

Gene-Environment Interaction: Definitions and Study Designs

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IOM Committee on Assessing Interactions Among Social
Behavioral, and Genetic Factors in Health
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Overview

- 1 Definitions of interaction
 - Statistical
 - Biological
- 1 Importance of measurement scale
- 1 Study designs

Interactions among social, behavioral and genetic factors in health

Statistical definition:

- A different effect of a *social or behavioral factor* on disease risk, in persons with *different genotypes*
- A different effect of a *genotype* on disease risk, in persons with different *social or behavioral factors*

Conditional Independence

- 1 Definition: Two factors are *conditionally independent* if the effect of one factor is the same within strata defined by the other
- 1 *Interaction* can be defined as the absence of conditional independence—i.e., the effect of a one factor differs across strata defined by the other
- 1 What do we mean by a “different effect”? -- it depends on the scale of measurement

Measurement Scale

1 Multiplicative scale

- Effects measured in ratios such as relative risks (as in most epidemiologic studies)
- No interaction: $r_{11}/r_{01} = r_{10}/r_{00}$
- Synergistic interaction: $r_{11}/r_{01} > r_{10}/r_{00}$
- Antagonistic interaction: $r_{11}/r_{01} < r_{10}/r_{00}$

	Exposure	
	E=1 (exposed)	E=0 (unexposed)
High-risk genotype		
G=1 (genotype present)	r_{11}	r_{01}
G=0 (genotype absent)	r_{10}	r_{00}

Measurement Scale

1 Additive scale

- Effects measured in risk differences
- No interaction: $r_{11} - r_{01} = r_{10} - r_{00}$
- Synergistic interaction: $r_{11} - r_{01} > r_{10} - r_{00}$
- Antagonistic interaction: $r_{11} - r_{01} < r_{10} - r_{00}$

	Exposure	
	E=1 (exposed)	E=0 (unexposed)
High-risk genotype		
G=1 (genotype present)	r_{11}	r_{01}
G=0 (genotype absent)	r_{10}	r_{00}

Measures of Effects of Genotype and Environment

I: Cohort Study

Disease status	Genotype present		Genotype absent	
	Exposed	Unexposed	Exposed	Unexposed
Affected	a	b	e	f
Unaffected	c	d	g	h
“Risk”	$r_{11}=a/(a+c)$	$r_{01}=b/(b+d)$	$r_{10}=e/(e+g)$	$r_{00}=f/(f+h)$
Relative risk	$RR_{11}=r_{11}/r_{00}$	$RR_{01}=r_{01}/r_{00}$	$RR_{10}=r_{10}/r_{00}$	$RR_{00}=1.0$ (ref.)

Measures of Effects of Genotype and Environment

II: Case-Control Study

Disease status	Genotype present		Genotype absent	
	Exposed	Unexposed	Exposed	Unexposed
Case	a	b	e	f
Control	c	d	g	h
Odds Ratio	$OR_{11}=ah/cf$	$OR_{01}=bh/df$	$OR_{10}=eh/gf$	$OR_{00}=1.0$ (ref.)

Comparing Multiplicative and Additive Measurement Scales

- 1 No interaction on a multiplicative scale:

$$RR_{11} = RR_{10} \times RR_{01}$$

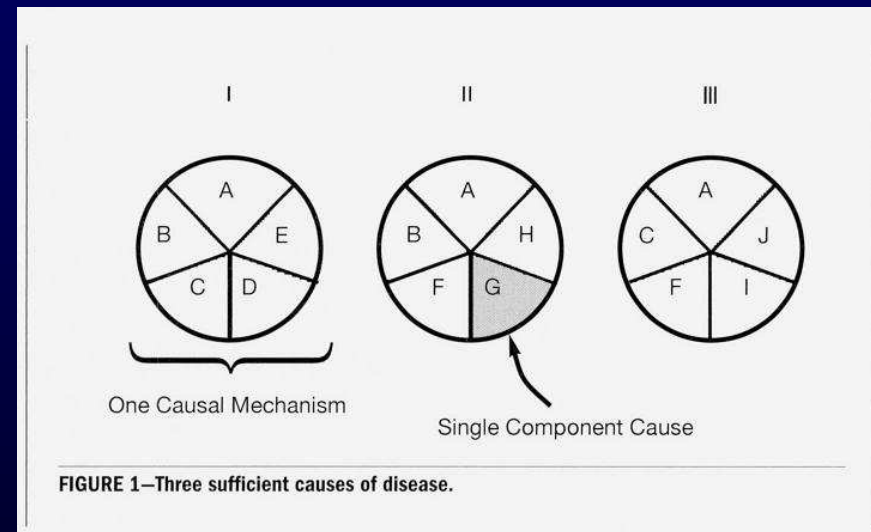
- 1 No interaction on an additive scale:

