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Genetic screening of cardiovascular disease:

an update

Monogenic Forms of Cardiovascular Disease

Janssens et al. Neth Heart J 2011;19:85-88

Genome-based predictive testing and personalized medicine already exists for monogenic forms of cardiovascular disease:

Long-QT syndrome: genetic background impacts on prognosis and therapeutic choices

Inherited primary arrhythmia syndromes: pre-symptomatic genetic testing leads to prophylactic therapy in a substantial number of patients

Familial idiopathic ventricular fibrillation: genetic testing might be the only way to identify individuals at risk

Hypertrophic cardiomyopathy: genetic cascade testing is a cost-effective way for identifying relatives at risk and primary prevention of sudden cardiac death

Familial Hypercholesteremia (FH)

Goldberg AC et al., Int J Lipidology 2011;Ned RM et al. PLoS Curr 2011

- one of the most common inherited disorders; the most common one known to cause premature CHD in people of European descent
- autosomal dominant disorder
- abnormally high circulating concentrations of LDL cholesterol predisposing to premature coronary heart disease/death
- the vast majority of people with FH have inherited a single mutation from one parent in either the LDL receptor (LDLR), apolipoprotein B (APOB), or proprotein convertase subtilisin/kexin type 9 (PCSK9) genes
- most individuals with FH remain undiagnosed/inadequately treated despite highly effective lipid-lowering drugs

Cascade Screening for FH

Ned RM et al. PLoS Curr 2011

- identify people at risk for a genetic condition through systematic family tracing
- recommended by UK National Institute for Health and Clinical Excellence NICE for close biological relatives of people with a clinical diagnosis of FH
- analytical validity: high number of common polymorphisms & scanning methods are not very efficient in detecting large-scale genetic rearrangements; many diagnostic labs are switching to direct sequencing
- clinical utility data from the U.K. has shown that cascade screening:

  reduces the average age at which FH patients are diagnosed

  results in increased percentages of people with FH on statins/lower lipid levels
- hard data lacking regarding effectiveness in improving health outcomes of in cascade screen detected patients

Genetic testing in predicting statin side effects

The prediction of adverse events based on genetic variation is a focus of intense investigation for statins, ADP receptor antagonists, and warfarin.

For the statin Simvastatin a SNP in the SLCO1B1 gene is very predictive of myopathy in patients undergoing high-dose regimen (*the SEARCH Collaborative Group; NEnglJMed 2008*)

Subgroup	TT/CT/CC		C Allele Frequency		Odds Ratio (95% CI) per C Allele	Odds Ratio (95% CI) for CC vs. TT
	No. of cases	No. of controls	No. of cases	No. of controls		
Type of myopathy						
Definite	12/15/14	70/17/3	0.52	0.13	5.2	27.2 (6.8–109.2)
Incipient	17/20/7	70/17/3	0.39	0.13	3.8	9.6 (2.2–41.1)
Age						
<65 yr	9/13/7	29/4/1	0.47	0.09	7.0	22.6 (2.4–208.7)
≥65 yr	20/22/14	41/13/2	0.45	0.15	3.6	14.3 (3.0–69.3)
Sex						
Male	19/25/17	52/13/2	0.48	0.13	5.0	23.3 (4.9–110.3)
Female	10/10/4	18/4/1	0.38	0.13	3.4	7.2 (0.7–73.5)
Glomerular filtration rate						
≥60 ml/min/1.73 m^2	20/26/17	53/11/2	0.48	0.11	5.4	22.5 (4.8–106.4)
<60 ml/min/1.73 m^2	9/9/4	17/6/1	0.39	0.17	2.8	7.6 (0.7–78.1)
Use of amiodarone						
No	24/32/19	59/16/3	0.47	0.14	4.3	15.6 (4.2–57.5)
Yes	5/3/2	11/1/0	0.35	0.04	8.1	No controls were CC
All	29/35/21	70/17/3	0.45	0.13	4.5	16.9 (4.7–61.1)

