 men (316 CVD events) was reanalysed, examining APOE-smoking interactions.
- Overall HR for smoking: 1.95 (1.52, 2.50) compared to non-smokers.
- CVD risk-raising effect of ε4+ allele was confined to smokers, with a significant interaction between daily cigarette consumption and APOE genotype on risk (p=0.03).

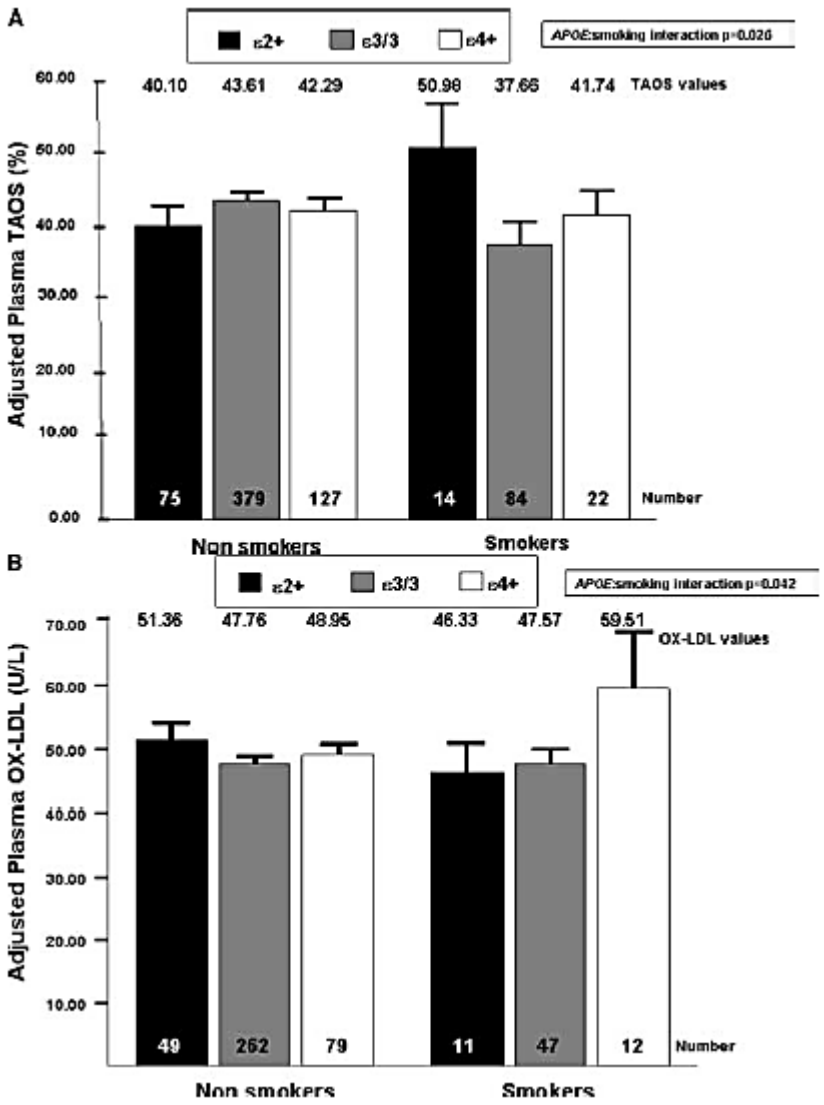




Talmud et al. Ann Hum Genet 2005

Gene – Smoking interactions & CVD risk

- The potential mechanism for this APOE ε4-smoking interaction was examined in a second study of 728 Caucasian patients with diabetes, where markers of reactive oxygen species were available.
- APOE genotype was not associated with plasma OX-LDL or total antioxidant status (TAOS) in non-smokers. However, in smokers ε4+ had 26.7% higher plasma OX-LDL than other genotypes ($p_{interaction}$=0.04), while ε2+ had 28.4% higher plasma TAOS than ε3ε3 & ε4+ combined ($p_{interaction}$=0.026).
- Therefore, a feasible mechanism for the APOE-smoking interaction is the reduced antioxidant capacity/increased OX-LDL of apoE4.



Talmud et al. Ann Hum Genet 2005

Gene – Smoking interactions, CAD risk & mortality

- **LUdwigshafen RIsk & Cardiovascular Health study**: Analyzed the association between APOE-genotype, smoking, angiographic CAD & mortality (n=3263)
- In persons undergoing coronary angiography, there is a significant interaction between APOE-genotype & smoking. The presence of the ε4 allele in current smokers increases cardiovascular & all-cause mortality.

Table 5 Hazard ratios for death from cardiovascular causes according to smoking and *APOE-genotype* in 3250 persons undergoing coronary angiography

Smoking status	Model 1 [HR (95% CI)]	*P*-value	Model 2 [HR (95% CI)]	*P*-value
Model A				
Never-smokers	1.0[reference]		1.0[reference]	
Ex-smokers	1.32 (1.05–1.66)	0.017	1.26 (1.00–1.59)	0.047
Current smokers[a]	1.94 (1.48–2.55)	<0.001	1.92 (1.45–2.54)	<0.001
Current smokers without ε4	1.74 (1.29–2.35)	<0.001	1.72 (1.27–2.33)	0.001
Current smokers with ε4	2.79 (1.82–4.29)	<0.001	2.81 (1.82–4.35)	<0.001
Model B				
Never-smokers	1.0[reference]		1.0[reference]	
Ex-smokers	1.30 (1.01–1.68)	0.046	1.23 (0.95–1.59)	0.112
Current smokers[a]	2.21 (1.64–2.98)	<0.001	2.18 (1.61–2.95)	<0.001
ε4 allele present	1.24 (1.00–1.54)	0.049	1.28 (1.03–1.59)	0.026
Ex-smokers × ε4	0.95 (0.59–1.52)	0.817	0.93 (0.58–1.49)	0.752
Current smokers × ε4	1.74 (0.98–3.09)	0.060	1.69 (0.95–3.01)	0.074

Model 1: adjusted for sex.
Model 2: multifactorially adjusted for sex, use of lipid-lowering drugs (>97%), cardiovascular risk factors [body mass index, diabetes mellitus, hypertension, LDL-C, HDL-C, triglycerides (log transformed), eGRF], and clinical presentation (no CAD, stable CAD, UAP, NSTEMI, or STEMI).
Model A: no interaction terms.
Model B: including smoking (never, previous, or current) and absence or presence of at least one ε4 allele as main effects and in addition an interaction term smoking × ε4.
[a] Includes both current smokers with and without ε4.

Grammer et al. Eur Heart J 2013

Gene – Smoking interactions & CHD risk

Atherosclerosis 237 (2014) 5–12

Contents lists available at ScienceDirect

Atherosclerosis

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

A systematic review and meta-analysis of 130,000 individuals shows smoking does not modify the association of *APOE* genotype on risk of coronary heart disease

Michael V. Holmes [a, b, *, 1], Ruth Frikke-Schmidt [c, e, f, 1], Daniela Melis [g, 1], Robert Luben [h], Folkert W. Asselbergs [i, j, k], Jolanda M.A. Boer [l], Jackie Cooper [g], Jutta Palmen [g], Pia Horvat [b], Jorgen Engmann [b], Ka-Wah Li [g], N. Charlotte Onland-Moret [m], Marten H. Hofker [n], Meena Kumari [b], Brendan J. Keating [a], Jaroslav A. Hubacek [o], Vera Adamkova [o], Ruzena Kubinova [p], Martin Bobak [b], Kay-Tee Khaw [h], Børge G. Nordestgaard [d, e, f, q], Nick Wareham [q], Steve E. Humphries [g], Claudia Langenberg [b, r], Anne Tybjaerg-Hansen [c, d, e, f, 1], Philippa J. Talmud [g, 1]

Grammer et al. Eur Heart J 2013

Gene – Smoking interactions & CHD risk

Genome-wide association study of gene by smoking interactions in coronary artery calcification

