Gene-Environment Interactions

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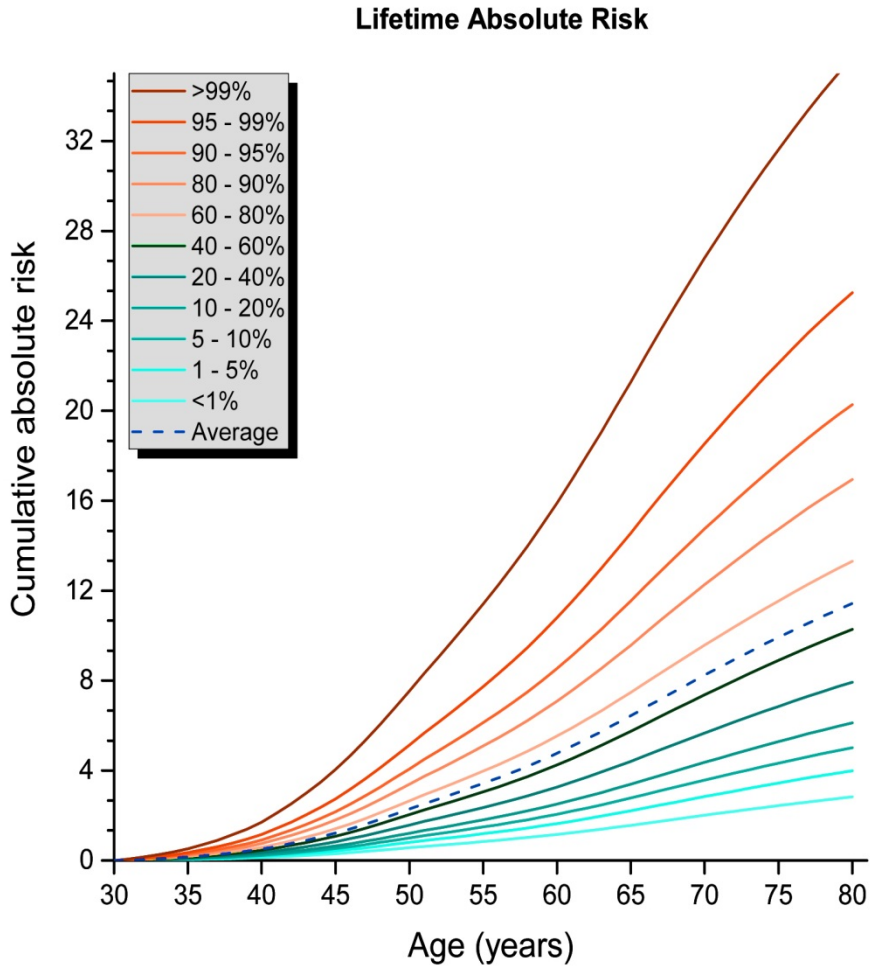
Differences in rates of most diseases between countries (and over time within countries) are due to differences in environmental and “lifestyle” risk factors – not genetic differences



Post-GWAS Polygenic Risk Scores are predictive – Breast Cancer

Maas, Chatterjee et al. JAMA Oncol 2016

Differences in individual risk of most diseases within countries are due to differences in both genetic and environmental and "lifestyle" risk factors.

We need to measure both.

How do they "interact"?

RATIONALES FOR STUDY OF Gene-Environment INTERACTION

- Explain more of the variance in disease risk

- Define susceptible sub-population in order to strengthen environmental association

- Provide individualized prevention advice

PHARMACOGENETICS

the study or clinical testing of genetic variation that gives rise to differing response to drugs

minimal exposure misclassification

obvious practical utility

Class	Genetic variant	Drug	Type of adverse reaction	Odds ratio
Phase I	*CYP2B6* reduced function alleles	Efavirenz	Neurological symptoms	Odds ratio for plasma concentration above therapeutic levels: 48.1
	CYP2D6 duplications	Codeine	Symptoms associated with opioid overdose	1.4
	CYP2D6 deficiency	Metoclopramide	Acute dystonic reactions	Only case reports
		Perhexiline	Neurotoxicity	Only case reports
	DPYD reduced function alleles	Fluoropyrimidines (capecitabine, fluorouracil and tegafur)	Severe systemic toxicity, mainly diarrhea, neutropenia, thrombocytopenia and cardiotoxicity	*2A: 15.2; D949V: 9.1
Phase II	*GSTM1* null	Isoniazid	DILI	2.2
	GSTT1 null		DILI	2.6
	*UGT1A1*28*	Irinotecan	Myelosuppression and neutropenia	9.3
	*UGT2B7*2*	Diclofenac	DILI	8.5
	TPMT deficiency	Mercaptopurine	Myelosuppression	het: 4.6; hom: 18.6
Transporter	Reduced *SLCO1B1* activity (rs4149056)	Simvastatin (80 mg daily)	Myopathy and rhabdomyolysis	het: 4.5; hom: 16.9
Major histocompatibility complex	*HLA-B*57:01*	Flucloxacillin	DILI	80.6
	*DRB1*07:01* and *DQA*02:01*	Ximelagatran	DILI	4.4
	*DRB1*15:01* and *HLA-A*02:01* and *HLA-B*18:01*	Amoxicillin-clavulanate	DILI	10.1
	*HLA-A*33:03*	Ticlopidine	DILI	36.5
	*DRB*15:01* and *DQA*01:02*	Lumiracoxib	DILI	5
	*HLA-B*57:01*	Abacavir	HSS	117
	*HLA-B*15:02* and *HLA-A*31:01*	Carbamazepine	HSS and SJS/TEN	10.8
	*HLA-B*15:02*	Phenytoin	SJS/TEN	25.2
	*HLA-B*58:01*	Allopurinol	SJS/TEN	394
	*HLA-B*58:01*	Nevirapine	DILI	3.5
	*HLA-DRB1*01*		DILI	2.9
	*HLA-C*04:01*		SJS/TEN	17.5

DILI drug-induced liver injury, *HSS* hypersensitivity syndrome, *SJS* Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis

Lauschke et al.
The AAPS Journal 2018

Table 3. Genetic Germline Variants that Modulate Drug Efficacy

Drug	Phenotype / Genetic variant	Mechanism	Effect size (R^2)
Codeine	CYP2D6 deficiency	Reduced metabolism to active substance (morphine)	Expected to be very high
Warfarin	Decreased CYP2C9 activity (*CYP2C9*2*)	Reduced inactivation of warfarin. Thus, reduced VKORC1 inhibition	3.8%
	Decreased CYP2C9 activity (*CYP2C9*3*)		8%
	Decreased CYP4F2 activity (*CYP4F2*3*)	Increased levels of vitamin K dihydroquinone, which is necessary for carboxylation of coagulation factors	1.1%
	Reduced VKORC1 activity (*VKORC1*2*)	Reduced levels of vitamin K dihydroquinone, which is necessary for carboxylation of coagulation factors	28.3%
Clopidogrel	Reduced CYP2C19 activity (*CYP2C19*2*)	Reduced bioactivation of the prodrug	12%
Proton pump inhibitors	Increased CYP2C19 activity (*CYP2C19*17*)	Increased inactivation to 5-hydroxyomeprazole in *H. pylori* eradication therapy	Eradication 72.7% in UM and 97.8% in PM
Atorvastatin	*LPA* (rs10455872); *APOE* (rs445925, rs4420638)	Decreased reduction in low-density lipoprotein cholesterol	4% combined

PM poor metabolizer, *UM* ultrarapid metabolizer

Lauschke et al.
The AAPS Journal 2018

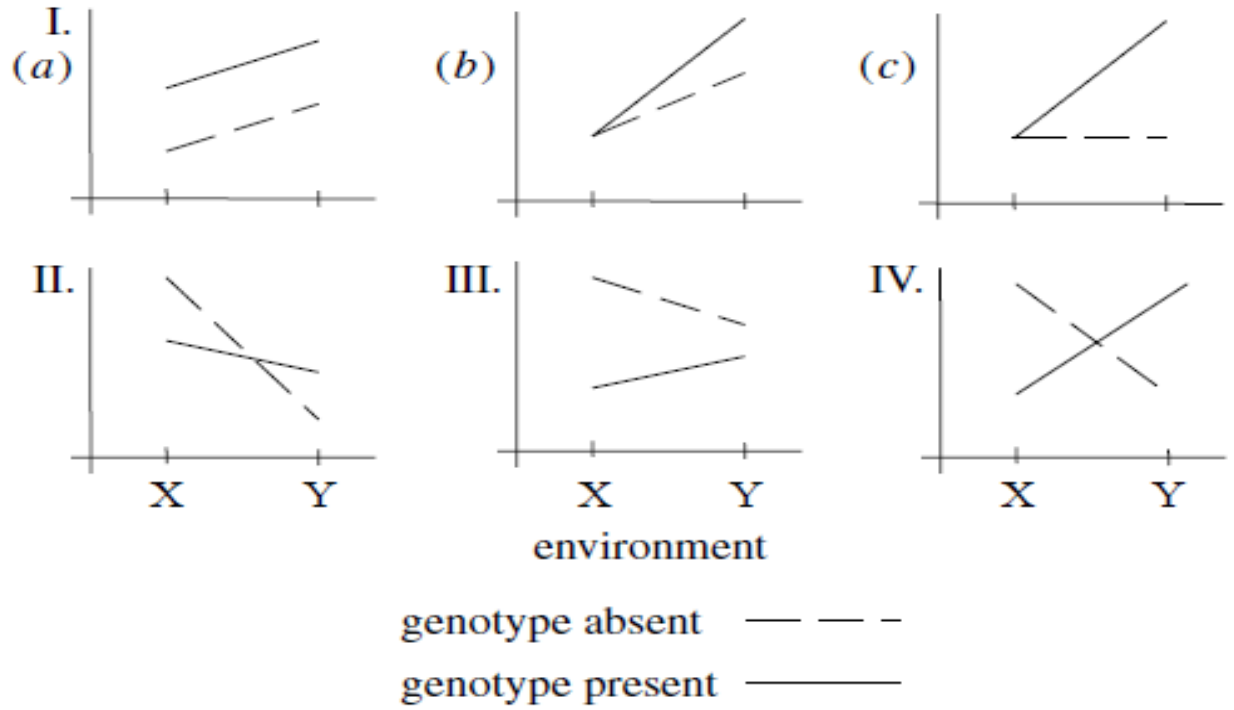


Figure 1. Four qualitative patterns of gene–environment interaction described by (and numbered after) Haldane (1938). The *y*-axis represents a trait value (e.g. mean height, disease prevalence or expected survival); the *x*-axis represents two environmental conditions.