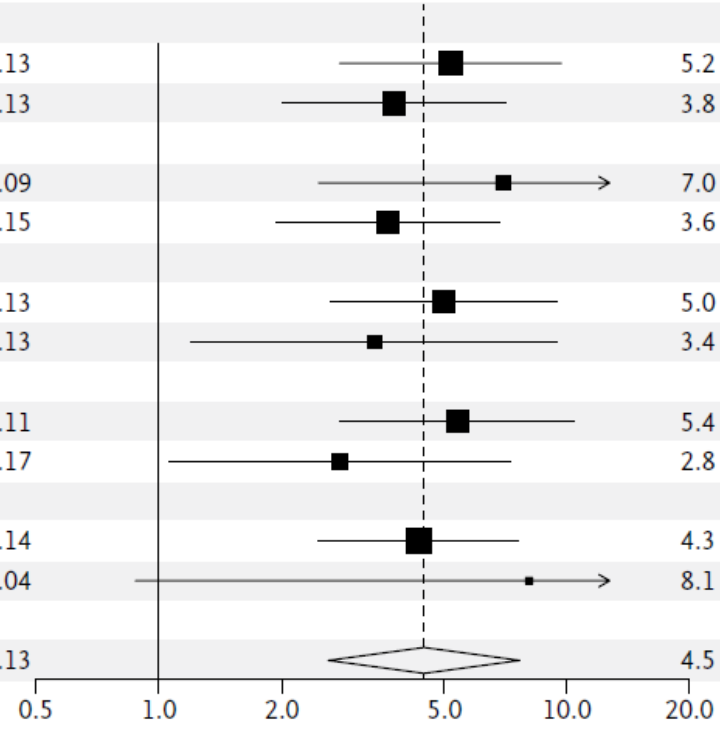
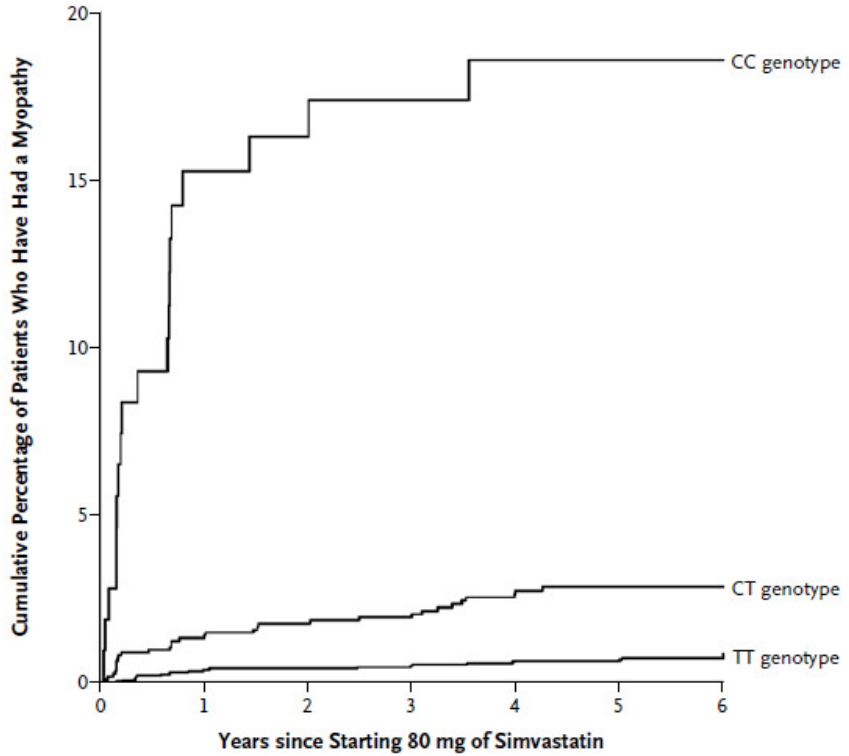


Figure 2. Odds Ratios for Myopathy Associated with the *SLCO1B1* rs4149056 Genotype among Subgroups of Patients Taking 80 mg of Simvastatin Daily.

Black squares indicate odds ratios (with area proportional to the amount of statistical information in each subdivision), and horizontal lines indicate 95% CIs (ending with an arrowhead when the CI extends beyond the scale). The overall odds ratio and its 95% CI are indicated by an unshaded diamond.



Genotype	Population Frequency	Cumulative No. and Percentages with Myopathy: Year 1				Year 5			
				Attributable to gentoype				Attributable to gentoype	
		no.	%	*no.*	*% of total*	*no.*	%	*no.*	*% of total*
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	32	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.56	43.3	60

Figure 3. Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to *SLCO1B1* rs4149056 Genotype.