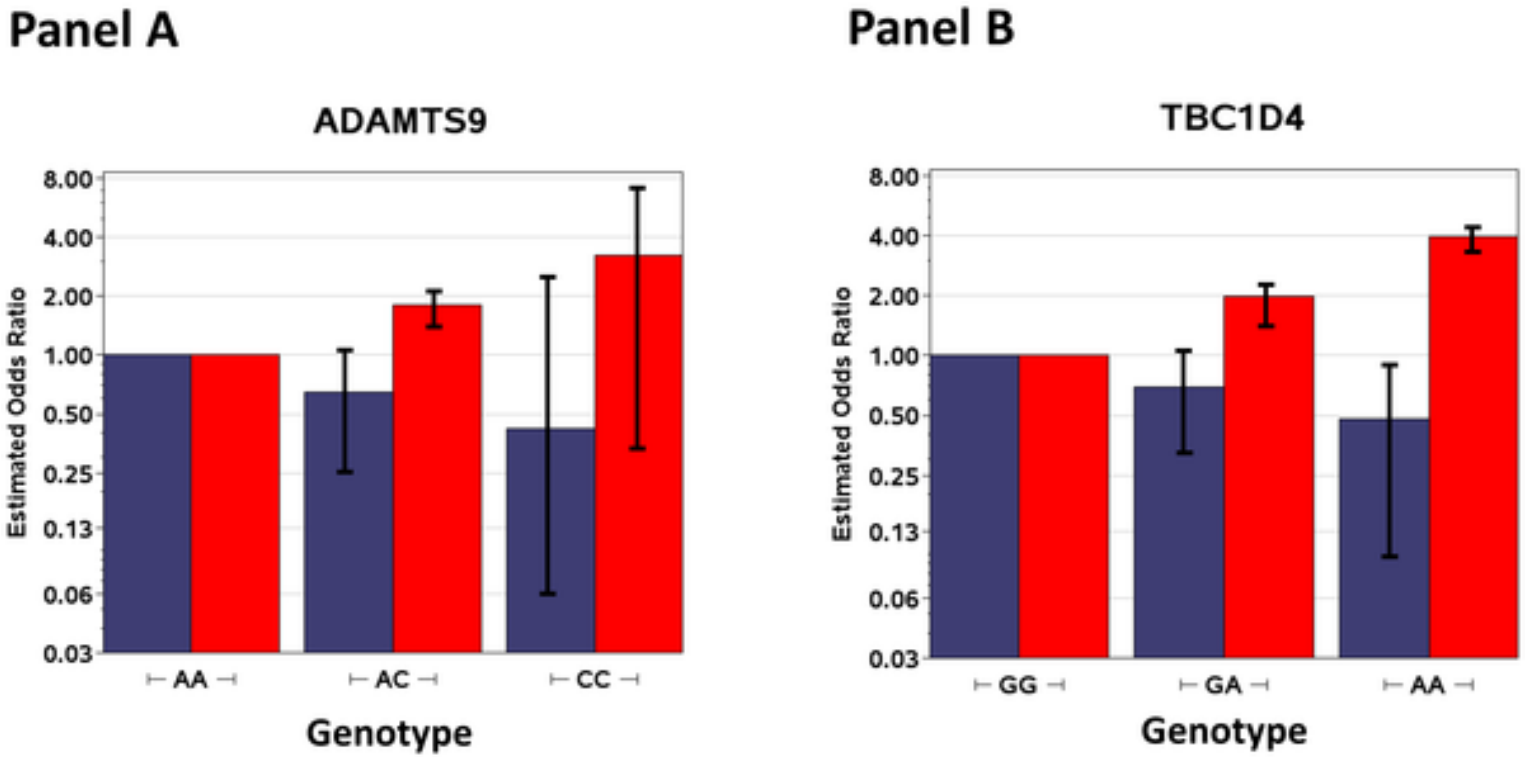


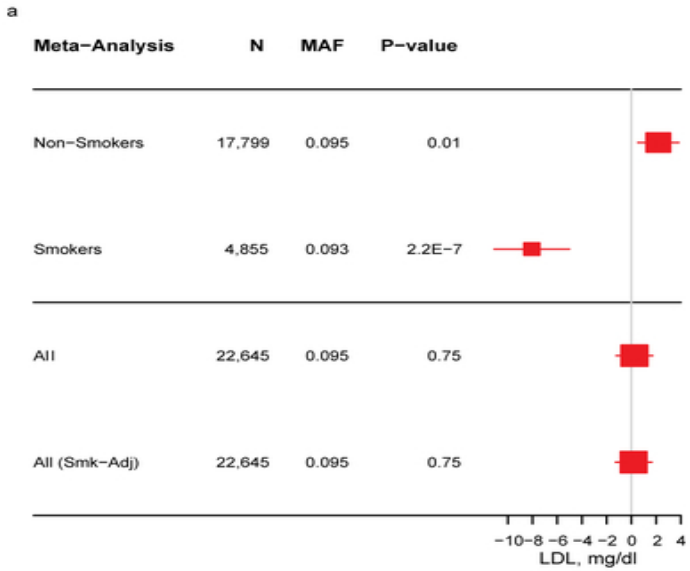
Figure 1. GxS interaction effects stratified by smoking status for ADAMST9 (rs4410439) (Panel A) and TBC1D4 (rs1560540) (Panel B) genotypes. The Figure shows the additive genotype effects (odds ratios) for each smoking strata used to calculate interaction tests (blue bars for nonsmokers and red bars for smokers). The odds ratios on the y-axis are plotted on the log scale with error bars for 95% confidence intervals, and the genotypes are shown on the x-axis.

Polfus et al. PLoS One 2013

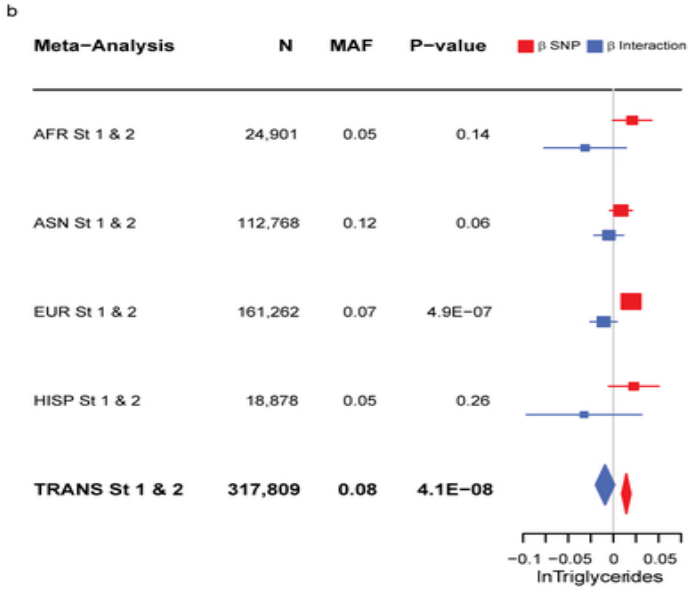
Gene – Smoking interactions & serum lipids

- The concentrations of HDL, LDL and TGL are influenced by smoking, but it is unknown whether genetic associations with lipids may be modified by smoking.
- Conducted a multi-ancestry genome-wide gene-smoking interaction study in 133,805 individuals with follow-up in an additional 253,467 individuals.
- Combined meta-analyses identified 13 new loci associated with lipids, some of which were detected only because association differed by smoking status.
- Demonstrate the importance of including diverse populations, particularly in studies of interactions with lifestyle factors, where genomic and lifestyle differences by ancestry may contribute to novel findings.

rs73453125 and LDL



rs10101067 (EYA1) and TGL

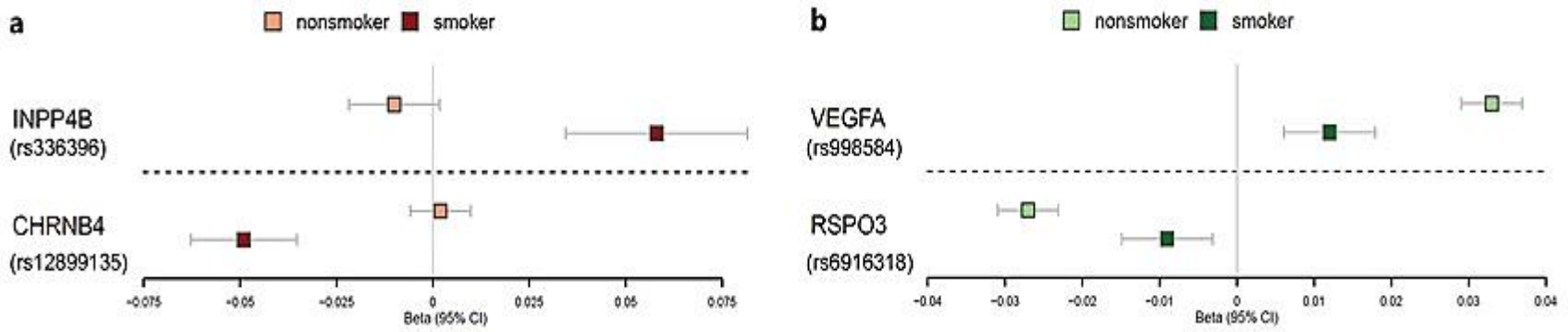


Bentley et al. Nat Genet. 2019 Apr;51(4):636-648

Gene – Smoking interactions & Obesity traits

Smoking-Interaction Loci Affect Obesity Traits: A Gene-Smoking Stratified Meta-Analysis of 545,131 Europeans

- UK Biobank (UKB) data (N=334,808) and the Genetic Investigation of ANthropometric Traits (GIANT) data (N=210,323)
- Identified four GWAs loci in interactions with the smoking status ($p_{stratified} < 5 \times 10^{-8}$): rs336396 (INPP4B) and rs12899135 (near CHRNB4) for BMI, and rs998584 (near VEGFA) and rs6916318 (near RSPO3) for WHRadjBMI.
- Findings suggest that obesity traits can be modified by the smoking status via interactions with genetic variants through various biological pathways.



Forest plots for gene-smoking interaction loci. Forest plots present the estimated effects (beta and 95% CI) for gene-smoking interaction loci of stratified by smoking status on (a) BMI and (b) WHRadjBMI.

Lee W.-J.et al. Lifestyle Genomics 2022;15:87–97

Review of Polygenic Gene-Environment Interaction in Tobacco, Alcohol, and Cannabis Use

- Studies testing the effect of single genetic variants on substance use have had modest success. This paper reviewed 39 studies using polygenic measures to test interaction with any type of environmental exposure (G×E) in alcohol, tobacco, and cannabis use. Studies using haplotype combinations, sum scores of candidate-gene risk alleles, and polygenic scores (PS) were included.

- Overall study quality was moderate, with lower ratings for the polygenic methods in the haplotype and candidate-gene score studies. Heterogeneity in investigated environmental exposures, genetic factors, and outcomes was substantial.

- Most studies (N = 30) reported at least one significant G×E interaction, but **overall evidence was weak**. The majority (N = 26) found results in line with differential susceptibility and diathesis-stress frameworks.

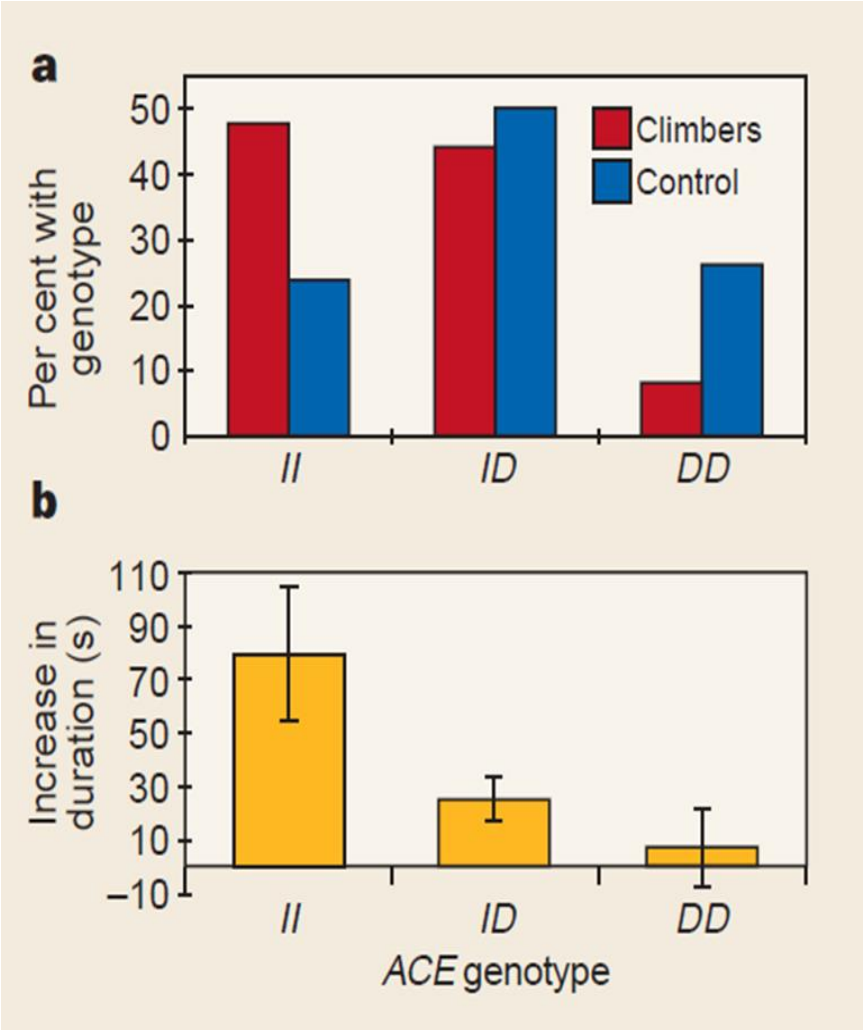
- Future studies should pay more attention to methodological and statistical rigor, and focus on replication efforts. **Additional work is needed before firm conclusions can be drawn about the importance of G×E in the etiology of substance use.**

Pasman et al. Behav Genet. 2019 Jul;49(4):349-365.

Gene – Physical Activity interactions

Gene – Physical Activity & Obesity

- The angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism was the first specific gene variant to be associated with human physical performance.
- The ‘insertion’ allele was associated with elite endurance performance among high-altitude mountaineers.
- Also, after physical training, repetitive weight-lifting is improved 11-fold in individuals homozygous for the ‘insertion’ allele compared with those homozygous for the ‘deletion’ allele.