“Interaction of nature and nurture”

Haldane JS, 1938

Multiple Comparisons Problem?

Multiple (genes and genetic models),

Multiple environment (risk factors, risk factor definitions),

Multiple models of interaction

Comparisons Problem

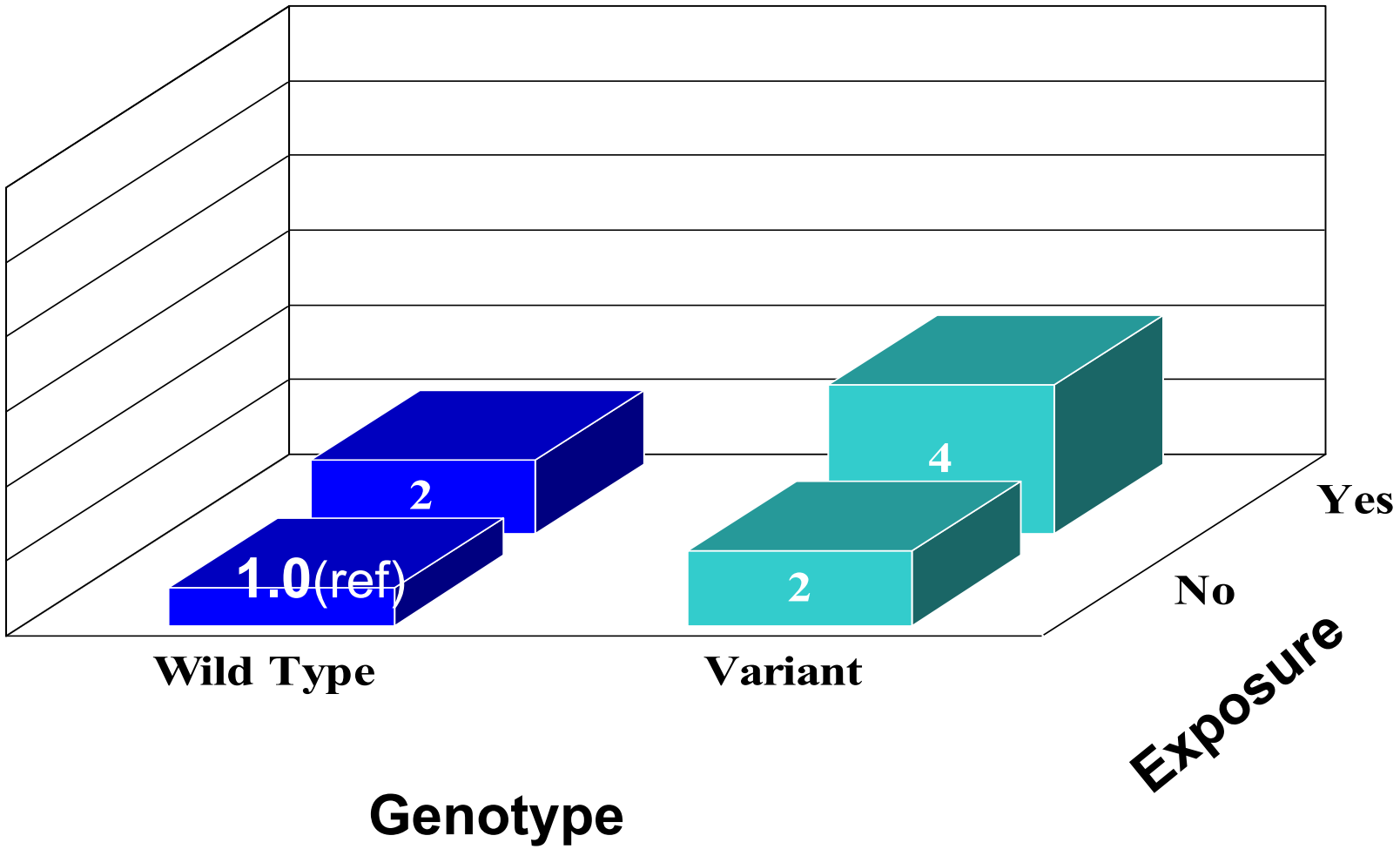
Solution: Multiple, large studies

Criteria: Strength of association

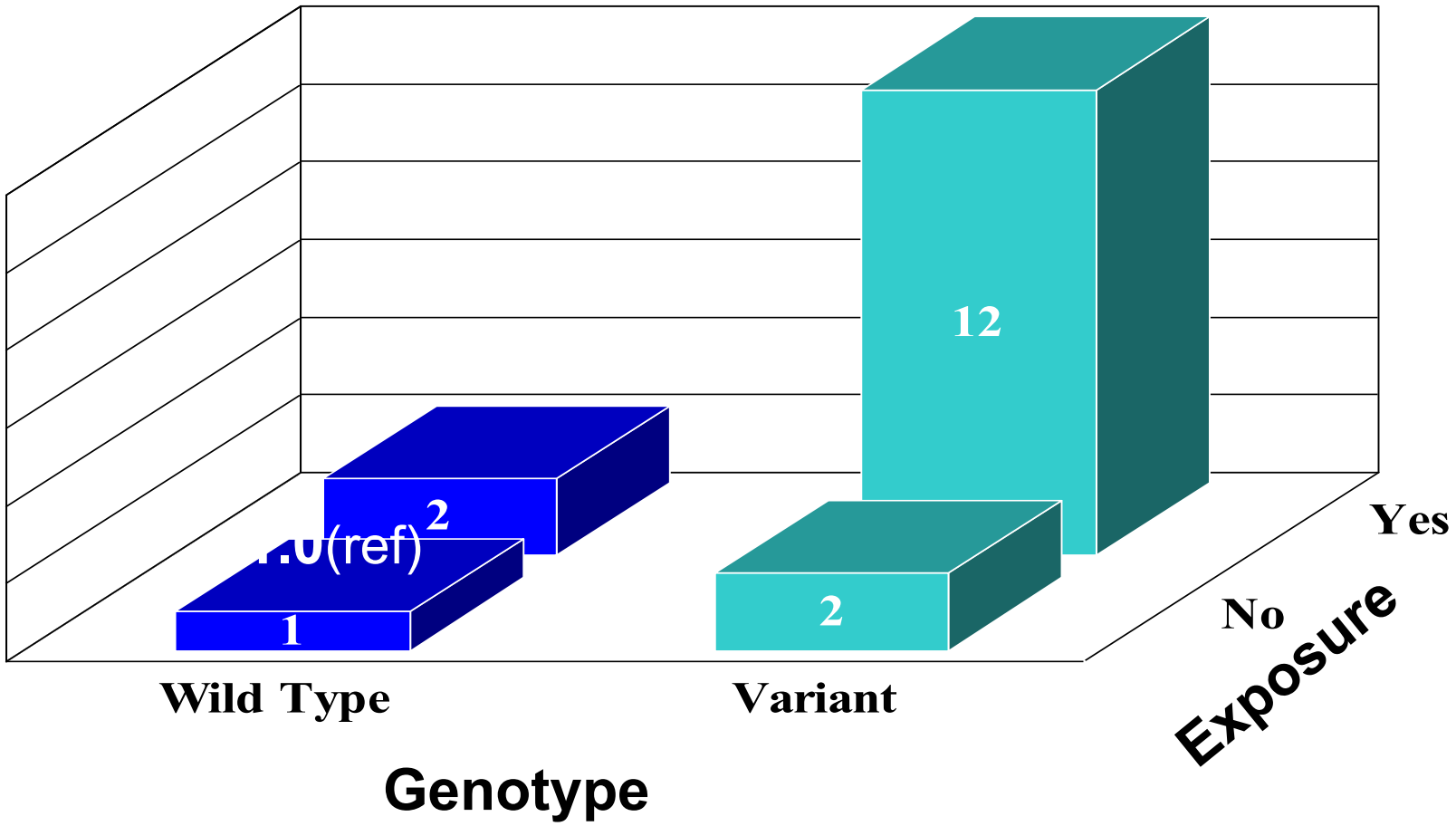
Biologic Plausibility

Consistency of findings

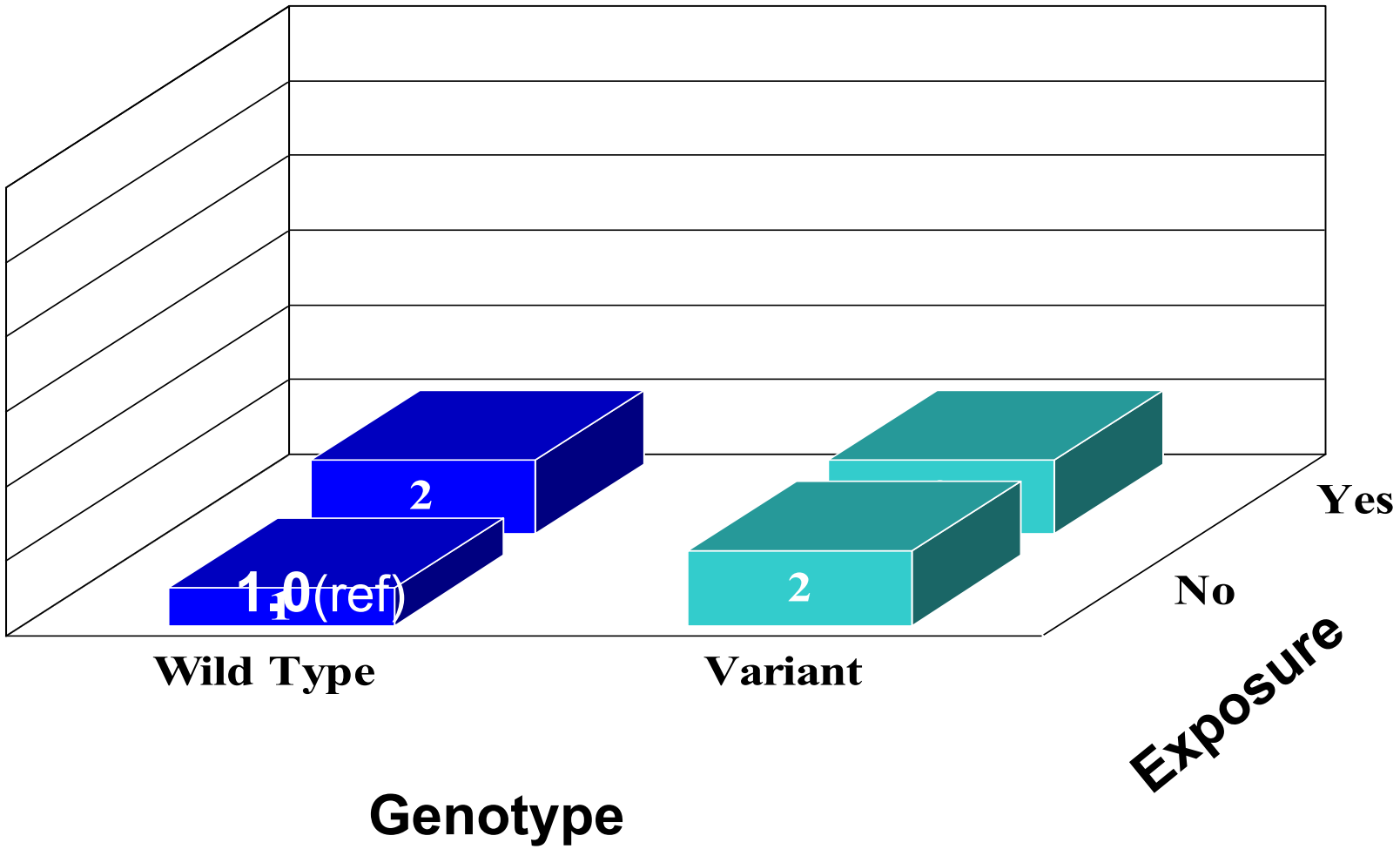
Gene-Environment Interaction



Gene-Environment Interaction



Gene-Environment Interaction



How common are env-env interactions?