Prevention of the common and complex forms of CVD

Non-modifiable risk factors:

1. age
2. gender
3. heredity (incl. African American ethnicity)

Modifiable risk factors:

- smoking
- physical inactivity
- obesity
- diabetes
- hypertension
- dyslipidemia
- low birth weight/developmental programming

Genome-based prediction of common diseases: advances and prospects

Janssen and van Duijn, Hum Mol Genetics 2008

- identification of sufficient cause mechanisms, and hence perfect risk prediction, is relatively straightforward for mono- and oligogenic disorders
- 'natural' limit to the predictive value of genetic profiling as common diseases are only partly influenced by genetic factors
- genetic testing may not improve the disease prediction beyond classical risk factors or new biomarkers, if most of the genes play a role through these risk factors
- genetic profiling may become useful for the identification of individuals at increased risk of disease to the same extent as traditional risk factors do

Selected studies on the prediction of complex diseases using multiple genes

Disease	Variant selection	AUC
Age-related macular degeneration	5 (out of 1536 tag SNPs in established genes)	0.80
Coronary heart disease	4 (out of 12)	0.62
Coronary heart disease	6 established variants	0.55
Hypertriglyceridemia	7 established variants	0.80
MI after surgery	3 (out of 48)	0.70
Systemic lupus erythematosus	From GWAS	0.67
Type 2 diabetes	3 established variants	0.55
Type 2 diabetes	3 (out of 19)	0.56
Type 2 diabetes	18 established variants	0.60
Type 2 diabetes	18 established variants	0.60

Evaluation of Genomic Applications in Practice and Prevention (EGAPP)

http://www.egappreviews.org/default.htm

The EGAPP initiative was launched by the CDC Office of Public Health Genomics in the fall of 2004.

The initiative's goal is to establish and evaluate a systematic, evidence-based process for assessing genetic tests and other applications of genomic technology in transition from research to clinical and public health practice.

Cardio-vascular disease	Recommendations from the EGAPP Working Group: Genomic profiling to assess cardiovascular risk to improve cardiovascular health	**Prediction:** association of genetic markers with disease risk	Insufficient evidence to recommend for or against use Read the EGAPP recommendation (December 2010)

Recommendations from the EGAPP Working Group: Genomic profiling to assess cardiovascular risk to improve cardiovascular health

Genetics IN Medicine • Volume 12, Number 12, December 2010

The Evaluation of EGAPP found insufficient evidence to recommend testing for the 9p21 genetic variant or 57 other variants in 28 genes to assess risk for cardiovascular disease (CVD) in the general population, specifically heart disease and stroke.

The magnitude of net health benefit from use of any of these tests alone or in combination is negligible

Discourage clinical use unless further evidence supports improved clinical outcomes

Based on the available evidence, the overall certainty of net health benefit is deemed "Low."

Evaluation of genomic tests offered by companies as of February 2008

Genetics In Medicine • Volume 12, Number 12, December 2010

Table 1 The 29 genes and their variants included in 8 genomic tests for heart health considered in this recommendation

Genes	Variant	Genes	Variant	Genes	Variant
ACE	Del, Ins	*CYP11B2*	T344C	*MTRR*	A66G
AGT	M235T	*F2*	G20210A	*NOS3*	G894T
AGTR1	A1166C	*F5*	G1691A		Intron4
APOB	XbaI	*GNB3*	C825T		T786C
	InsDel	*GPX1*	ALA_n (n = 5,6,7)	*PAI-1*	G455A
	EcoRI	*IL1B*	C511T	*PON1*	Q192R
APOC3	Sst-1	*IL6*	G174C		L55M
	T455C	*LPL*	S447X	*SELE*	S128R
	C482T		A291S	*SOD2*	C47T
APOE	ϵ_n (n = 2, 3, 4)		PvuII	*SOD3*	—
CBS	c.844ins68	*ITGB3*	C1565T	*TNF*	G308A
CETP	TaqIB (C629A)	*MTHFR*	C677T		G238A
CYBA	C242T	*MTR*	A2756G	9p21	Multiple SNPs

SNPs, single nucleotide polymorphisms.