$$RR_{11} = RR_{10} + RR_{01} - 1$$

- 1 These will never be equivalent unless either $RR_{10} = 1$ or $RR_{01} = 1$ (i.e., no effect of one risk factor in the absence of the other)

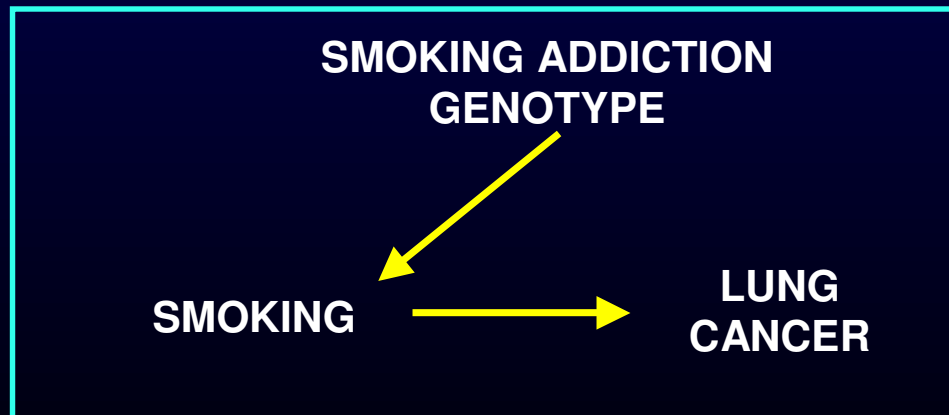
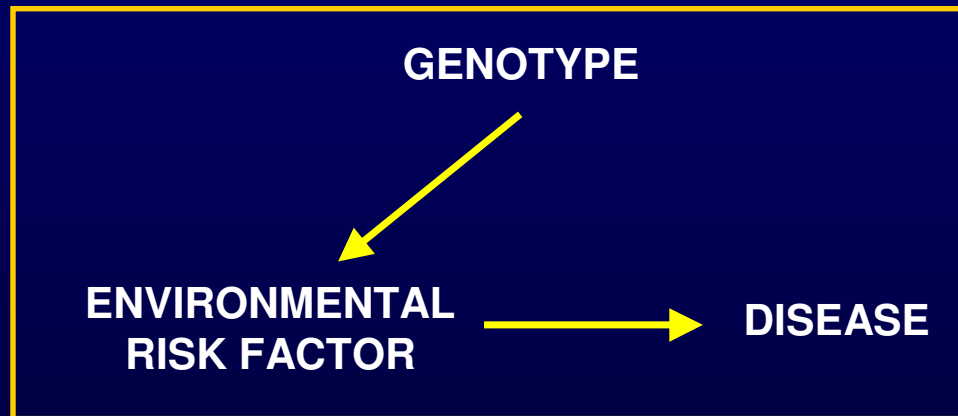
Concepts of Interaction in Epidemiology

- 1 A disease may result from many alternative “sufficient causes” (each possibly involving multiple “component causes”)
- 1 Two factors “interact” (in a biological sense) if they are components of the same sufficient cause
- 1 If two factors are part of different sufficient causes, their combined effects on risk will be additive
- 1 This implies interaction should be measured on an additive scale

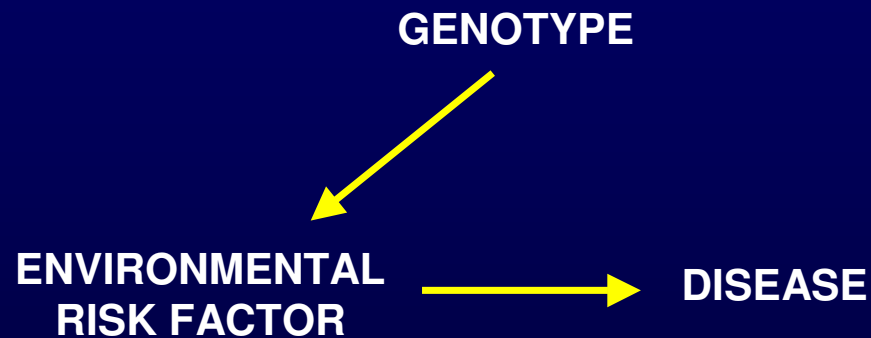


Rothman KJ, Greenland S. Am J Public Health. 2005;95 Suppl 1:S144-50.