- Smoking/alcohol in esophageal cancer
- BMI/menopausal status in breast cancer
- PMH/BMI in breast cancer
- Aflatoxin/HBV in liver cancer
- Radiation/young age in breast cancer
- Radiation/smoking in lung cancer
- Skin type/UV and skin cancer

- Interactions that depart from the multiplicative model are the exception not the rule

Despite interest in GxE, there are few agreed-upon successes where the effect of exposure differs across genotypes (and vice versa).

McAllister et al. *Am J Epidemiol.* 2017;186(7):753–761

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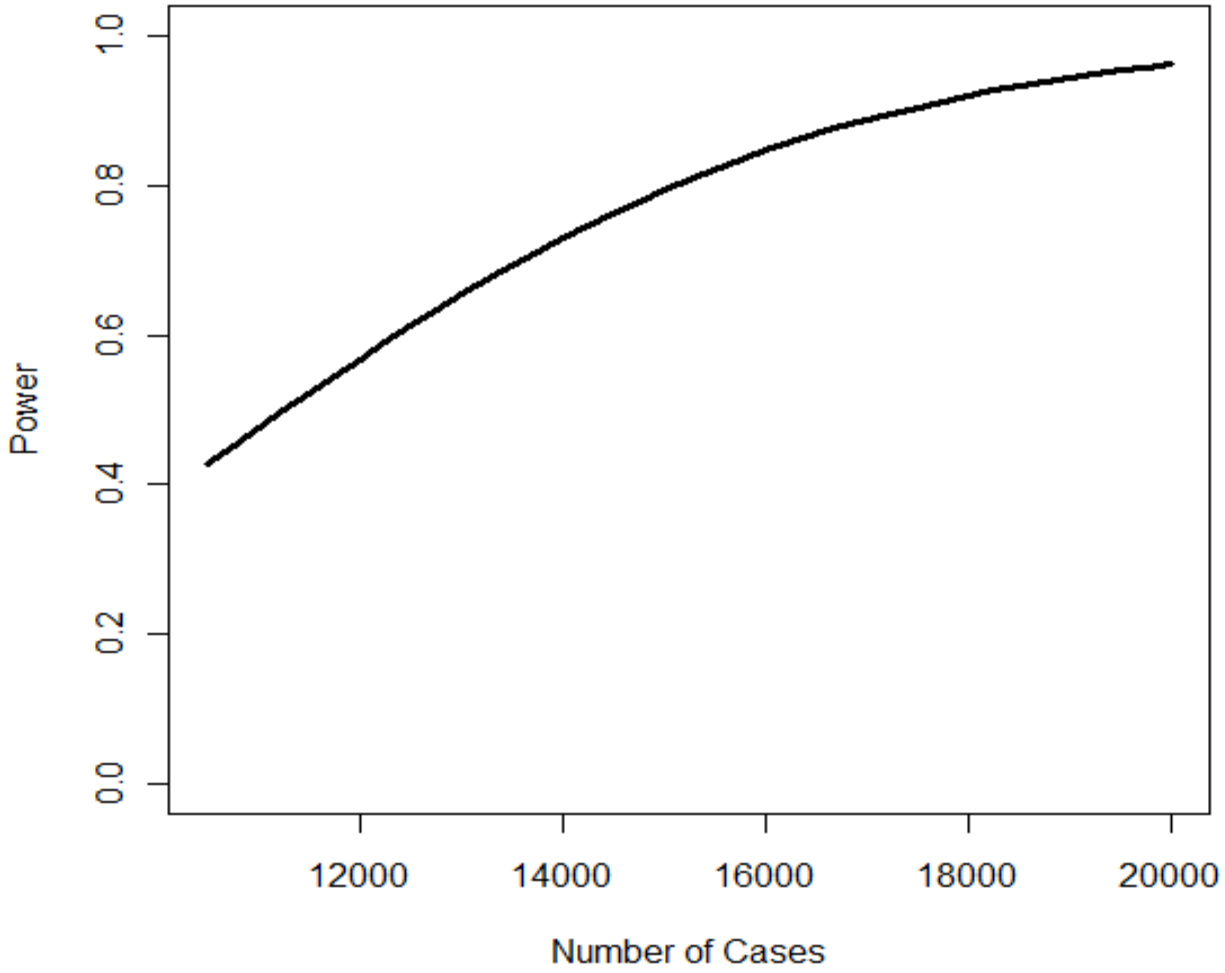
McAllister et al. *Am J Epidemiol.* 2017;186(7):753–761

Why so few supra- or sub-multiplicative interactions?

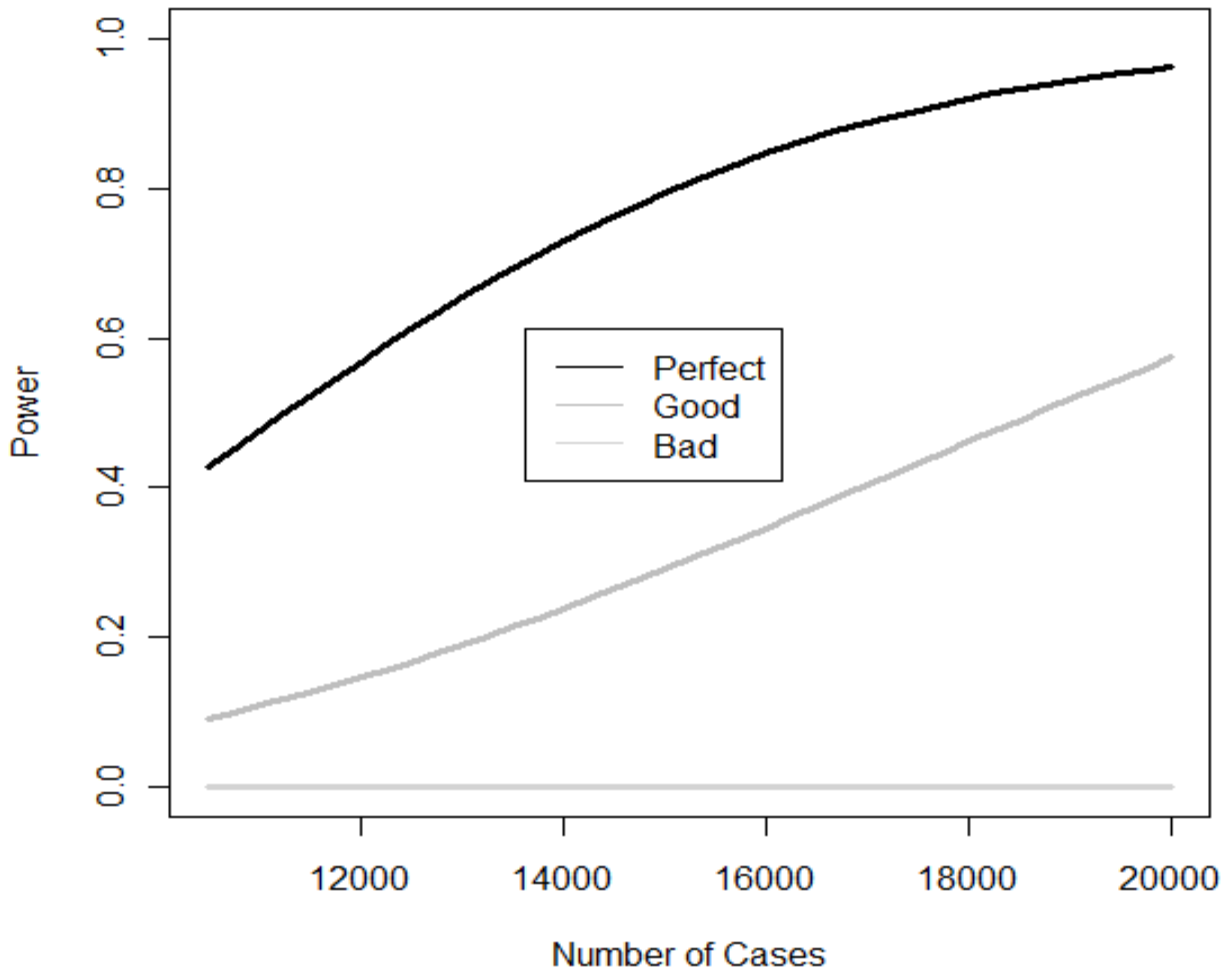
- Poor measurement of genes?
- Low power of studies
- Poor measurement of environment?
- There aren't many to find?