A multilocus genetic risk score for coronary heart disease

Ripatti S et al. Lancet 2010

Genetic risk score based on 13 SNPs identified the 20% of individuals of European ancestry who are at roughly 70% increased risk of a first coronary heart disease event

But:

not useful for risk discrimination

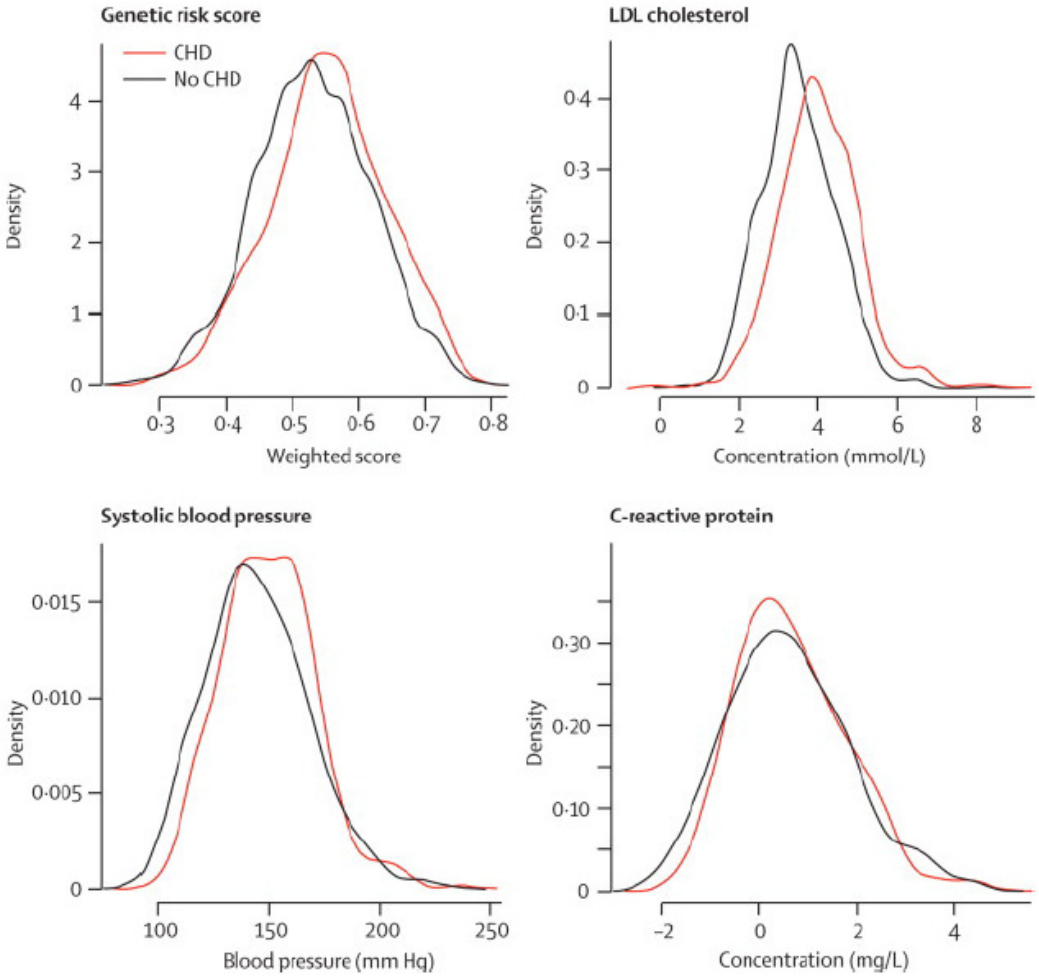
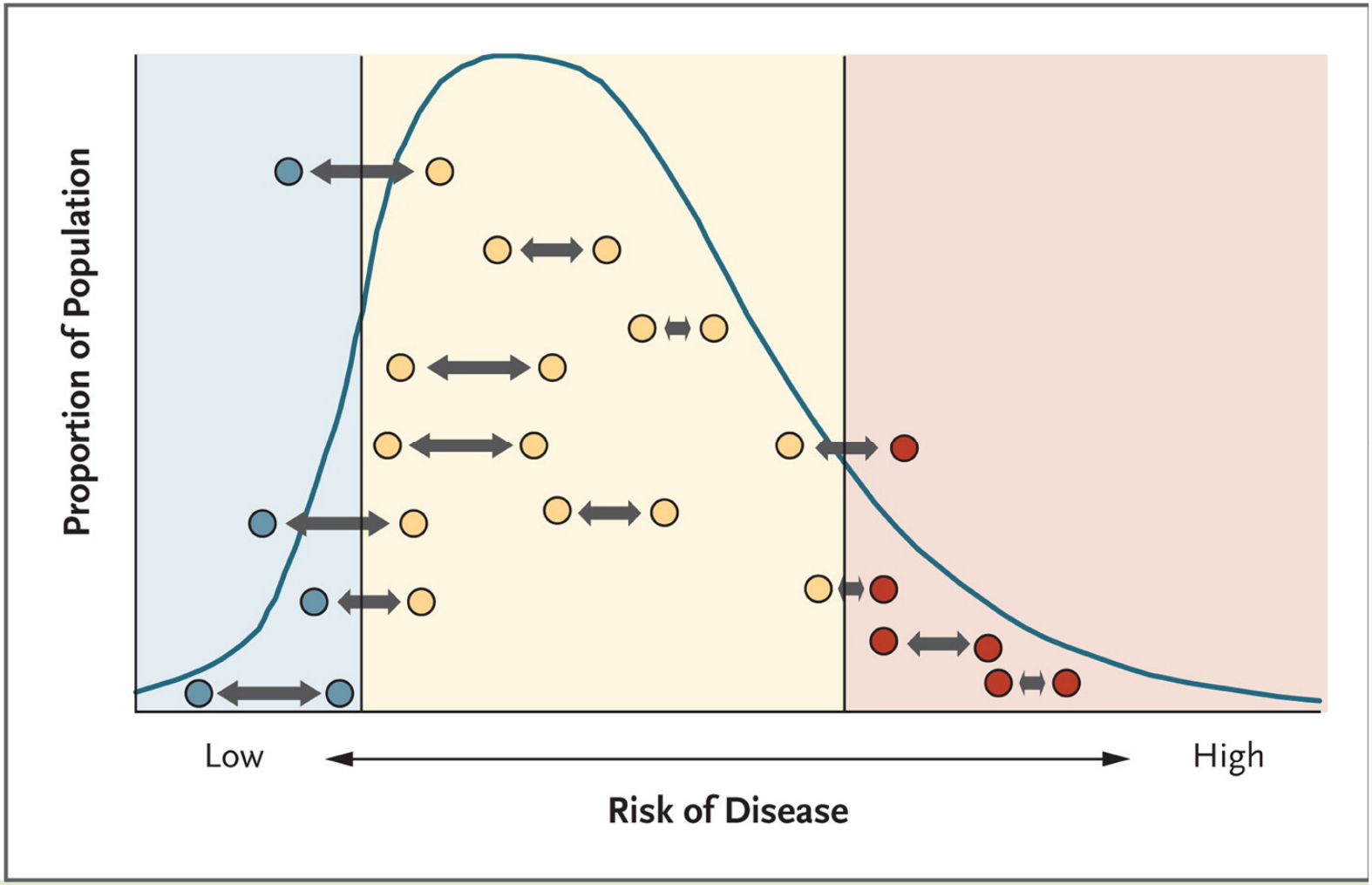