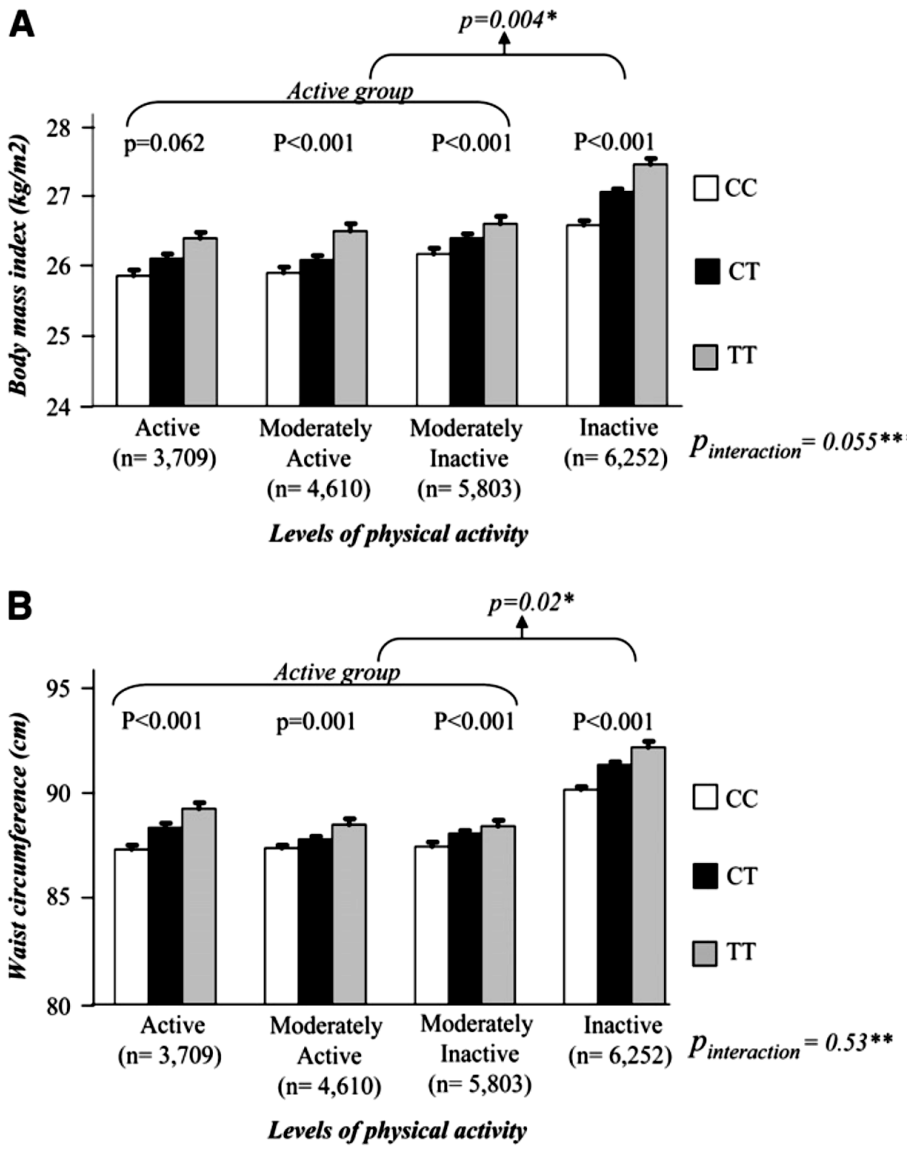
Montgomery et al. Human gene for physical performance. *Nature* 1998

Gene – Physical Activity & Obesity

- **EPIC study & Norfolk Study**: The FTO variant rs1121980 (C>T) was genotyped in 20,374 participants (39-79 y) & its effect was examined in relation to PA.

- In active individuals the risk T-allele increased BMI by 0.25 per allele, BUT the increase in BMI was significantly more pronounced (76%) in inactive individuals (0.44 per risk allele). ($P_{interaction}$=0.004).
- Similar effects were observed for WC ($P_{interaction}$=0.02).

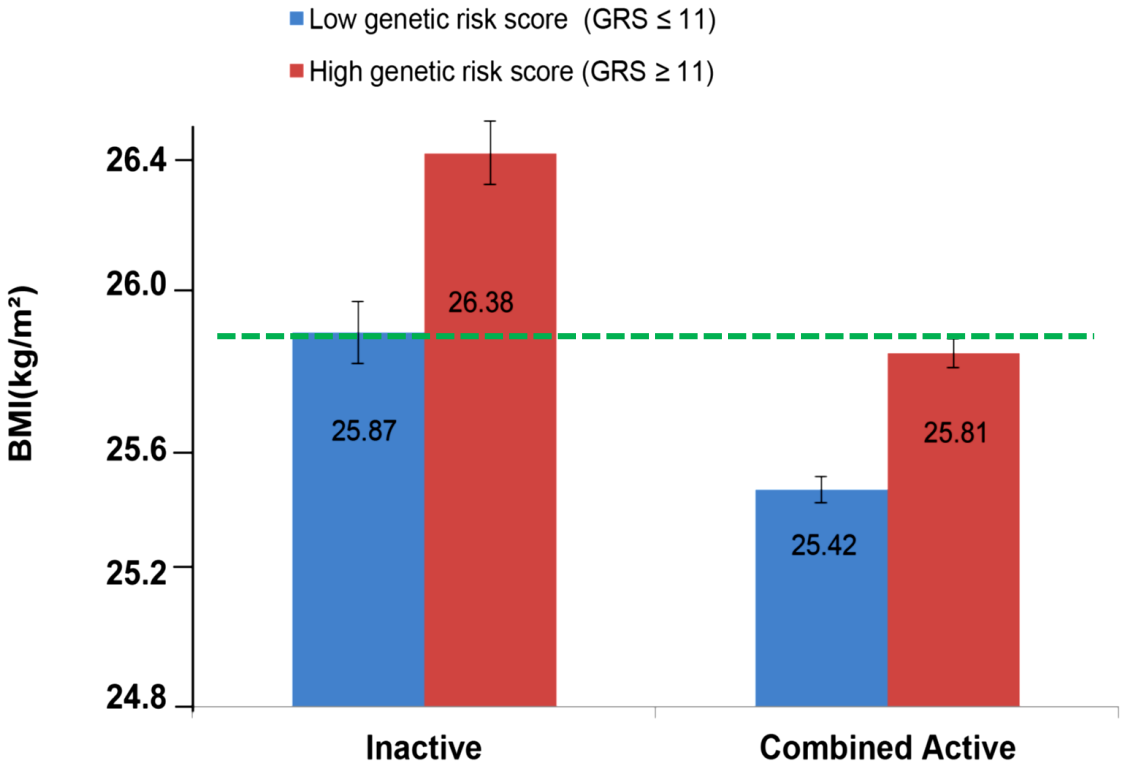
- **Conclusion**: PA attenuates the effect of the FTO rs1121980 genotype on BMI and WC. Public health implications: Genetic susceptibility to obesity induced by FTO variation can be overcome, at least in part, by adopting a physically active lifestyle.



Vimaleswaran et al. AJCN *2009*

Gene – Physical Activity & BMI

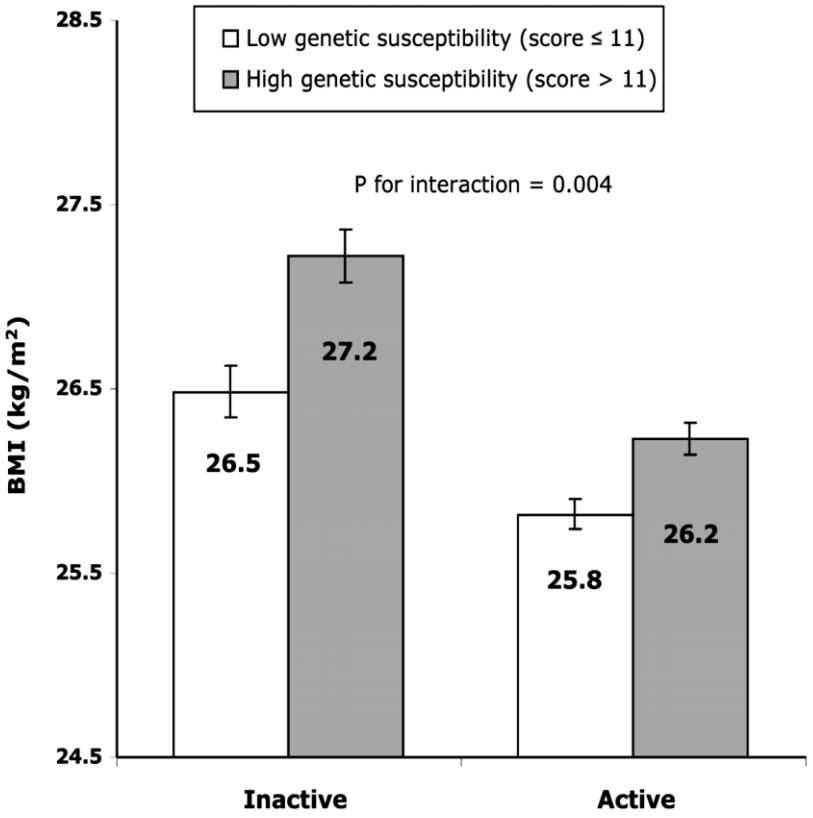
- Meta-analysis of 111,421 samples from 11 cohorts of European ancestry with high levels of PA.
- Genetic risk score from 12 obesity-susceptibility loci.
- The meta-analysis yielded a statistically significant GRS – PA interaction effect estimate ($P_{interaction}$=0.015).



Ahmand et al. *PLOS Genet 2013*

Gene – Physical Activity & BMI

- **EPIC study**: Population-based sample of 20,430 individuals (aged 39–79 y) with an average follow-up period of 3.6 y.
- Genetic risk score from 12 obesity-susceptibility loci.
- Each additional BMI-increasing allele was associated with 0.154 (±0.012) kg/m^2 increase in BMI ($p=6.73x10^{-37}$). This association was significantly more pronounced in inactive than in active people ($p_{interaction}=0.004$).
- Similarly, each additional BMI increasing allele increased the risk of obesity 1.12-fold (95%CI: 1.09-1.14) in the whole population, but significantly more in inactive than in active individuals ($p_{interaction}=0.015$).
- PA modified the association between the genetic predisposition score & change in BMI during follow-up ($p_{interaction}=0.028$).

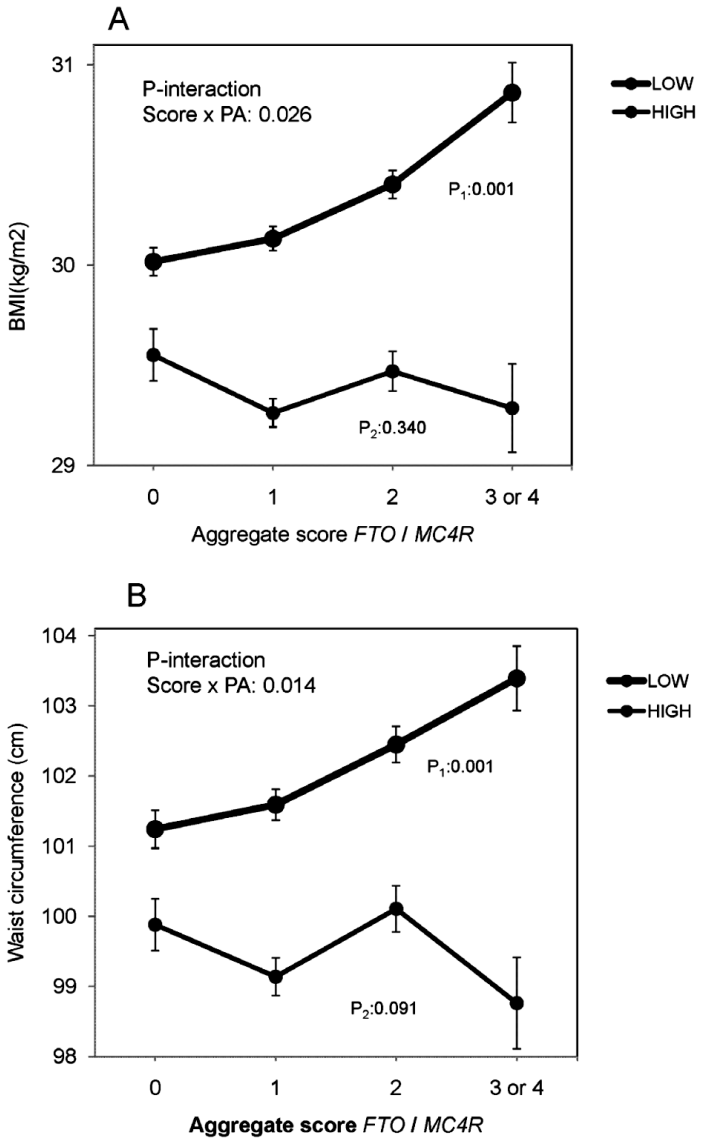


- **Conclusions**: Living a physically active lifestyle is associated with a 40% reduction in the genetic predisposition to common obesity, as estimated by the number of risk alleles carried for any of the 12 recently GWAS identified loci.