OR_G = 1.00
OR_E = 1.50
Pr(E) = 0.33
α = 10^{-7}

OR_{GE} = 1.35

Sample sizes needed are large



"Good"
Sensitivity=77%
Specificity=99%

"Bad"
Sensitivity=30%
Specificity=50%

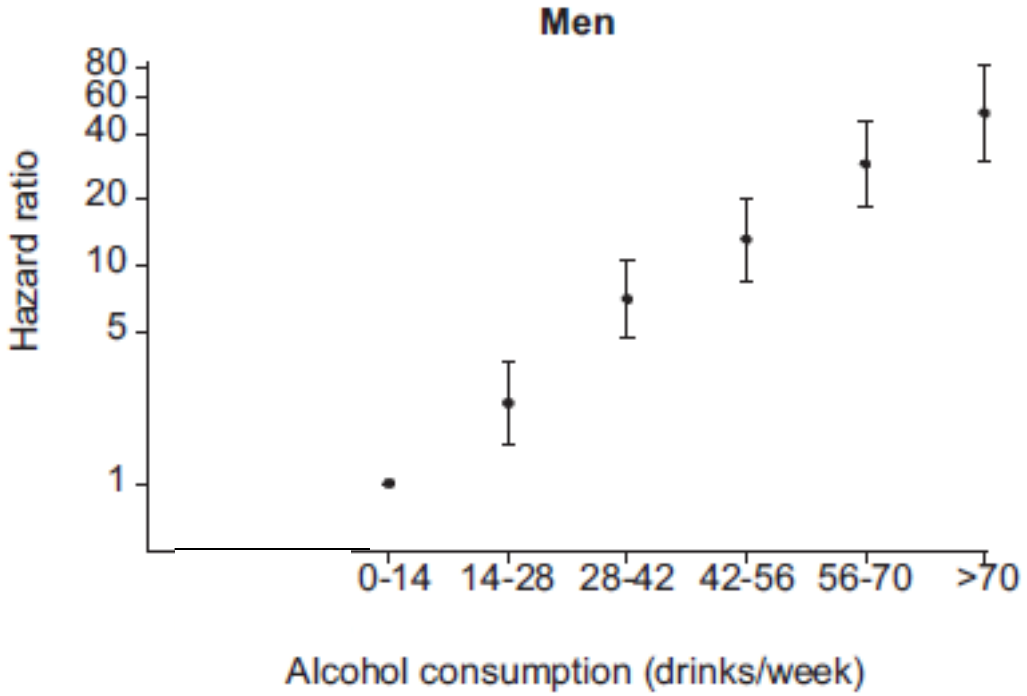
Misclassification of exposure degrades power

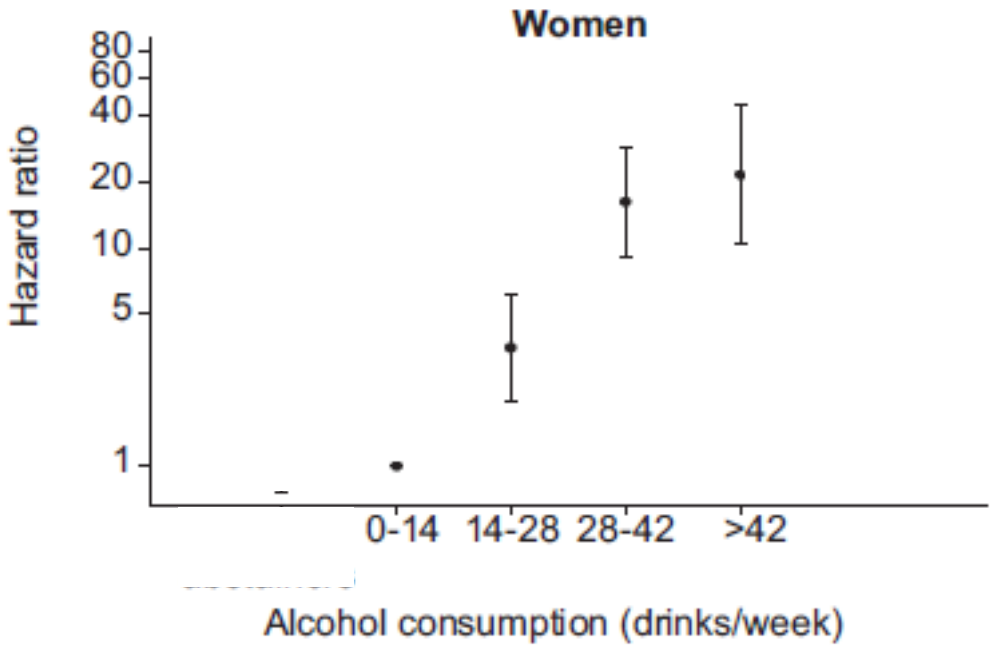
Lindstrom et al. (2009)