Figure.
Distributions at baseline of genetic risk score, LDL cholesterol, systolic blood pressure, and log-transformed C-reactive protein by 10-year incident coronary heart disease event status in FINRISK 1992 and 1997 cohorts
Data for C-reactive protein only available in FINRISK 1997. CHD=coronary heart disease.

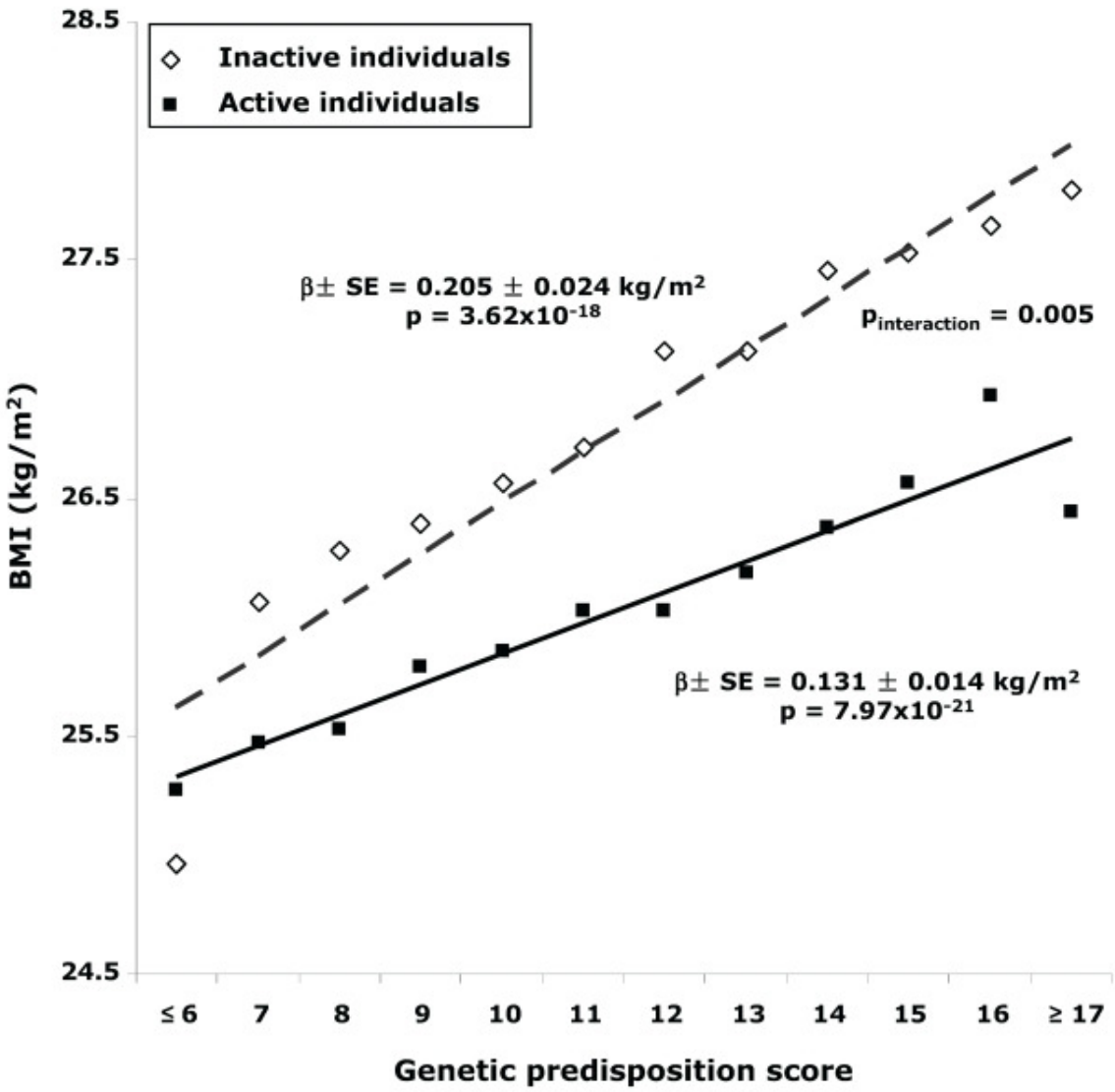
Reclassification of Persons at Various Levels of Risk, According to Risk Thresholds