Shengxu et al. *PLOS Med 2010*

Gene – Physical Activity interactions & Obesity

- **PREDIMED study**: 7,052 high CVD risk subjects (3,008 men & 4,044 women)
- **AIM**: To investigate whether MC4R rs17782313 & FTO rs9939609 associations with body-weight are modulated by diet & physical activity (PA)
- FTO rs9939609 was associated with higher BMI, WC & obesity (P<0.05). A similar, but not significant trend was found for MC4R.
  Their additive effects (aggregate score) were significant (OR:1.07; 95%CI 1.01-1.13)
- Statistical interactions with PA were observed.
  In active individuals, the associations with higher BMI, WC or obesity were not detected.
- **Conclusion**: PA modulate the effects of FTO & MC4R polymorphisms on obesity.



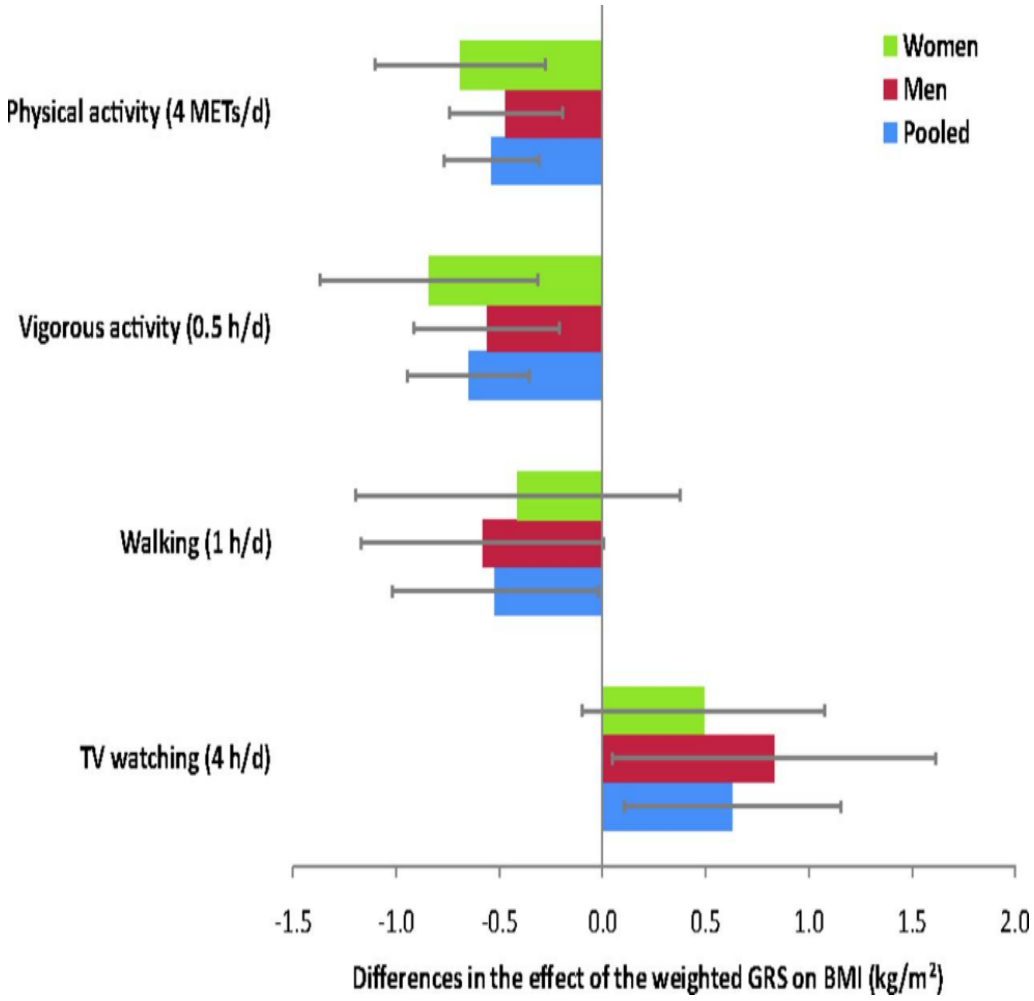
Corella et al. PLOS one 2012

Gene – Physical Activity interactions & Obesity

- **Prospective cohort study**: analyzed interactions between TV watching, leisure time physical activity, & genetic predisposition in relation to BMI in 7740 women & 4564 men from NHS & HPFS

- Genetic risk score: based on 32-BMI associated SNPs. Outcome measure: Repeated measurement of BMI over follow-up

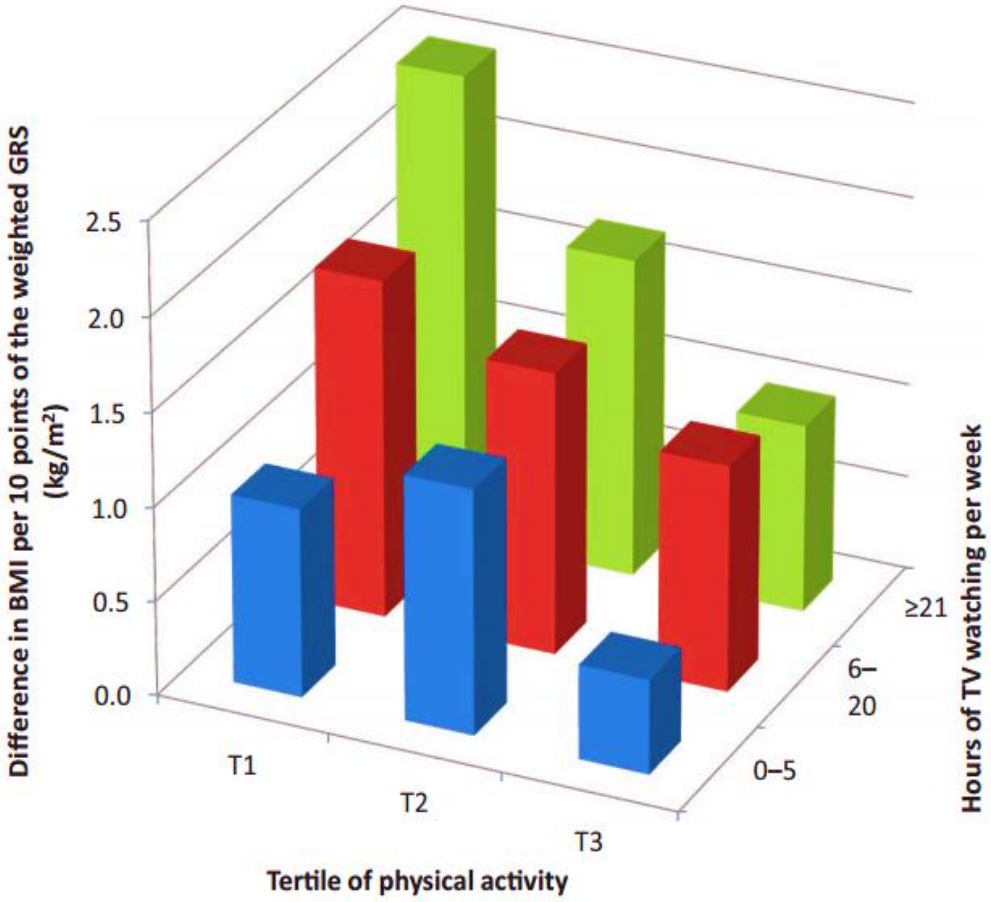
- The genetic association with BMI was strengthened with increased hours of TV watching ($p_{interaction}$<0.001). In contrast, the genetic association with BMI was weakened with increased levels of physical activity.



Qi et al. *Circulation 2012*

Gene – Physical Activity interactions & Obesity

- The modifying effects of TV watching & PA on genetic associations with BMI were independent of each other.
- **Conclusion**: A sedentary lifestyle may enhance the predisposition to elevated adiposity, whereas greater leisure time physical activity may mitigate the genetic association.



Difference in BMI per 10 points of the weighted genetic risk score (GRS) according to joint classification of physical activity and TV watching.

Qi et al. *Circulation 2012*

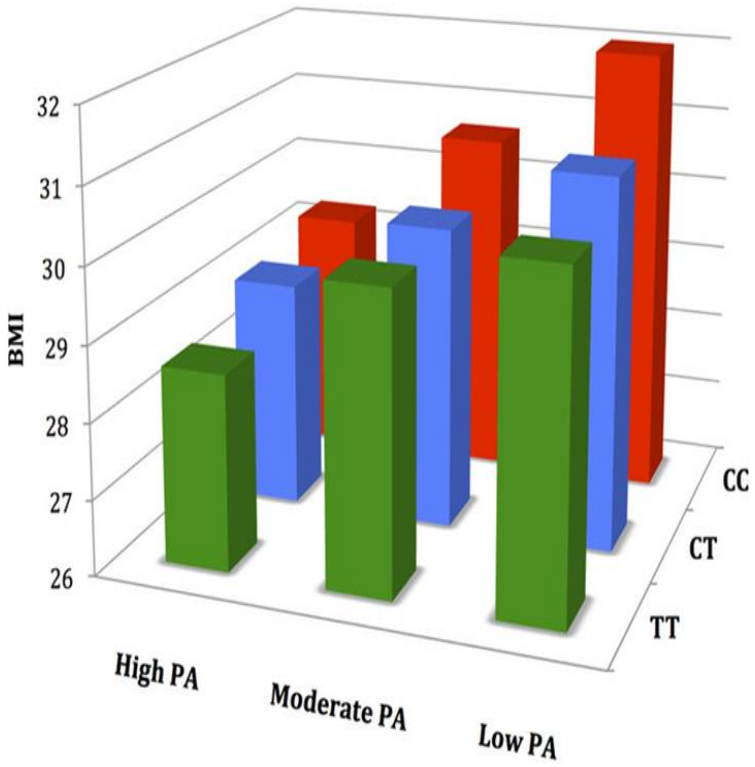
Gene – Physical Activity & Obesity

- **Multi-ethnic prospective cohort EpiDREAM**: Analyzed the impact of PA on the association between 14 obesity predisposing variants (analyzed independently and as a GRS) & baseline/follow-up obesity measures (n=17423 from 6 ethnic groups).