MODEL A: Genotype Increases Expression of Risk Factor

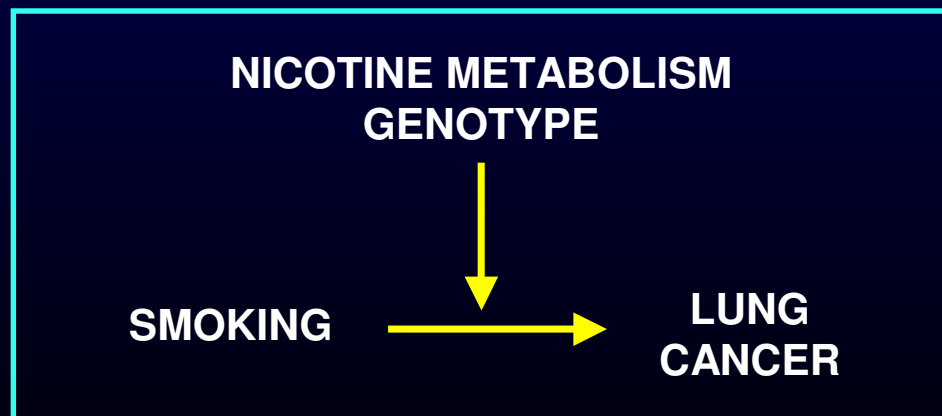
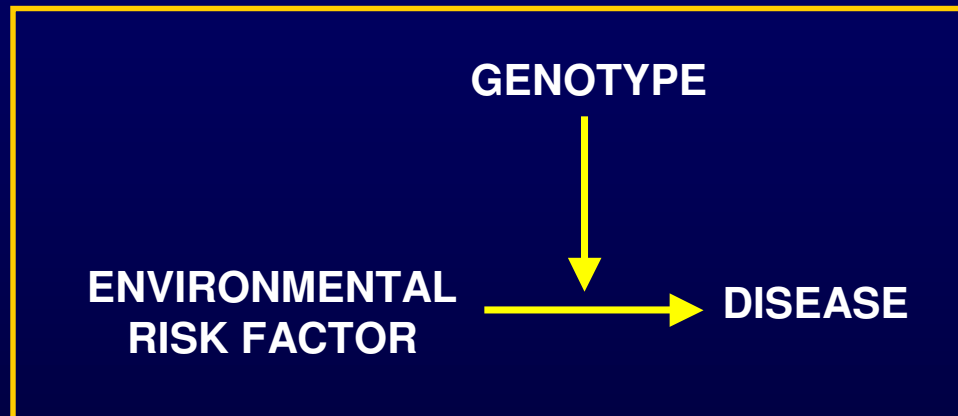


MODEL A: Genotype Increases Expression of Risk Factor

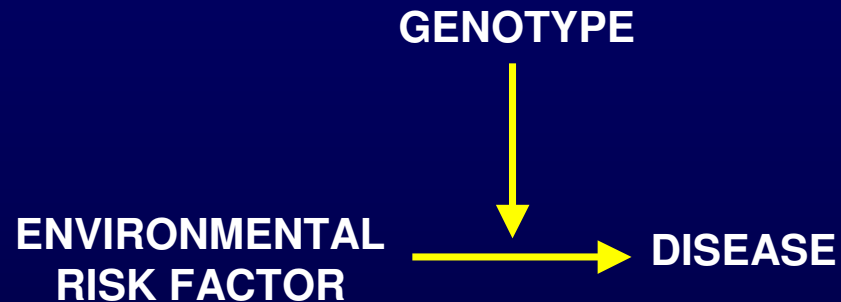


Relative Risks:			
High risk genotype		Low risk genotype	
Exposed	Unexposed	Exposed	Unexposed
+	1	+	1