Risk of alcoholic liver cirrhosis
Danish Cancer, Diet and Health cohort

Adj. smoking, education, waist circumference

Askgaard et al. J Hepatol. 2015

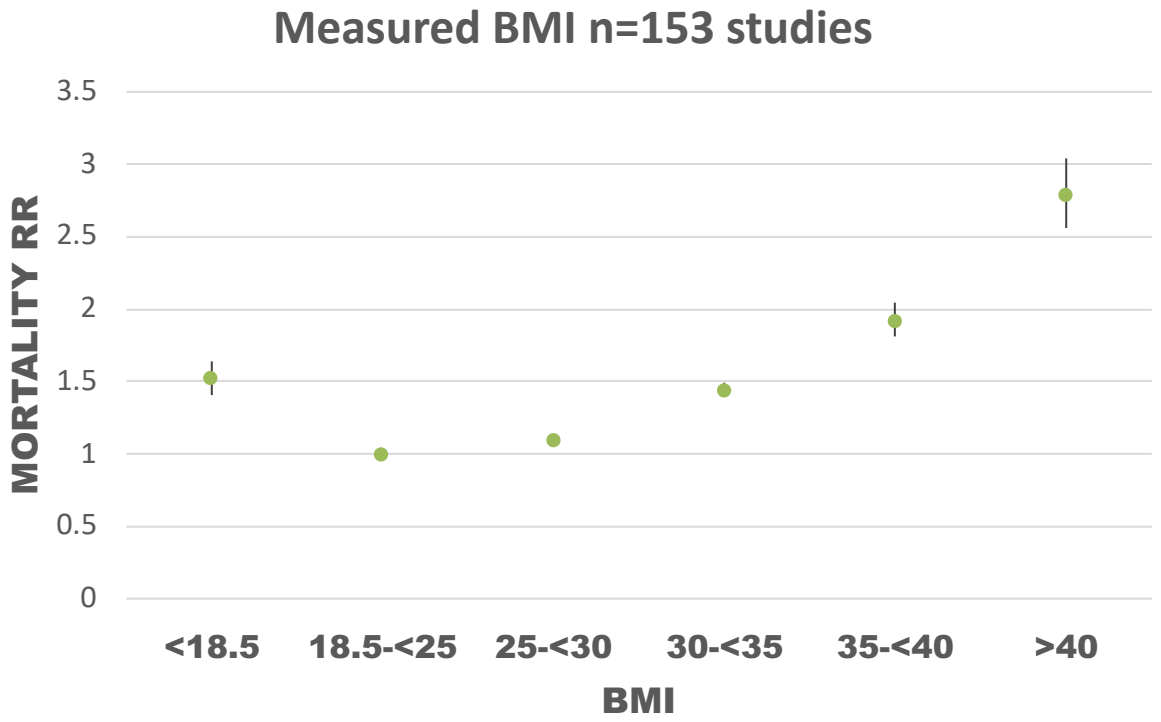




BMI
Vs Mortality

Global BMI
Mortality
Collaboration

Lancet 2016



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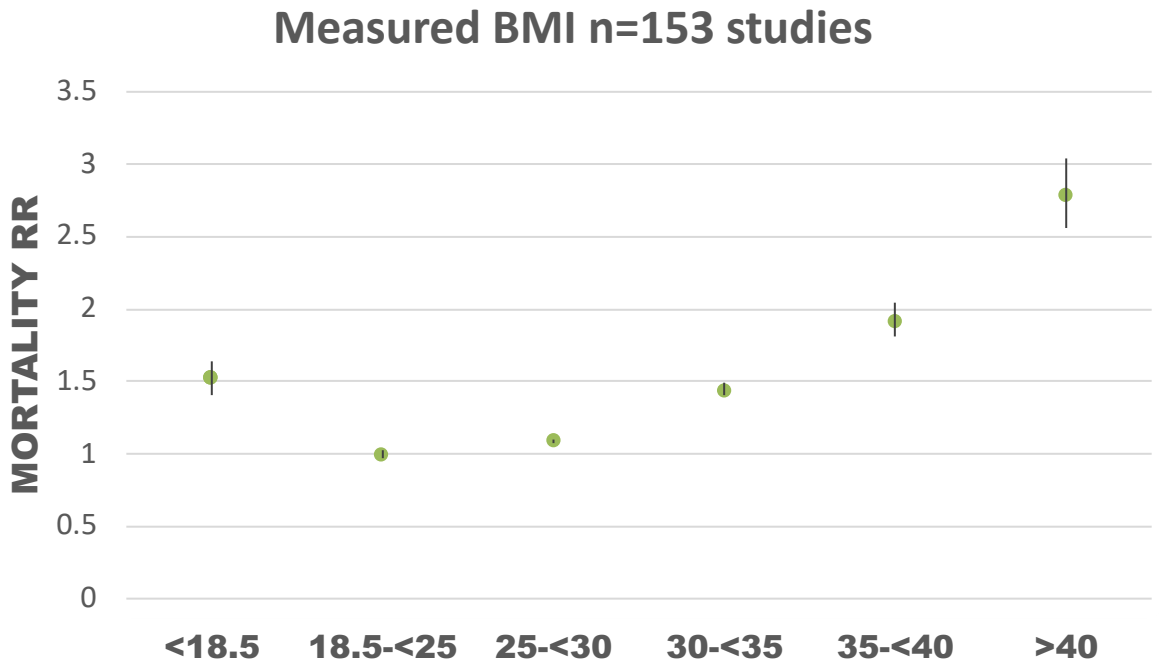
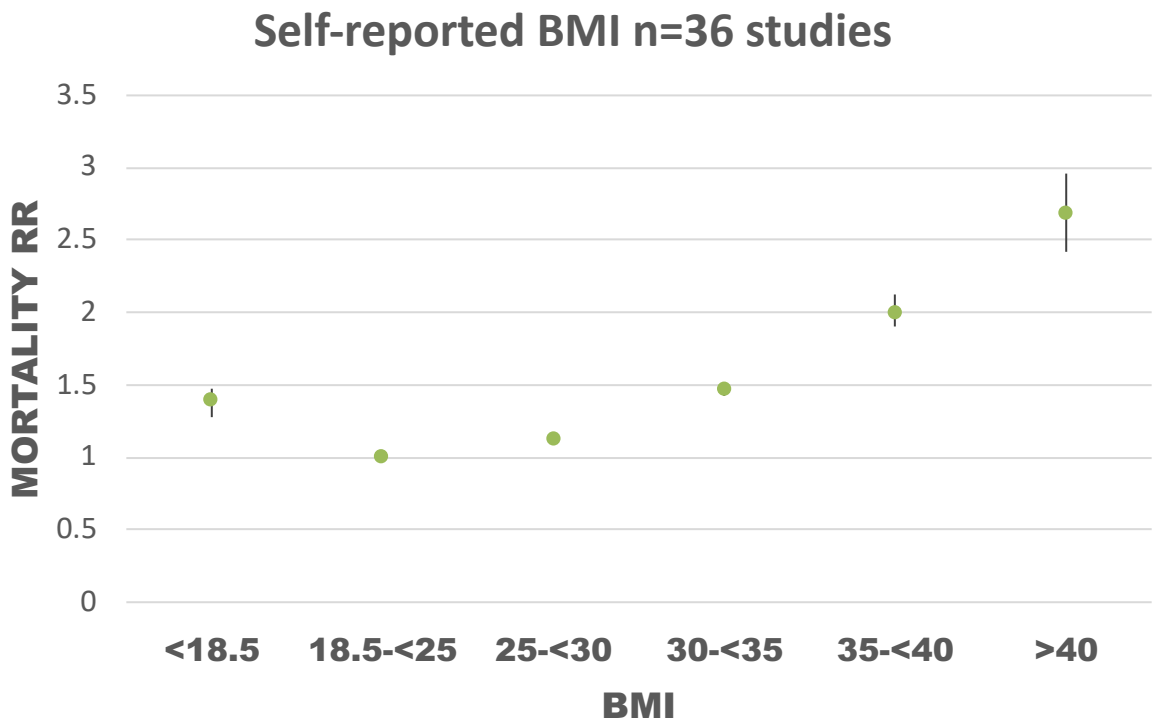
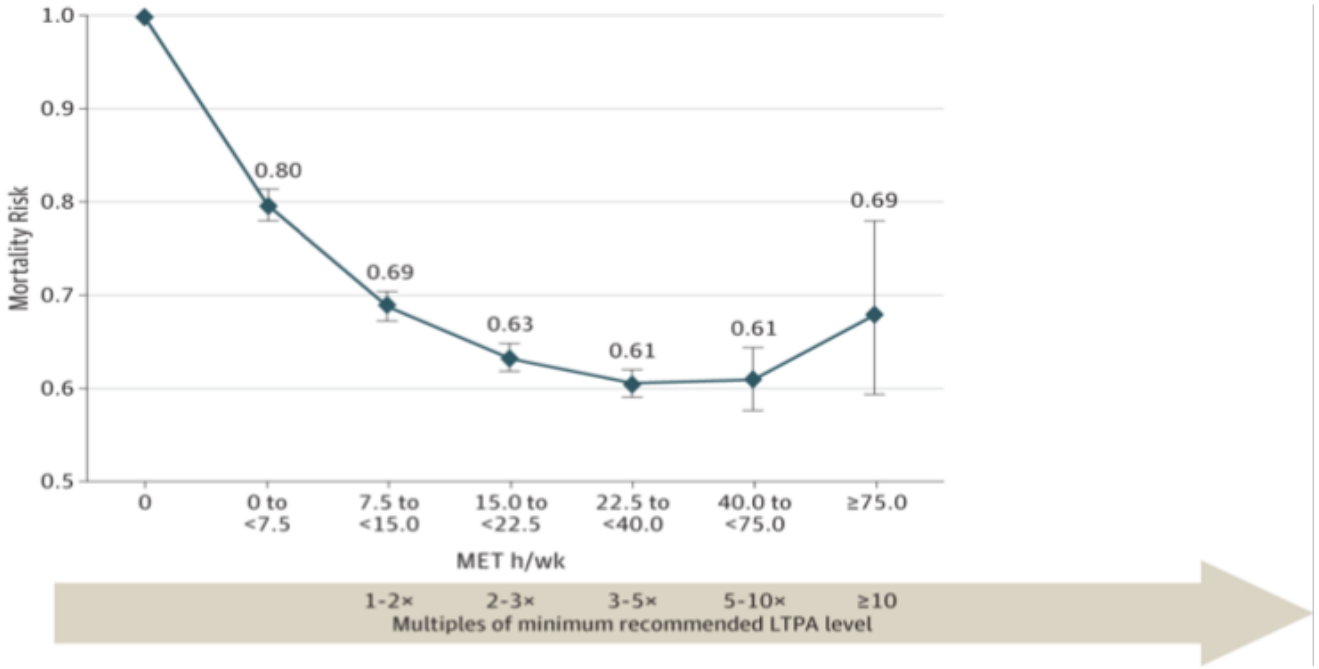




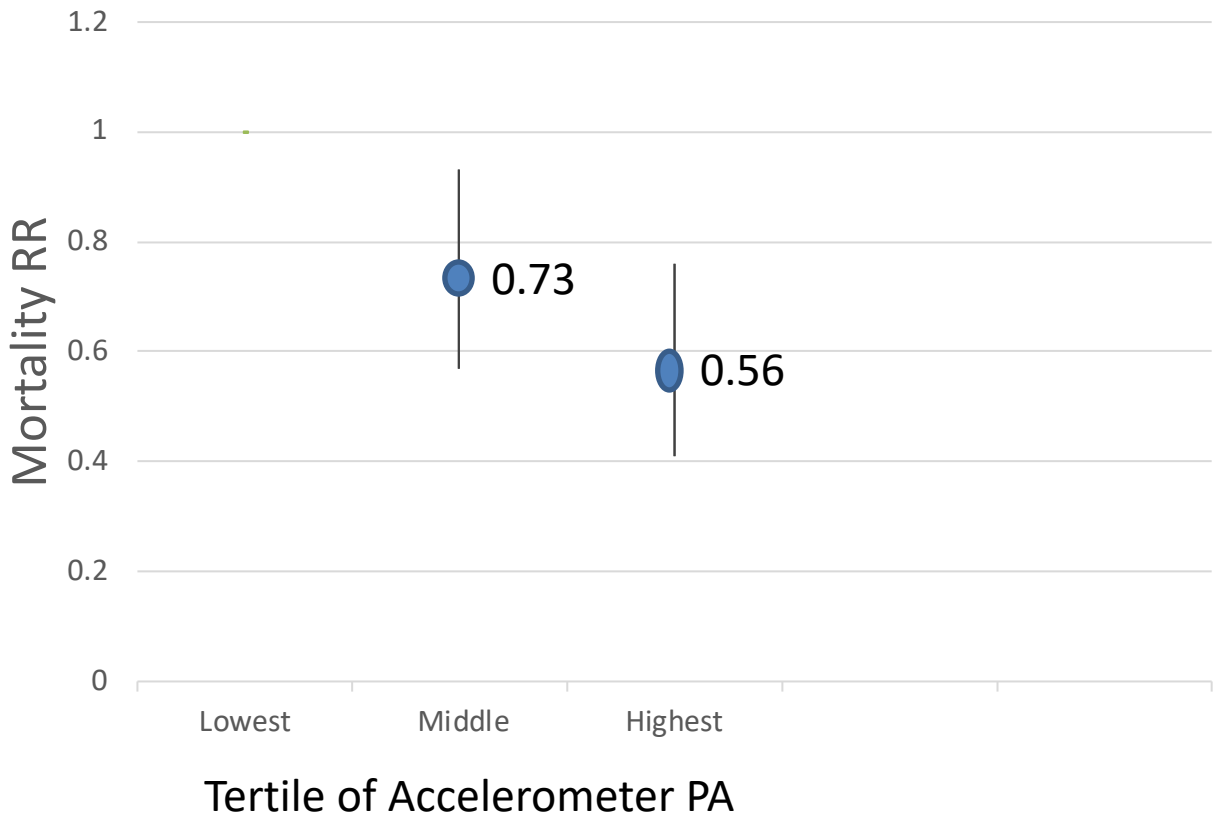
From: **Leisure Time Physical Activity and MortalityA Detailed Pooled Analysis of the Dose-Response Relationship**

JAMA Intern Med. 2015;175(6):959-967. doi:10.1001/jamainternmed.2015.0533



Hazard Ratios (HRs) and 95% CIs for Self-reported Leisure Time Moderate- to Vigorous-Intensity Physical Activity and Mortality

Triaxial accelerometer-measured PA vs Mortality in the WHI



Womens' Health Initiative, n=6,382, 450 deaths. LaMonte et el. J Am Geriatr Soc. 2017

MODELLING GENE-ENVIRONMENT INTERACTIONS

DO CLASSIC BREAST CANCER RISK FACTORS SYNERGIZE WITH GWAS SNPS?