- Increased PA was associated with decreased BMI/BAI at baseline/follow-up.
- FTO rs1421085, CDKAL1 rs2206734, TNNl3K rs1514176, GIPR rs11671664 and the GRS were associated with obesity measures at baseline and/or follow-up.
- Both basic and quantitative PA measures attenuated the association between FTO rs1421085 risk allele and BMI/BAI at baseline and follow-up.

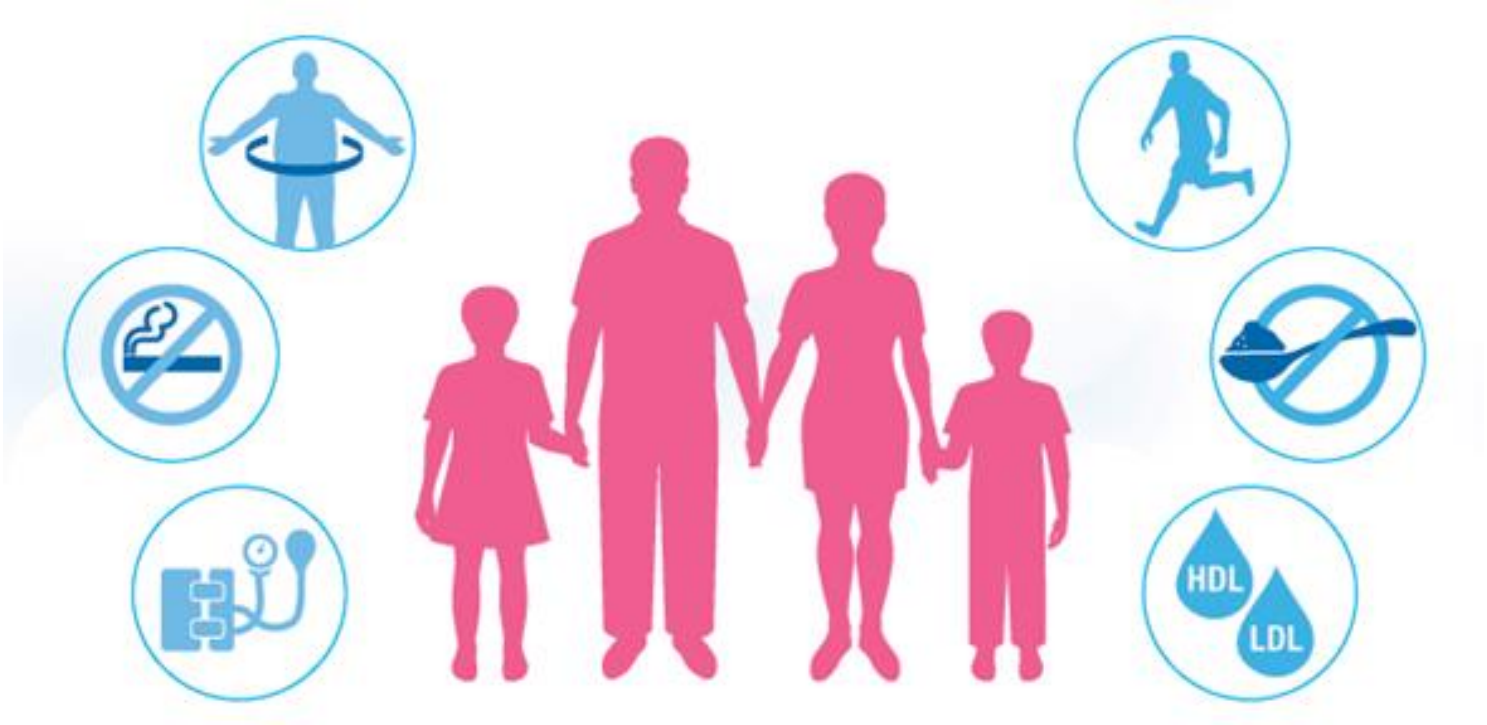
- **Conclusion**: PA can blunt the genetic effect of FTO rs1421085 on adiposity by 36-75% in a longitudinal multi-ethnic cohort. Findings suggest that obesity prevention programs emphasizing vigorous PA for genetically at risk subgroups may be a valuable contribution to the global fight against obesity.

Reddon et al. *Scientific Reports 2016*



Mean baseline BMI values stratified by physical activity level (PA) & FTO rs1421085 genotype

Gene – Lifestyle interactions



Gene – Lifestyle interactions & CVD risk

The NEW ENGLAND JOURNAL of MEDICINE

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.

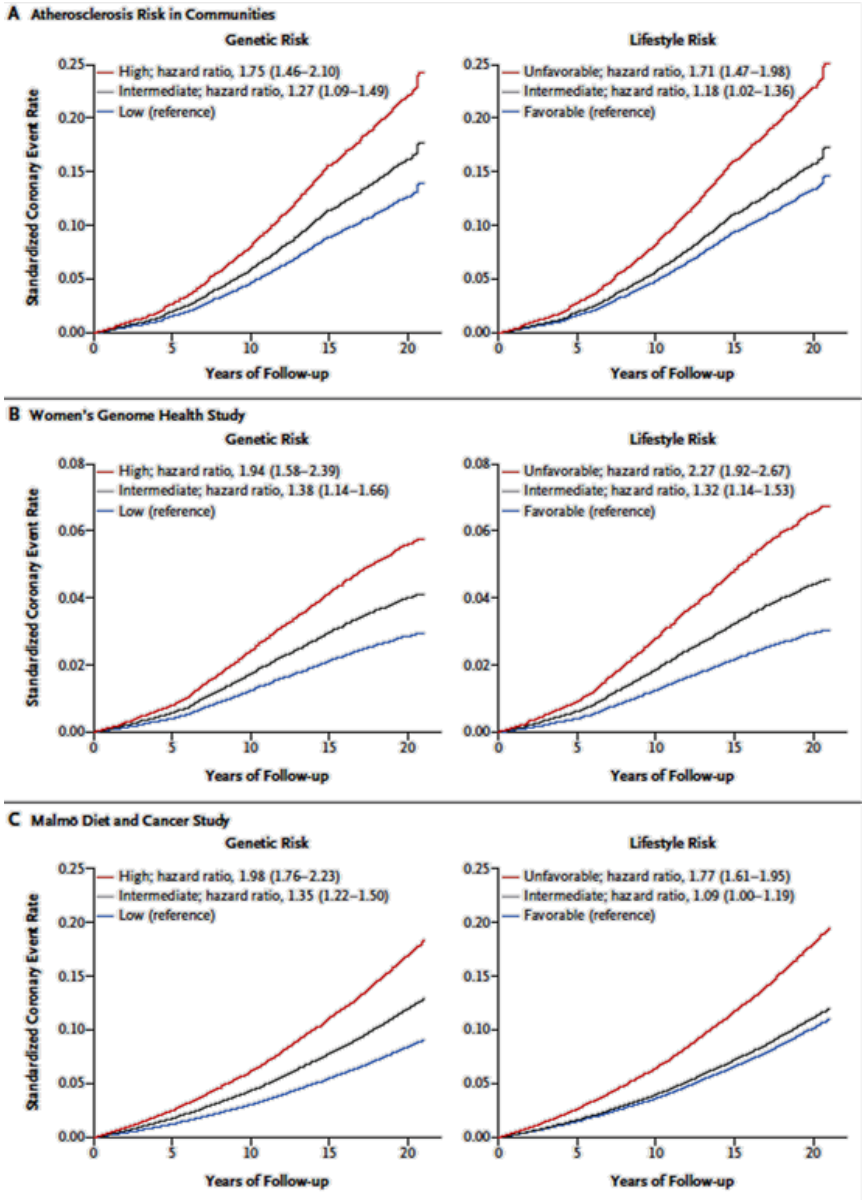
- Analyzed data for participants in 3 prospective cohorts (n=51,425) & 1 cross-sectional study (n=4,260) to test the hypothesis that both genetic factors & baseline adherence to a healthy lifestyle contribute independently to the risk of incident coronary events & the prevalent subclinical burden of atherosclerosis.
- Determined the extent to which a healthy lifestyle is associated with a reduced risk of CAD among participants with a high genetic risk.

- **Polygenic risk score**: up to 50 GWAs SNPs associated with CAD

- **Healthy lifestyle**: each individual was also scored for adherence to 4 healthy lifestyle behaviors described by the AHA: no smoking, no obesity, weekly physical activity, and a healthy diet. A favorable lifestyle was defined as at least 3 of the 4 healthy lifestyle factors.

Khera et al. *NEJM 2016*

Genetic Risk, Adherence to a Healthy Lifestyle & CAD

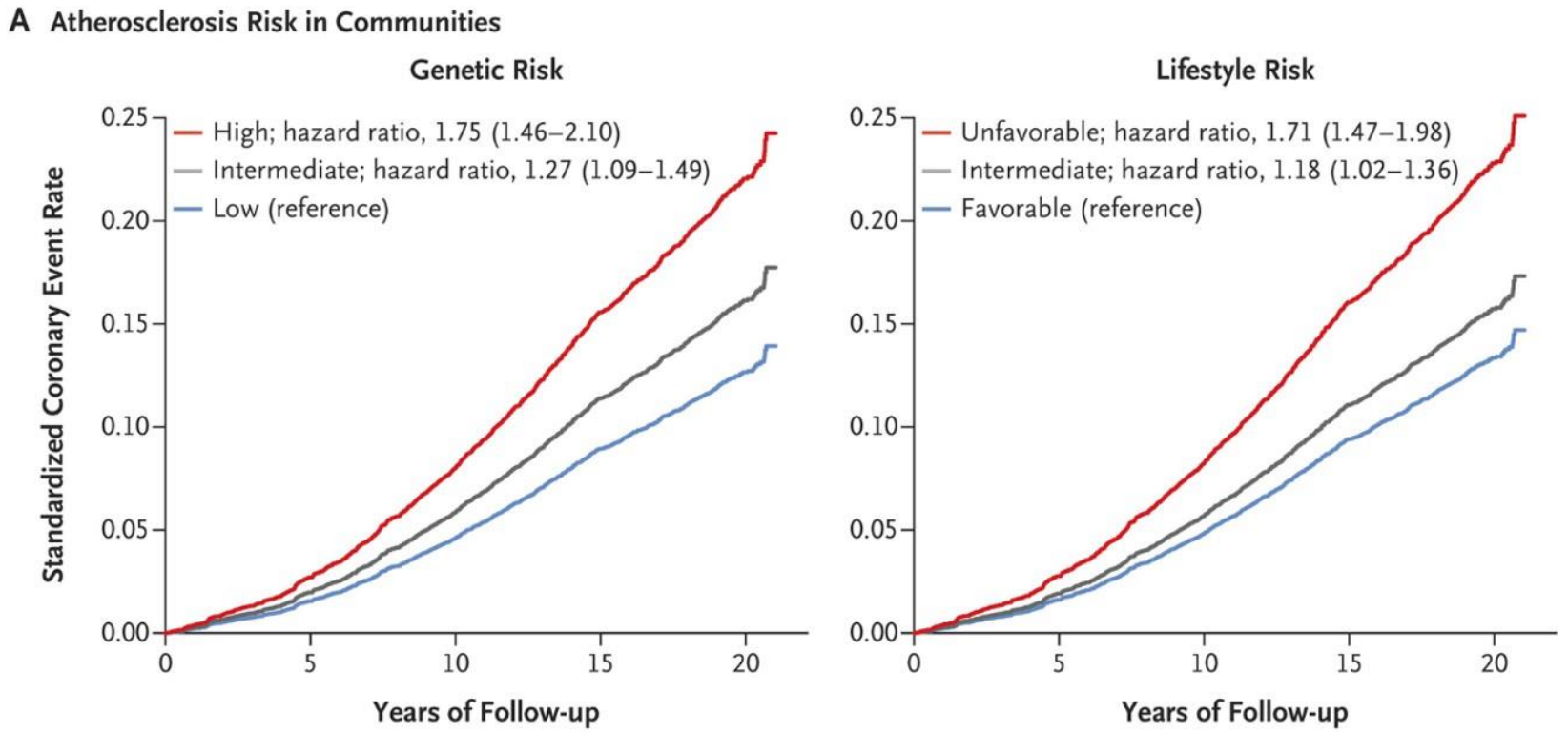


Khera et al. *NEJM 2016*

- Across 3 studies involving >50,000 participants, genetic & lifestyle factors were independently associated with susceptibility to CAD.