MODEL B: Genotype Exacerbates Effect of Risk Factor

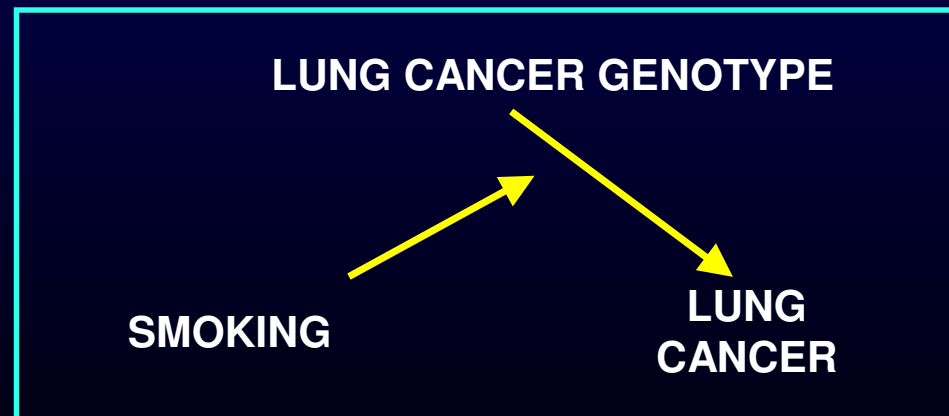
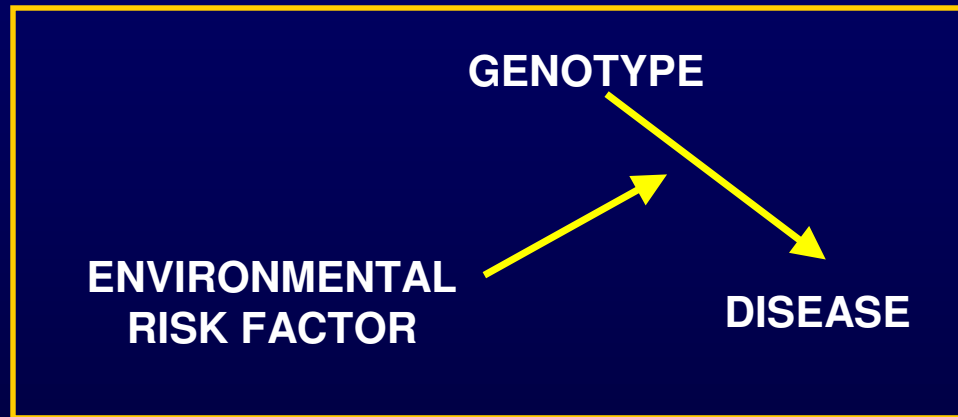


MODEL B: Genotype Exacerbates Effect of Risk Factor

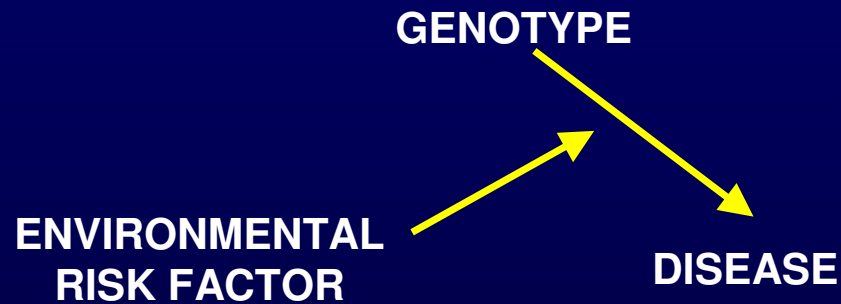


Relative Risks:			
High risk genotype		Low risk genotype	
Exposed	Unexposed	Exposed	Unexposed
++	1	+	1