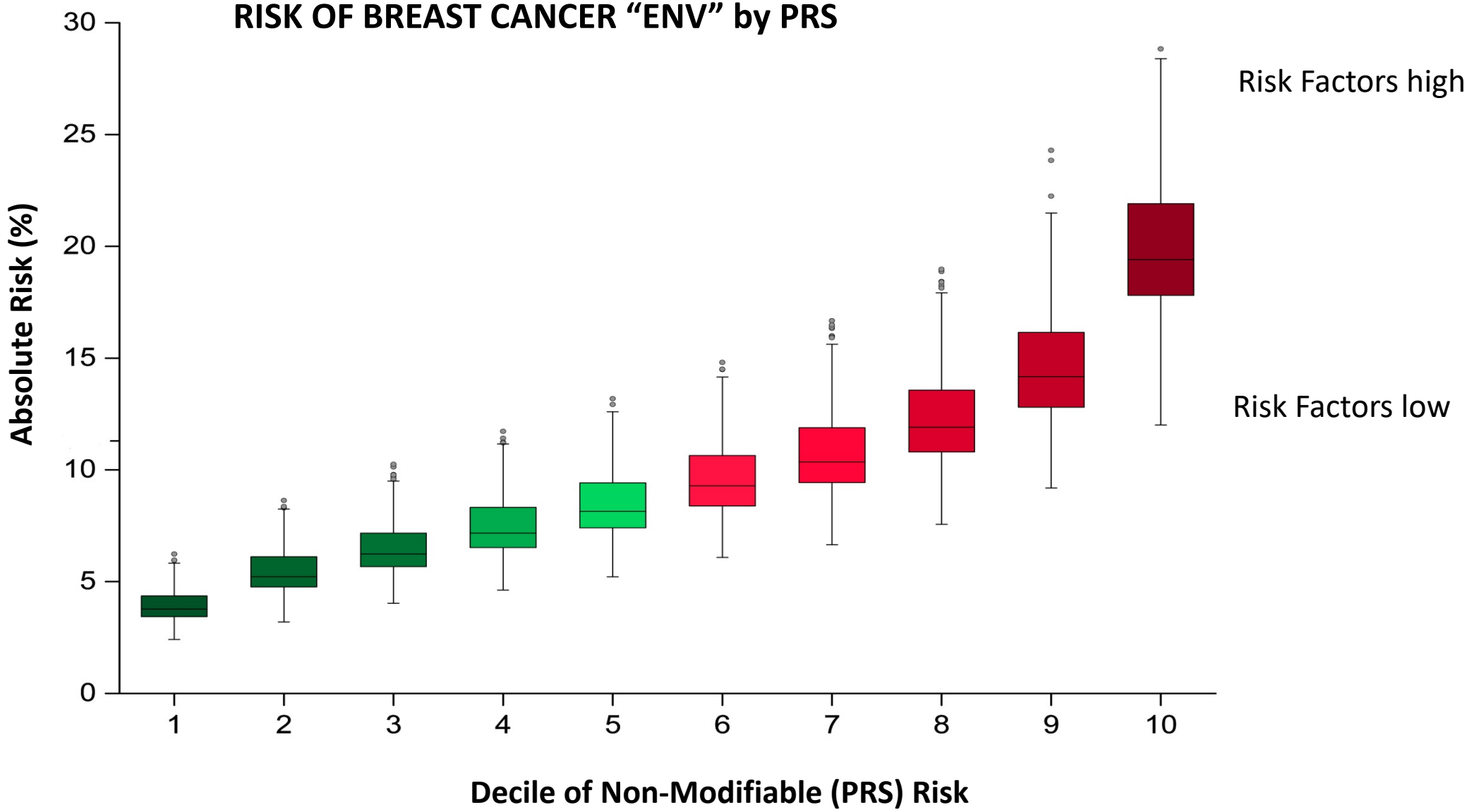
16,285 BC cases and 19,376 controls

39 GWAS-assoc SNPS x 8 "Env" Risk Factors

AAM
Parity
AAMeno
Height
BMI
FH
Smoking
Alcohol

"After correction for multiple testing, no significant [multiplicative] interaction between SNPs and established risk factors...was found."

Campa et al, JNCI 2011, Barrdahl et al, BPC3, HMG 2014



Maas, Chatterjee et al. JAMA Oncol, 2016

MORE BREAST CANCERS COULD BE PREVENTED IN HIGH RISK STRATA

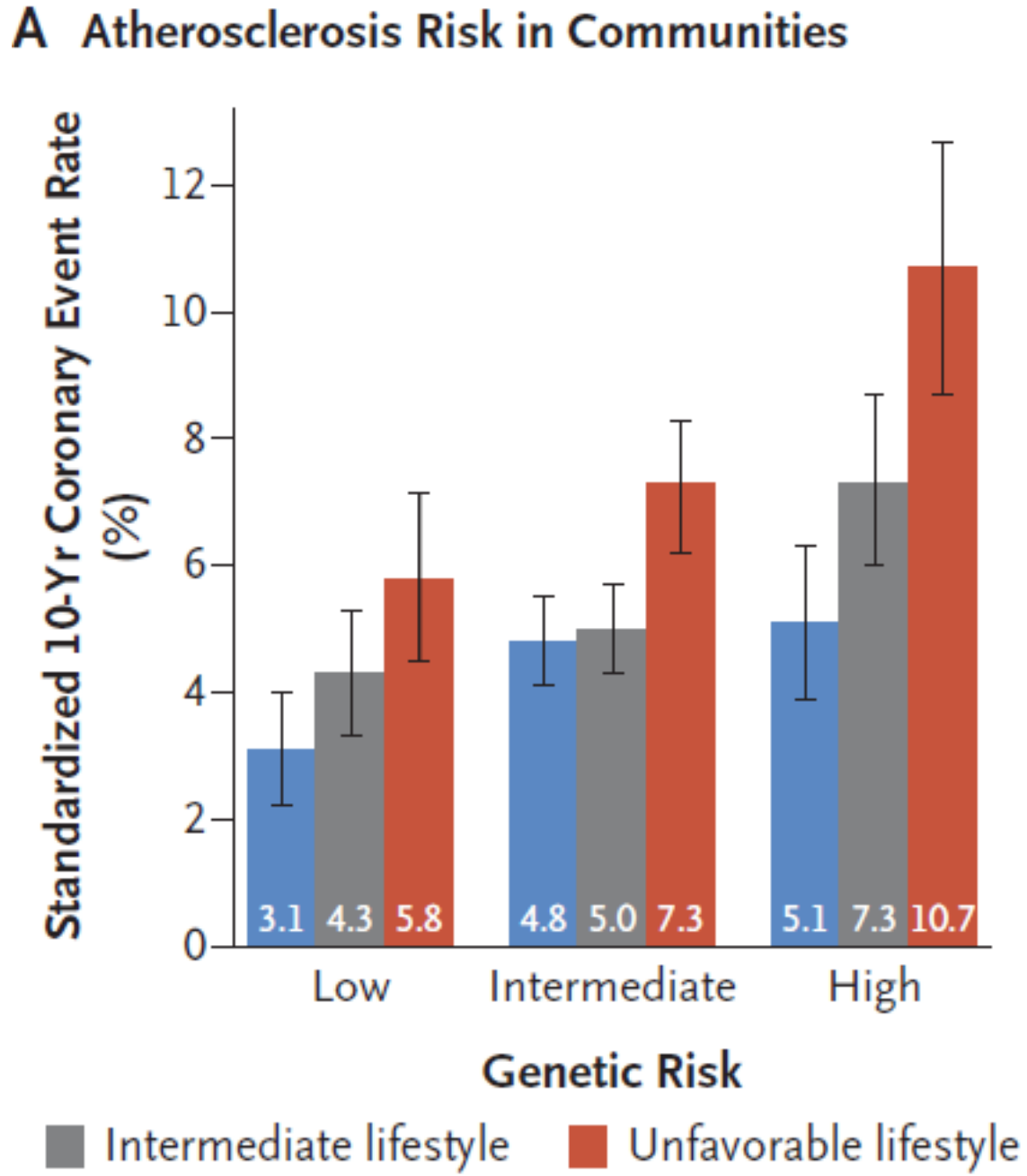
Percentage preventable breast cancers by removal of modifiable risk-factors (overall and in categories of non-modifiable risk quintiles)

	All Modifiable Factors Simultaneously	
	% Preventable	% Total
NonMod Risk Quintile 1	12.3	4.03
NonMod Risk Quintile 2	16.0	5.23
NonMod Risk Quintile 3	18.7	6.14
NonMod Risk Quintile 4	22.4	7.34
NonMod Risk Quintile 5	30.6	10.01
Overall	100.0	32.75

Maas, Chatterjee et al. JAMA Oncol, 2016

PRS, Lifestyle and CHD

Khera et al. NEJM 2016



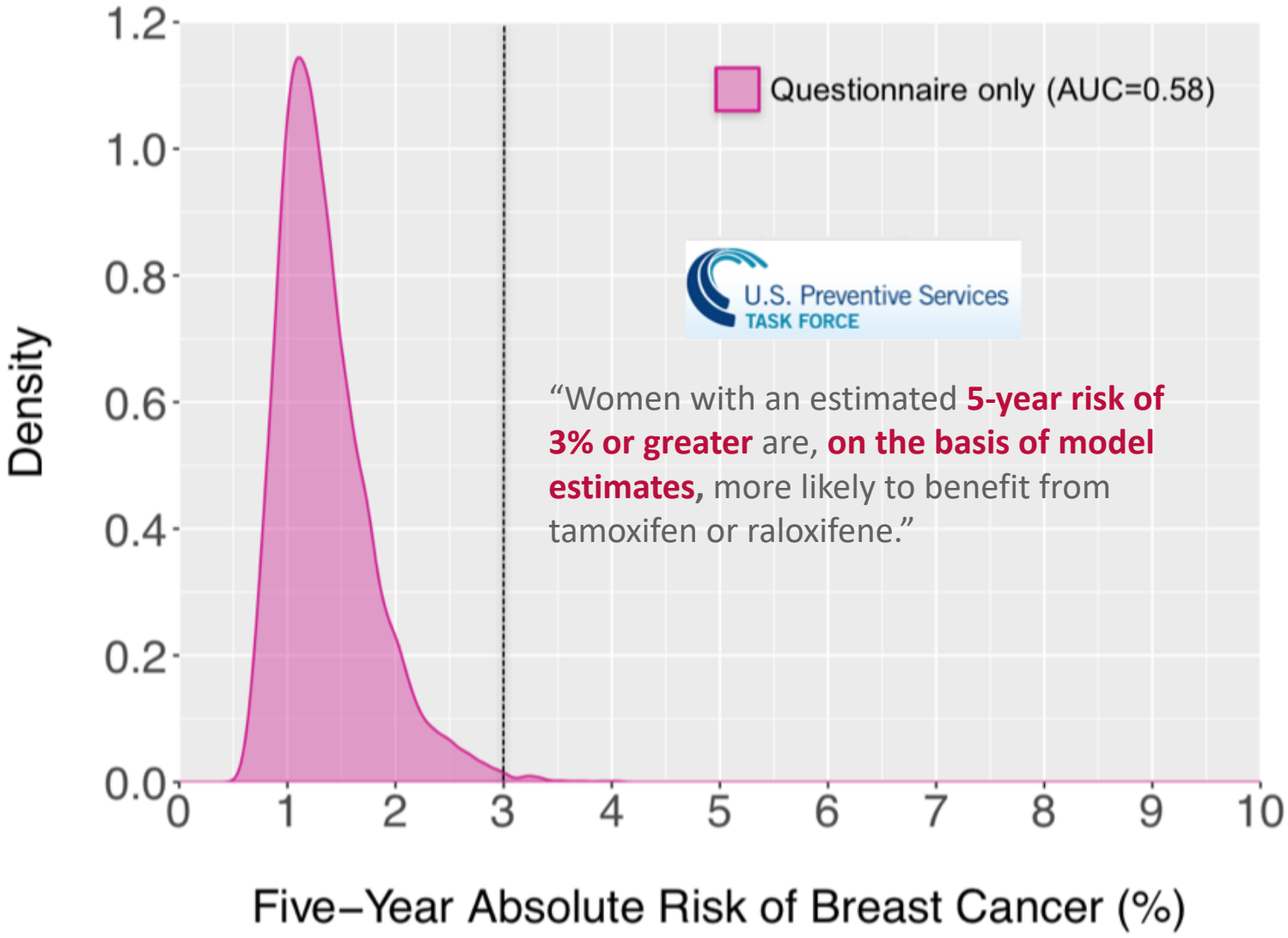
With some exceptions (e.g. drug idiosyncracies) genetic and environmental and “lifestyle” risk factors are independent and the risks multiply.