Standardized Coronary Events Rates, according to Genetic & Lifestyle Risk in the Prospective Cohorts.

Genetic Risk, Adherence to a Healthy Lifestyle & CAD

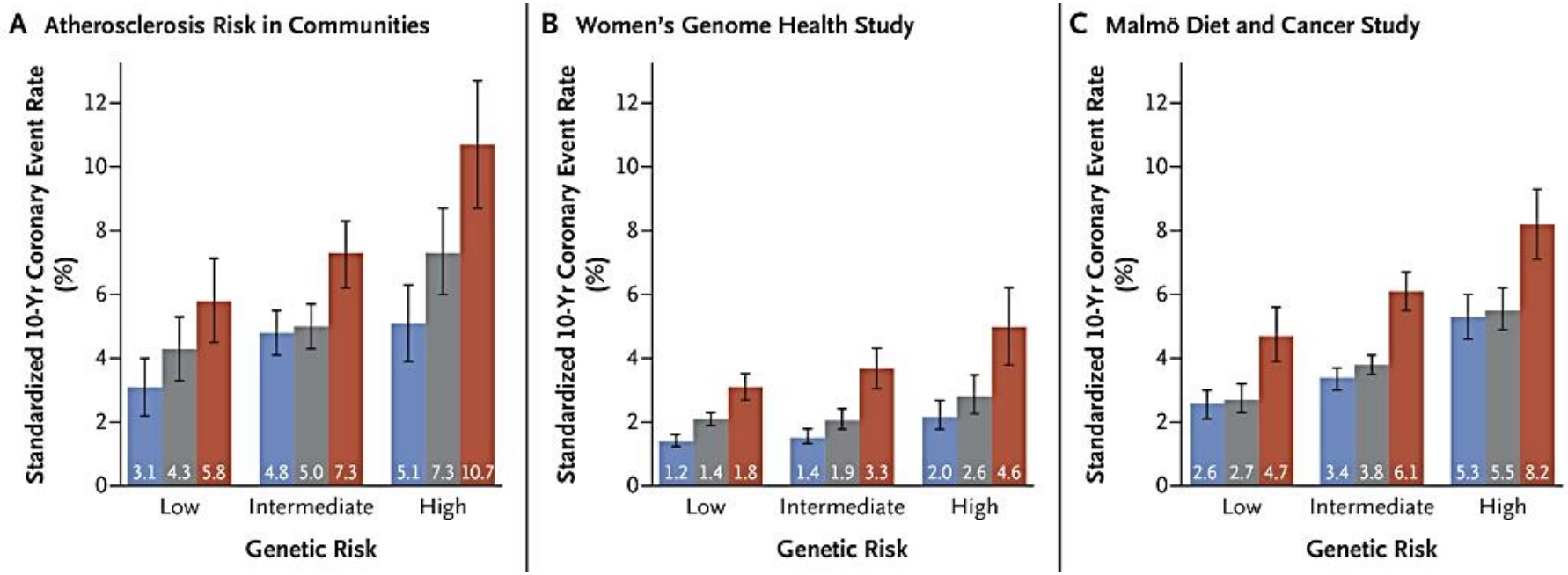


- The RR of incident CAD was 91% higher among participants at high genetic risk (Q4) than among those at low genetic risk (Q1) (HR:1.91; 95%CI: 1.75-2.09).

Khera et al. NEJM 2016

Genetic Risk, Adherence to a Healthy Lifestyle & CAD

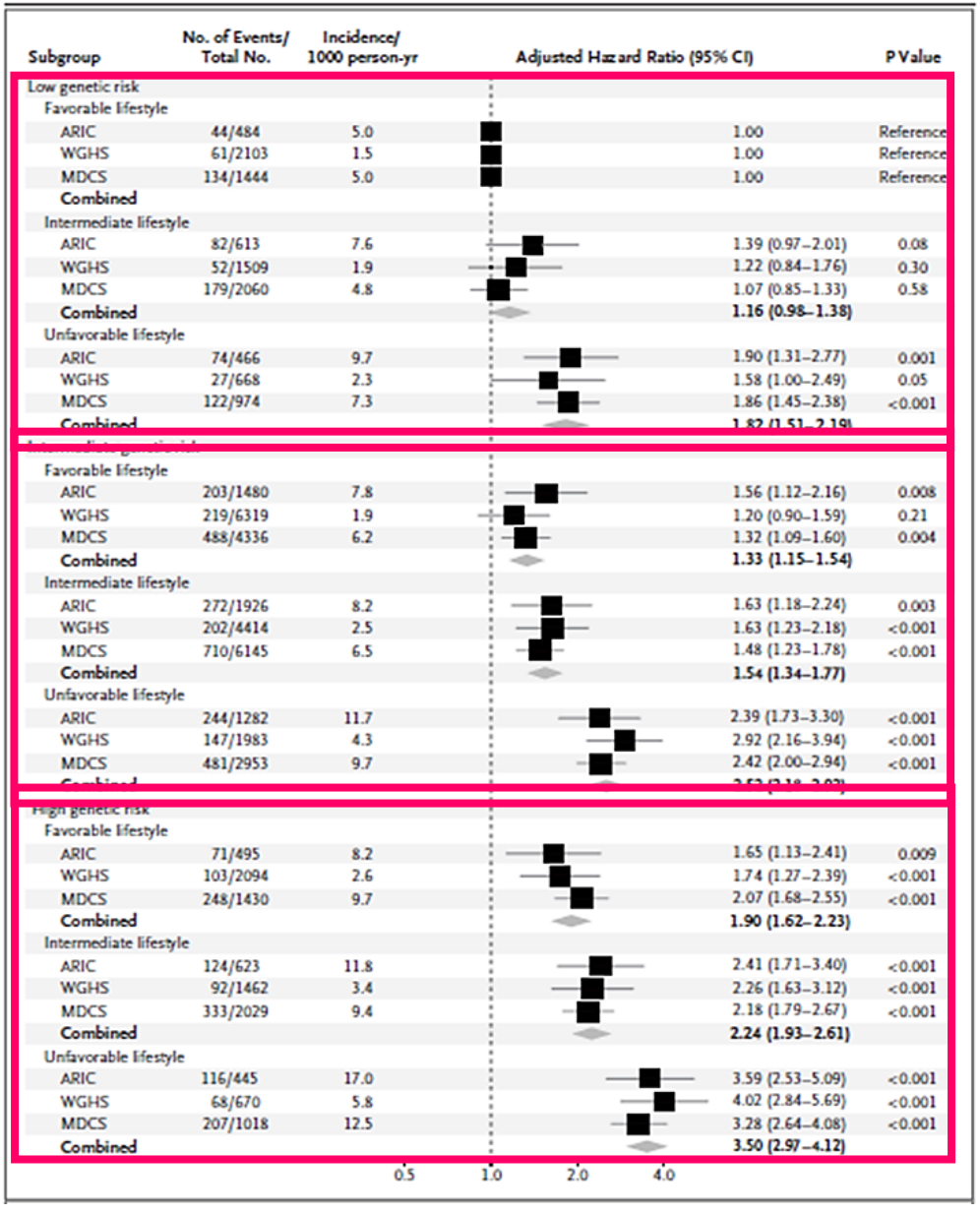
- Among participants at high genetic risk, a favorable lifestyle was associated with a 46% lower relative risk of coronary events than an unfavorable lifestyle (HR: 0.54; 95%CI: 0.47-0.63).



10-Year Coronary Event Rates, According to Lifestyle and Genetic Risk in the Prospective Cohorts.

Khera et al. *NEJM 2016*

Genetic Risk, Adherence to a Healthy Lifestyle & CAD



Subgroup	No. of Events/ Total No.	Incidence/ 1000 person-yr	Adjusted Hazard Ratio (95% CI)	P Value
Low genetic risk				
Favorable lifestyle				
ARIC	44/484	5.0	1.00	Reference
WGHS	61/2103	1.5	1.00	Reference
MDCS	134/1444	5.0	1.00	Reference
Combined				
Intermediate lifestyle				
ARIC	82/613	7.6	1.39 (0.97–2.01)	0.08
WGHS	52/1509	1.9	1.22 (0.84–1.76)	0.30
MDCS	179/2060	4.8	1.07 (0.85–1.33)	0.58
Combined			**1.16 (0.98–1.38)**	
Unfavorable lifestyle				
ARIC	74/466	9.7	1.90 (1.31–2.77)	0.001
WGHS	27/668	2.3	1.58 (1.00–2.49)	0.05
MDCS	122/974	7.3	1.86 (1.45–2.38)	<0.001
Combined			**1.82 (1.51–2.19)**	
Favorable lifestyle				
ARIC	203/1480	7.8	1.56 (1.12–2.16)	0.008
WGHS	219/6319	1.9	1.20 (0.90–1.59)	0.21
MDCS	488/4336	6.2	1.32 (1.09–1.60)	0.004
Combined			**1.33 (1.15–1.54)**	
Intermediate lifestyle				
ARIC	272/1926	8.2	1.63 (1.18–2.24)	0.003
WGHS	202/4414	2.5	1.63 (1.23–2.18)	<0.001
MDCS	710/6145	6.5	1.48 (1.23–1.78)	<0.001
Combined			**1.54 (1.34–1.77)**	
Unfavorable lifestyle				
ARIC	244/1282	11.7	2.39 (1.73–3.30)	<0.001
WGHS	147/1983	4.3	2.92 (2.16–3.94)	<0.001
MDCS	481/2953	9.7	2.42 (2.00–2.94)	<0.001
Combined			**2.53 (2.18–2.93)**	
High genetic risk				
Favorable lifestyle				
ARIC	71/495	8.2	1.65 (1.13–2.41)	0.009
WGHS	103/2094	2.6	1.74 (1.27–2.39)	<0.001
MDCS	248/1430	9.7	2.07 (1.68–2.55)	<0.001
Combined			**1.90 (1.62–2.23)**	
Intermediate lifestyle				
ARIC	124/623	11.8	2.41 (1.71–3.40)	<0.001
WGHS	92/1462	3.4	2.26 (1.63–3.12)	<0.001
MDCS	333/2029	9.4	2.18 (1.79–2.67)	<0.001
Combined			**2.24 (1.93–2.61)**	
Unfavorable lifestyle				
ARIC	116/445	17.0	3.59 (2.53–5.09)	<0.001
WGHS	68/670	5.8	4.02 (2.84–5.69)	<0.001
MDCS	207/1018	12.5	3.28 (2.64–4.08)	<0.001
Combined			**3.50 (2.97–4.12)**	