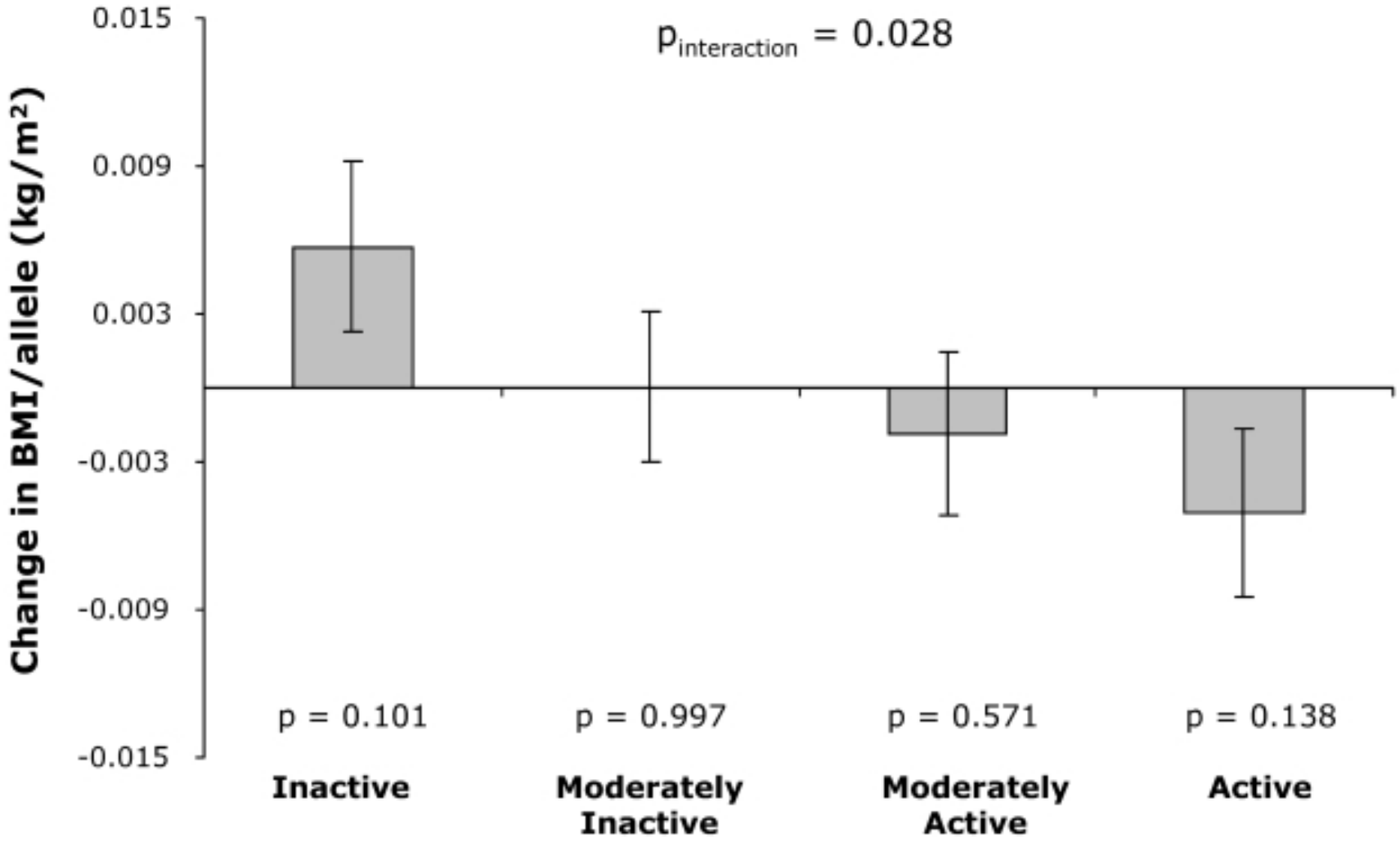
Manolio TA, NEnglJMed 2010



Physical activity attenuates the genetic predisposition to obesity in 20,000 men and women from EPIC-Norfolk prospective population study

Li S et al. PLoS Med 2010;7:1-9




$p_{interaction}$ = 0.028
Change in BMI/allele (kg/m²)
0.015
0.009
0.003
-0.003
-0.009
-0.015
p = 0.101
p = 0.997
p = 0.571
p = 0.138
Inactive
Moderately Inactive
Moderately Active
Active

What Do These Findings Mean ?

The findings indicate that:

- the genetic predisposition to obesity can be reduced by approximately 40% by having a physically active lifestyle

- while the whole population benefits from increased physical activity levels, individuals who are genetically predisposed to obesity would benefit more than genetically protected individuals

The sense and nonsense of direct-to-consumer genetic testing for cardiovascular disease.

Janssens et al. Neth Heart J 2011;19:85-88

Five reasons why these tests are not useful

(1)the predictive ability is still limited

(2)the **risk** models used by the companies are based on assumptions that have not been verified

(3)the predicted risks keep changing when new variants are discovered and added to the test

(4)the tests do not consider non-genetic factors in the **prediction** of cardiovascular disease **risk**

(5)the test results will not change recommendations of preventive interventions.

Patient-Physician Situation

•predictive genetic testing for multifactorial forms of cardiovascular disease clearly lacks benefits for the public.

•although evidence for beneficial vs. adverse effect of a genetic test result on behavioural change is currently lacking……

in the case the patient has already undergone testing, the physician may try to use the result to reinforce motivation for lifestyle change

Public Health Situation

- increase genetic literacy of health care workforce and public
- no recommendations for using genetics in predictive testing/screening
- more applied research on clinical utility
- focus prevention efforts on non-genetic risk factors