Inclusion of Gene-Gene and Gene-Environment Interactions Unlikely to Dramatically Improve Risk Prediction for Complex Diseases

Hugues Aschard,[1,2,*] Jinbo Chen,[3] Marylin C. Cornelis,[4] Lori B. Chibnik,[5] Elizabeth W. Karlson,[6] and Peter Kraft[1,2,6]

The American Journal of Human Genetics (2012), doi:10.1016/j.ajhg.2012.04.017

Five-year absolute risk projection for US Caucasian women aged 50



Chatterjee, Garcia-Closas Submitted

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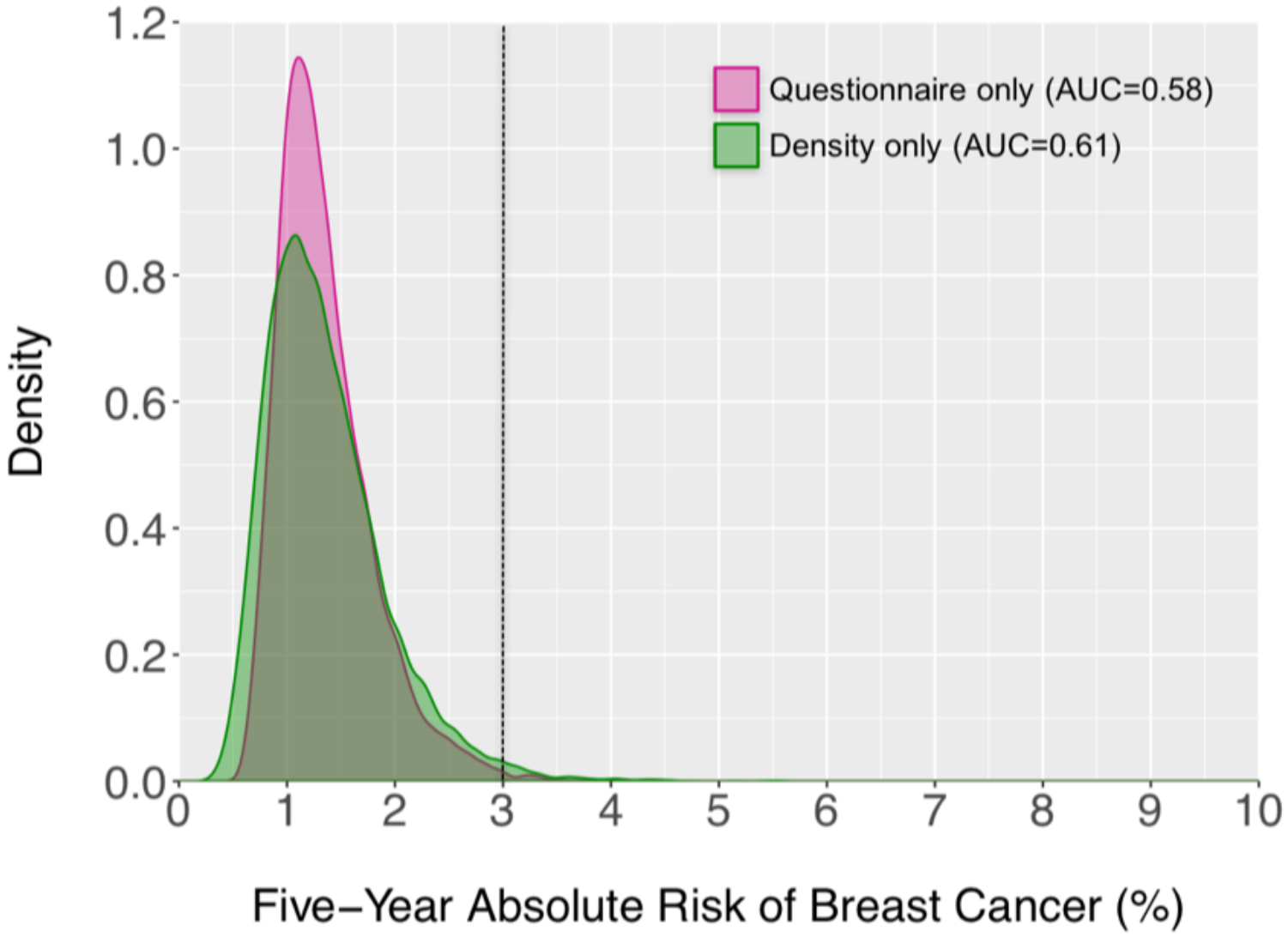

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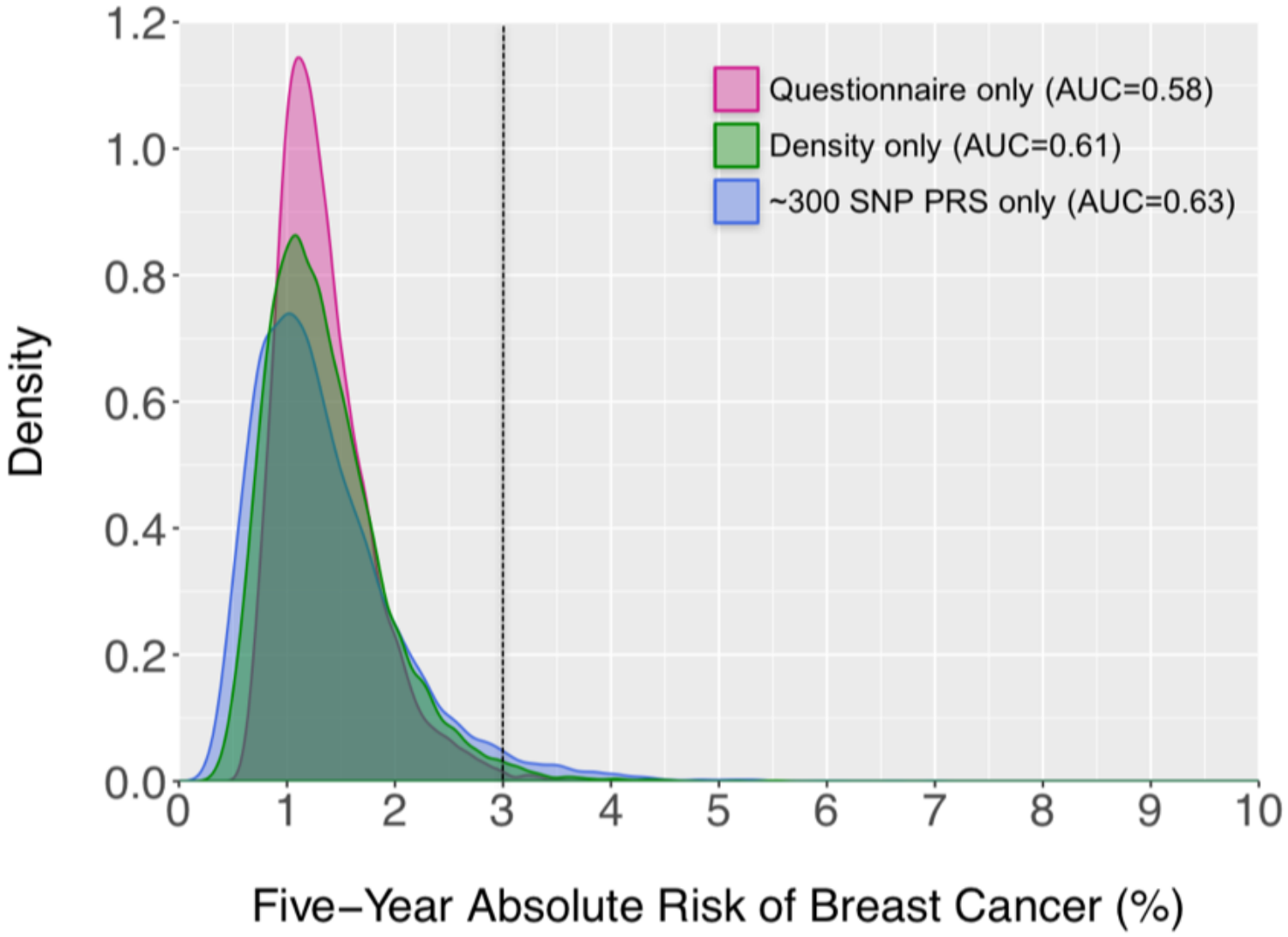