0.5 1.0 2.0 4.0

Khera et al. *NEJM 2016*

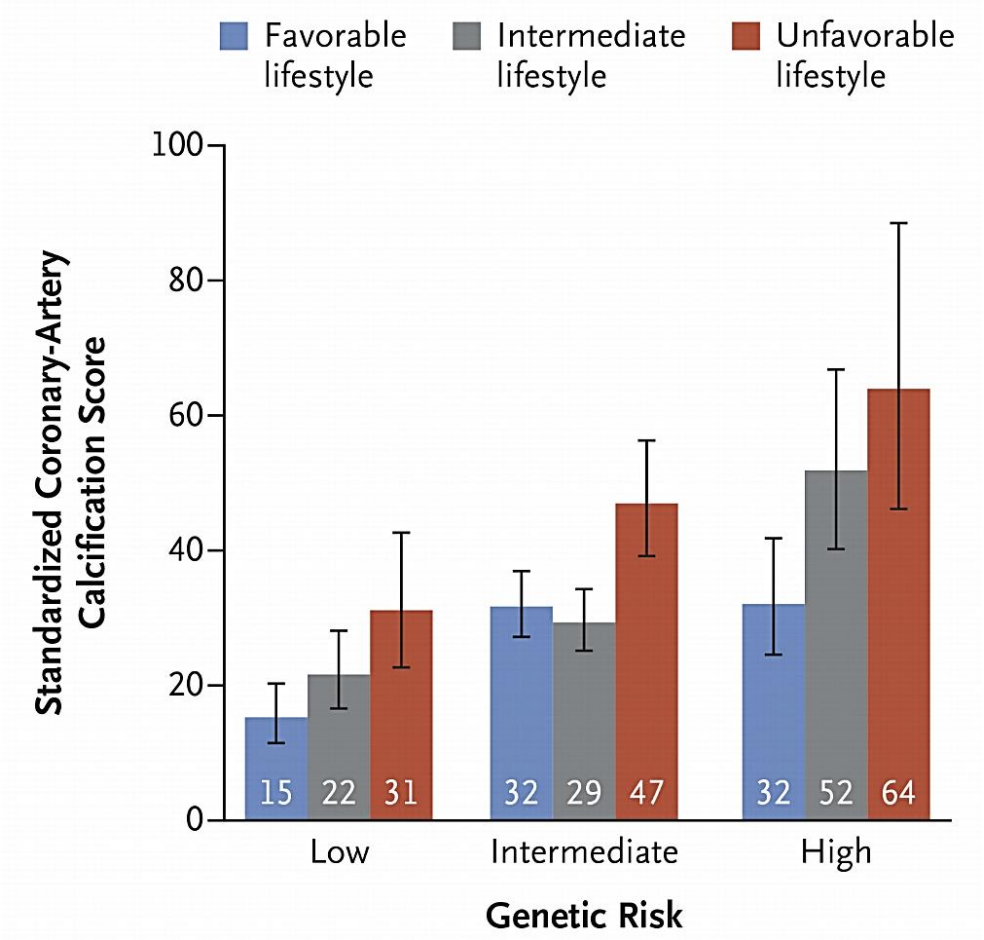
- A favorable lifestyle (defined as at least 3 of the 4 healthy lifestyle factors) was associated with a substantially lower risk of CAD than an unfavorable lifestyle (defined as no or only 1 healthy lifestyle factor), regardless of the genetic risk category

- Among participants at high genetic risk, a favorable lifestyle was associated with a 46% lower relative risk of coronary events than an unfavorable lifestyle (HR: 0.54; 95%CI: 0.47-0.63).

Risk of Coronary Events, According to Genetic & Lifestyle Risk in the Prospective Cohorts.

Genetic Risk, Adherence to a Healthy Lifestyle & CAD

Khera et al. *NEJM 2016*



- In the BioImage Study, a favorable lifestyle was associated with significantly less coronary-artery calcification within each genetic risk category.

- **CONCLUSION**: Across 4 studies involving 55,685 participants, genetic & lifestyle factors were independently associated with susceptibility to coronary artery disease.
  Among participants at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower relative risk of coronary artery disease than was an unfavorable lifestyle.

Gene – Lifestyle interactions & CVD risk - II

Original Investigation

FREE

August 2018

Associations of Combined Genetic and Lifestyle Risks With Incident Cardiovascular Disease and Diabetes in the UK Biobank Study

M. Abdullah Said, BSc[1]; Niek Verweij, PhD[1]; Pim van der Harst, MD, PhD[1,2,3]

» Author Affiliations | Article Information

JAMA Cardiol. 2018;3(8):693-702. doi:10.1001/jamacardio.2018.1717

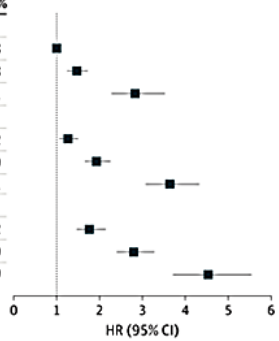
- **OBJECTIVE**: To investigate the association of combined health behaviors and factors within genetic risk groups with CAD, atrial fibrillation (AF), stroke, hypertension, and T2D as well as to investigate the interactions between genetic risk and lifestyle.
- Analyzed data for 339.003 unrelated individuals of white British descent (UK Biobank).
- **Polygenic risk scores**: CAD: 169 SNPs; AF:25 SNPs; Stroke: 11 SNPs; Hypertension:107 SNPs; T2D: 38 SNPs
- **Lifestyle**: individuals were also scored for adherence to 4 lifestyle behaviors (AHA guidelines): smoking, obesity, physical activity, and diet. Overall lifestyle was categorized into **ideal** (having at least 3 ideal lifestyle factors), **poor** (having at least 3 poor lifestyle factors), or **intermediate** (all other combinations).

Said et al. JAMA Cardiol 2018

Genetic Risk, Lifestyle Risk & incident CVD (UK Biobank)

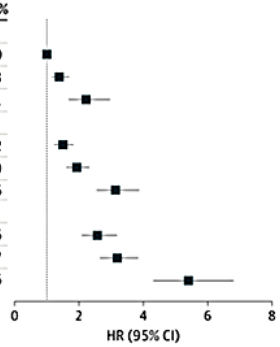
A Coronary artery disease

Group	HR (95% CI)	AR, %
Low genetic risk		
Ideal lifestyle	1 [Reference]	1.28
Intermediate lifestyle	1.48 (1.26-1.74)	2.38
Poor lifestyle	2.85 (2.29-3.53)	4.81
Intermediate genetic risk		
Ideal lifestyle	1.28 (1.09-1.51)	1.62
Intermediate lifestyle	1.95 (1.68-2.27)	3.09
Poor lifestyle	3.65 (3.08-4.33)	5.91
High genetic risk		
Ideal lifestyle	1.79 (1.48-2.16)	2.22
Intermediate lifestyle	2.82 (2.41-3.29)	4.29
Poor lifestyle	4.54 (3.72-5.54)	6.99



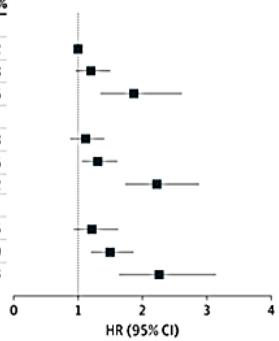
B Atrial fibrillation

HR (95% CI)	AR, %
1 [Reference]	0.90
1.40 (1.16-1.70)	1.53
2.24 (1.69-2.97)	2.31
1.51 (1.24-1.84)	1.32
1.94 (1.62-2.33)	2.09
3.15 (2.56-3.88)	3.26
2.58 (2.09-3.19)	2.26
3.20 (2.66-3.85)	3.37
5.41 (4.29-6.81)	5.46



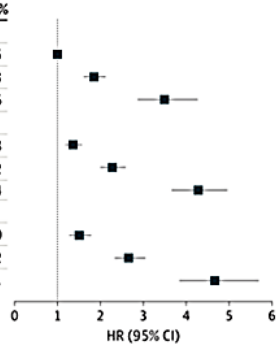
C Stroke

Group	HR (95% CI)	AR, %
Low genetic risk		
Ideal lifestyle	1 [Reference]	0.62
Intermediate lifestyle	1.20 (0.96-1.49)	0.88
Poor lifestyle	1.87 (1.34-2.61)	1.46
Intermediate genetic risk		
Ideal lifestyle	1.11 (0.88-1.41)	0.68
Intermediate lifestyle	1.31 (1.06-1.61)	0.96
Poor lifestyle	2.23 (1.73-2.88)	1.72
High genetic risk		
Ideal lifestyle	1.22 (0.93-1.62)	0.75
Intermediate lifestyle	1.50 (1.20-1.86)	1.09
Poor lifestyle	2.26 (1.63-3.14)	1.73



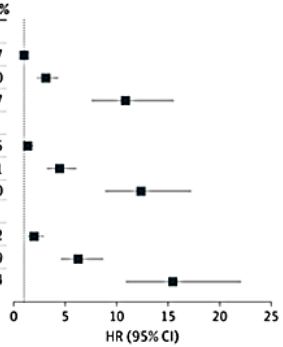
D Hypertension

HR (95% CI)	AR, %
1 [Reference]	2.15
1.86 (1.62-2.13)	4.43
3.50 (2.87-4.27)	8.16
1.37 (1.19-1.58)	2.88
2.28 (2.01-2.60)	5.32
4.26 (3.66-4.96)	9.84
1.52 (1.29-1.79)	3.10
2.67 (2.34-3.05)	6.02
4.68 (3.85-5.69)	10.71



E Type 2 diabetes

Group	HR (95% CI)	AR, %
Low genetic risk		
Ideal lifestyle	1 [Reference]	0.27
Intermediate lifestyle	3.09 (2.22-4.30)	1.00
Poor lifestyle	10.82 (7.54-15.54)	3.87
Intermediate genetic risk		
Ideal lifestyle	1.33 (0.93-1.90)	0.35
Intermediate lifestyle	4.40 (3.19-6.07)	1.41
Poor lifestyle	12.33 (8.84-17.22)	4.50
High genetic risk		
Ideal lifestyle	1.94 (1.30-2.90)	0.52
Intermediate lifestyle	6.27 (4.53-8.68)	1.99
Poor lifestyle	15.46 (10.82-22.08)	5.54



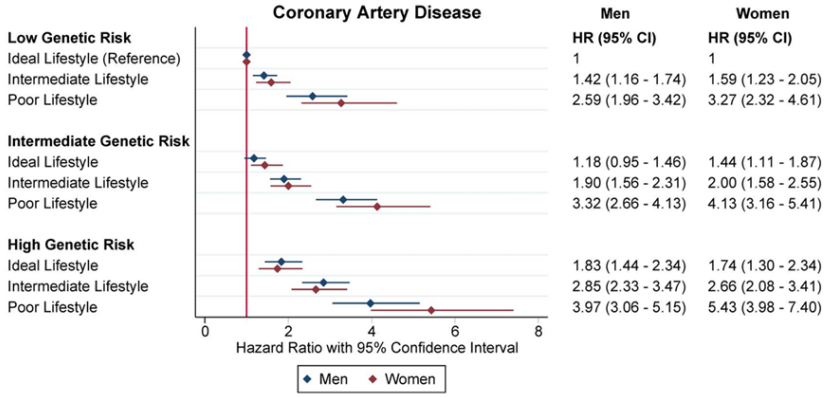
Said et al. *JAMA Cardiol 2018*

- Genetic risk and lifestyle were independent predictors of incident events.
- Compared with ideal lifestyle in the low genetic risk group, poor lifestyle in the high genetic risk group was associated with a HR (95%CI):
  - ✓ **CAD**: 4.54 (3.72-5.54)
  - ✓ **AF**: 5.41 (4.29-6.81)
  - ✓ **Hypertension**: 4.68 (3.85-5.69)
  - ✓ **Stroke**: 2.26 (1.63-3.14)
  - ✓ **T2D**: 5.46 (10.82-22.08)
- No significant interactions were found between behavioral lifestyle and GR of any outcome

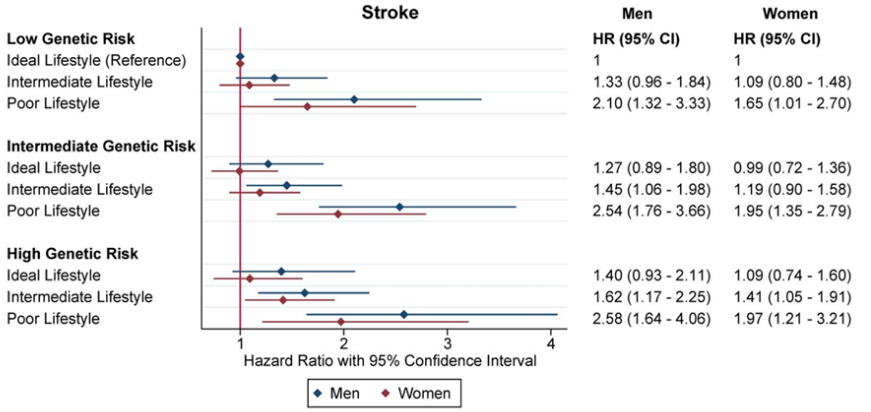
Genetic Risk, Lifestyle Risk & incident CVD (UK Biobank)

Said et al. *JAMA Cardiol 2018*

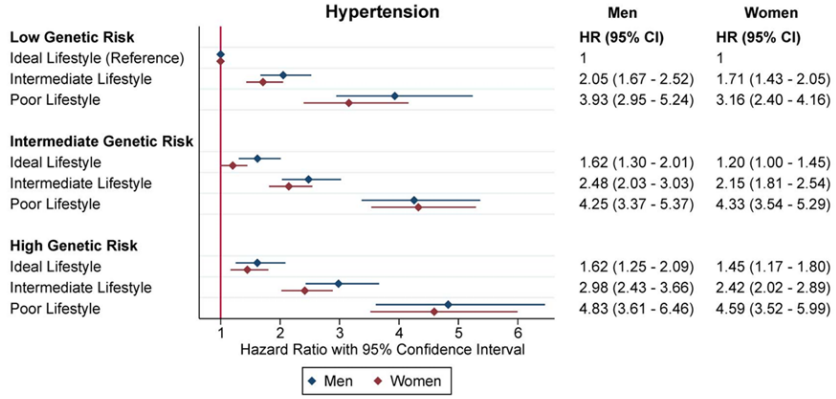
eFigure 2. Risk of incident coronary artery disease associated with genetic risk and lifestyle stratified by sex



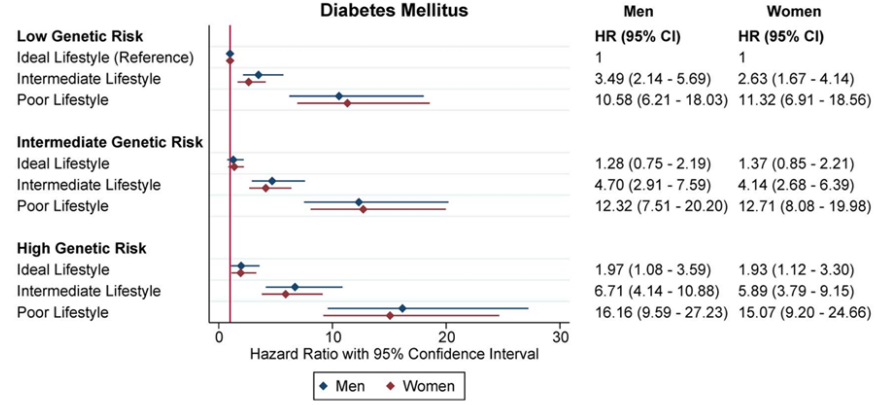
eFigure 4. Risk of incident stroke associated with genetic risk and lifestyle stratified by sex



eFigure 5. Risk of incident hypertension associated with genetic risk and lifestyle stratified by sex



eFigure 6. Risk of incident diabetes associated with genetic risk and lifestyle stratified by sex



Genetic Risk, Lifestyle Risk & incident CVD (UK Biobank)

Said et al. *JAMA Cardiol 2018*

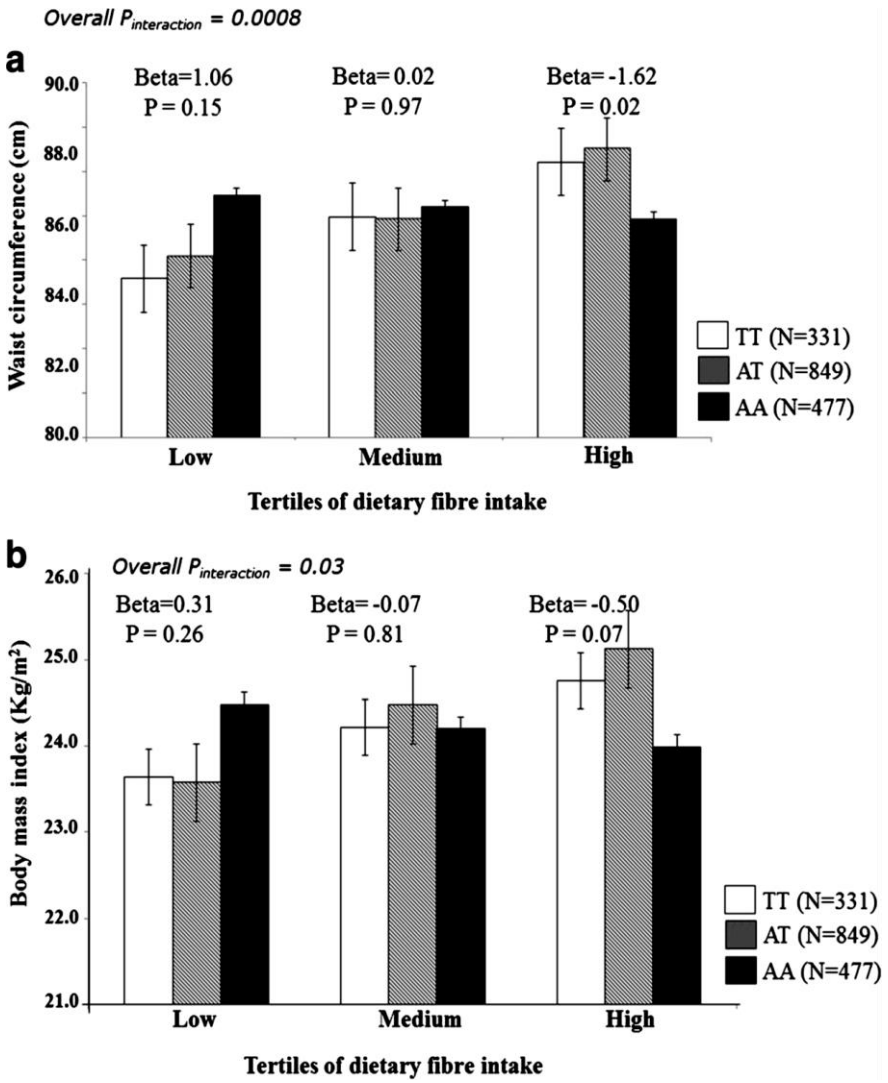
- The study was the first to report associations of combined health behaviors and factors in different GR groups for AF, stroke, hypertension, and T2D.
- The effects of combined health behaviors and factors across GR groups are in line with a previous report for CAD (Khera et al. *NEJM 2016*) which studied a smaller population of 55.685 participants with 5103 (9.2%) new-onset events. The general risk patterns associated with lifestyle and GR were similar in both studies.
- However, the present study suggests the HR associated with poor lifestyle and high GR may be 1.3-fold (95% CI, 1.25-1.34) higher compared with the previous report. Compared with the previous report, the present study included more SNPs associated with CAD (169 vs 50) to increase power for estimating the GR. Furthermore, information on lifestyle behaviors and factors were collected uniformly for all participants in the UK Biobank study, whereas each of the 4 cohorts included in the previous report used different methods to collect this data.

- **CONCLUSION**: poor behavioral lifestyle was a strong incremental risk factor of new-onset CVD and diabetes in this large cohort. This study showed that GR and combined health behaviors and factors have a log-additive effect on the risk of new-onset diseases but that there were no interactions between these risk factors. **Behavioral lifestyle changes should be encouraged for all through comprehensive multifactorial approaches, although high-risk individuals may be selected based on their GR**.

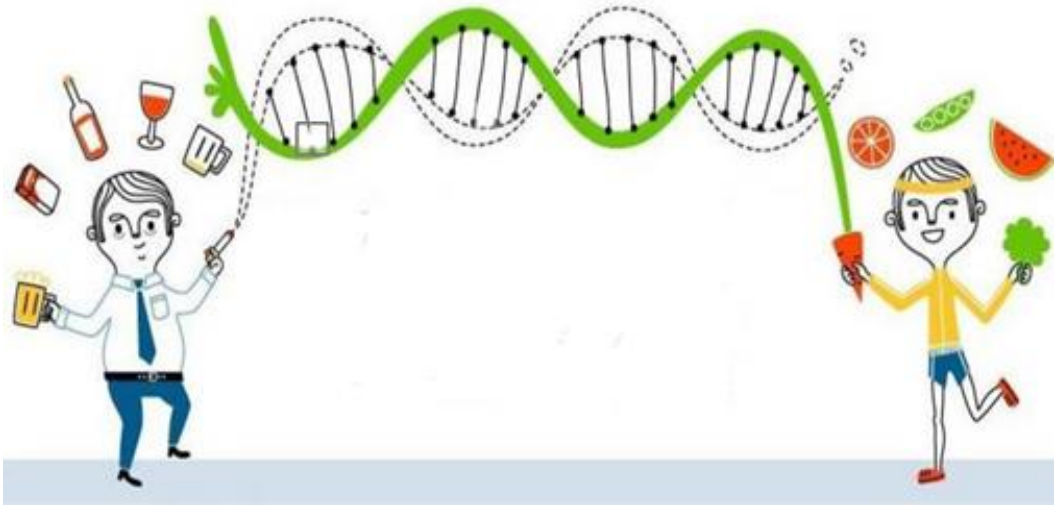
Gene – Lifestyle factors & Obesity

- First study to provide evidence for a gene-diet & gene-physical activity interaction on obesity and T2DM in an Asian Indian population.
- Interaction of the FTO gene SNP (rs11076023) with dietary fibre intake on WC & BMI. Individuals with AA genotype who are in the 3rd tertile of dietary fibre intake had 1.62 cm decrease in WC & 0.50 kg/m^2 decrease in BMI compared to those with 'T' allele carriers.
- Furthermore, among those who were physically inactive, the 'A' allele carriers had 1.89 times increased risk of obesity than those with 'CC' genotype ($P=4.0\times10^{-5}$).

- **Conclusion**: The association between FTO SNPs & obesity might be influenced by CHO & dietary fibre intake and physical inactivity.



Vimaleswaran et al. *Nutrition & Metabolism* 2016



Σας ευχαριστώ για την προσοχή σας!