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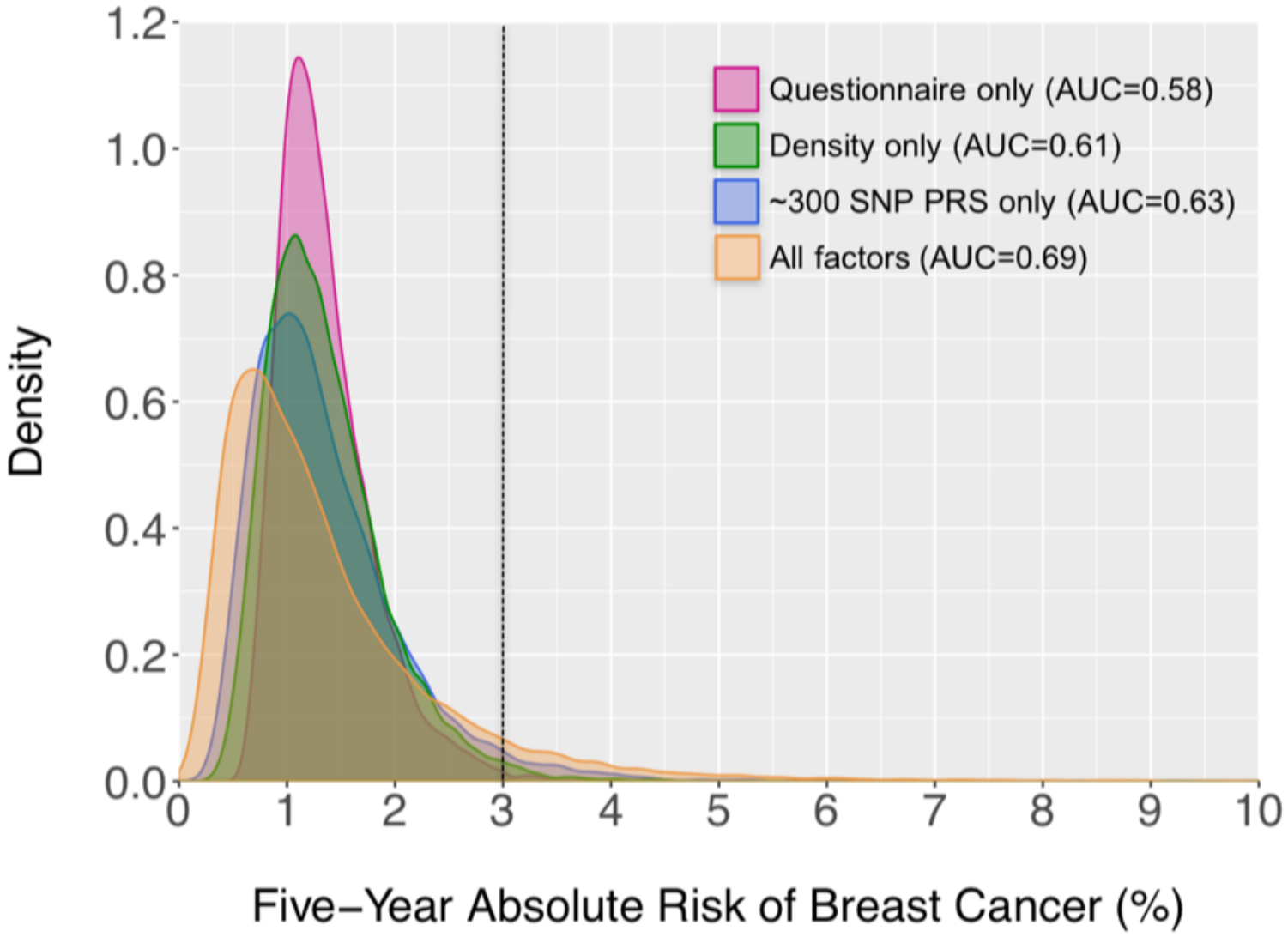
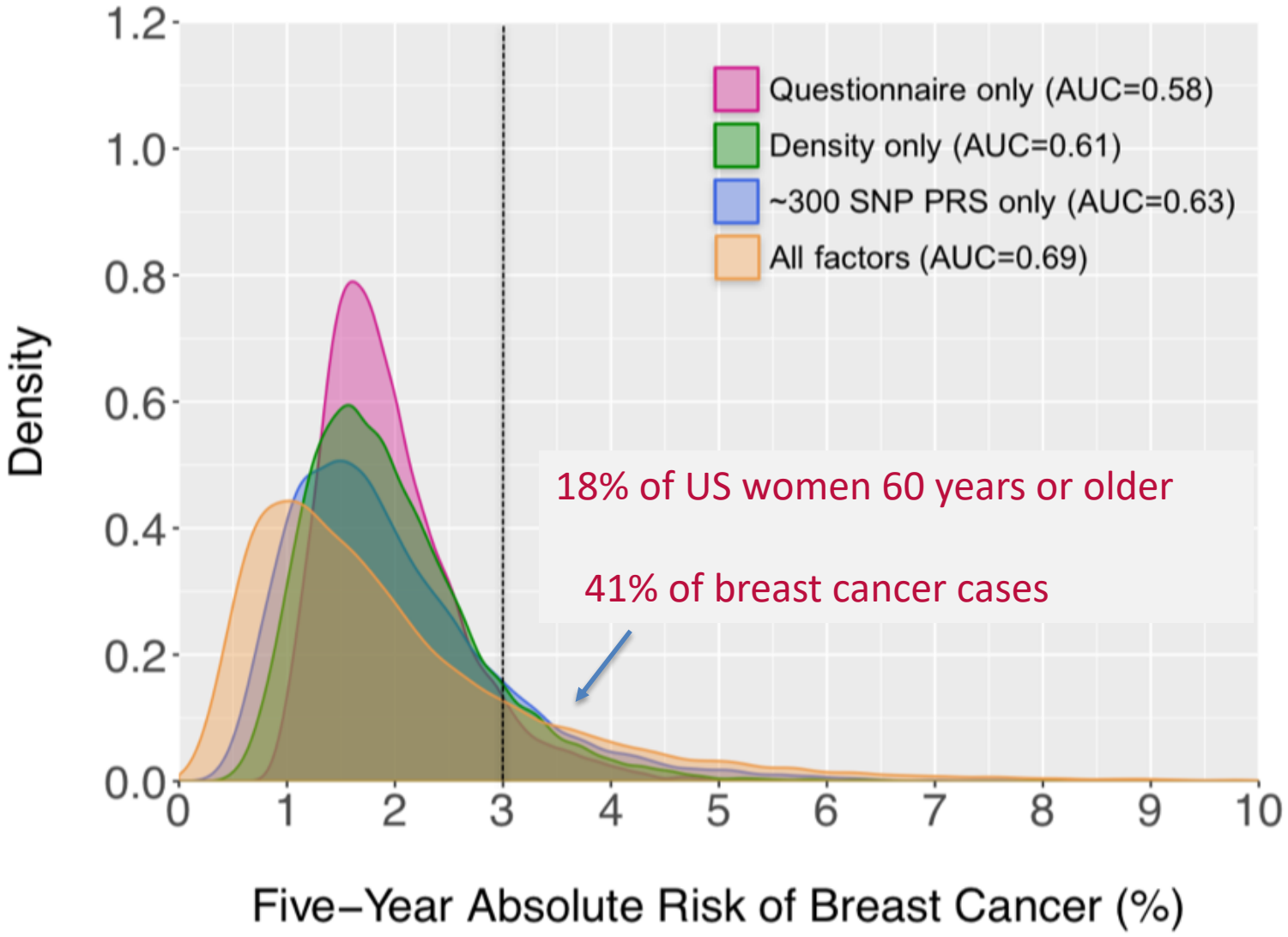


Chatterjee, Garcia-Closas Submitted

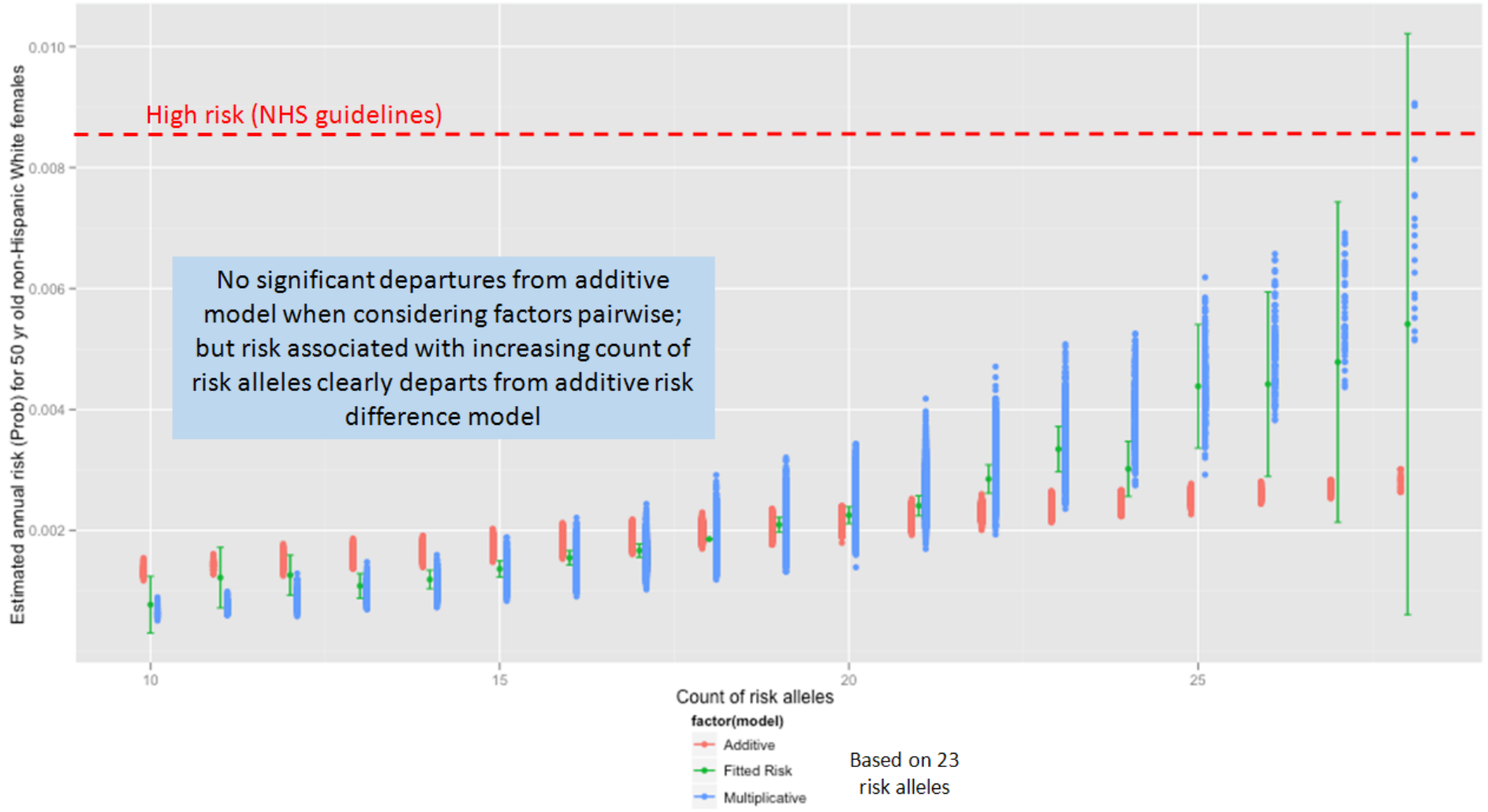
Five-year absolute risk projection for US Caucasian women aged 60



SUMMARY

- In ten more years we have discovered few examples of synergy between genes and environment
- Gene variants that dramatically alter drug metabolism can dramatically alter drug SFX and efficacy
- Most genetic and environmental risk factors conform to the multiplicative model
- This is good news! It makes risk prediction algorithms more stable
- The multiplicative model implies that environmental risk reduction in those at high genetic risk prevents more cases
- It conforms to our new understanding of highly polygenic risk and complex environmental causation

SNP-SNP risks simply multiply



Joshi et al, AJE 2014