MODEL C: Risk Factor Exacerbates Effect of Genotype

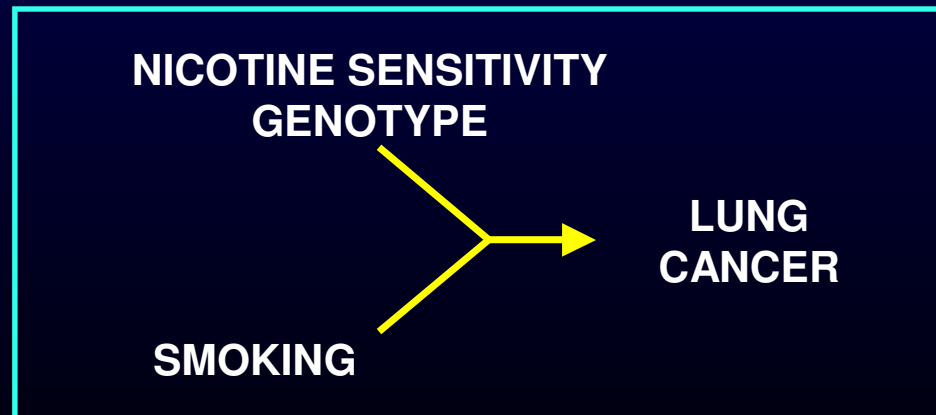
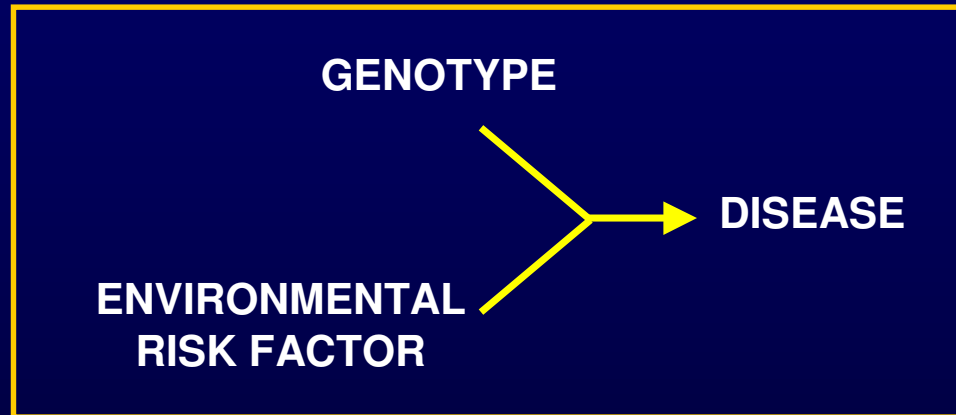


MODEL C: Risk Factor Exacerbates Effect of Genotype

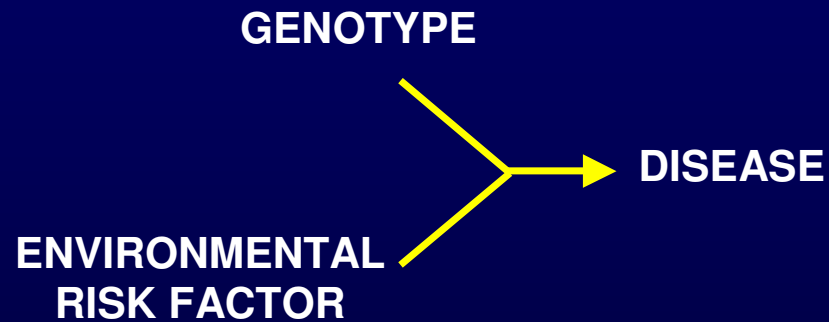


Relative Risks:			
High risk genotype		Low risk genotype	
Exposed	Unexposed	Exposed	Unexposed
++	+	1	1

MODEL D: Both Genotype and Risk Factor Required to Increase Risk

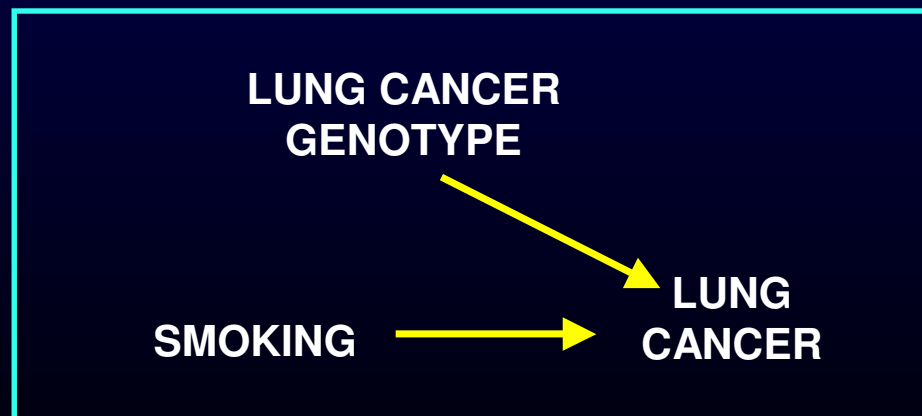
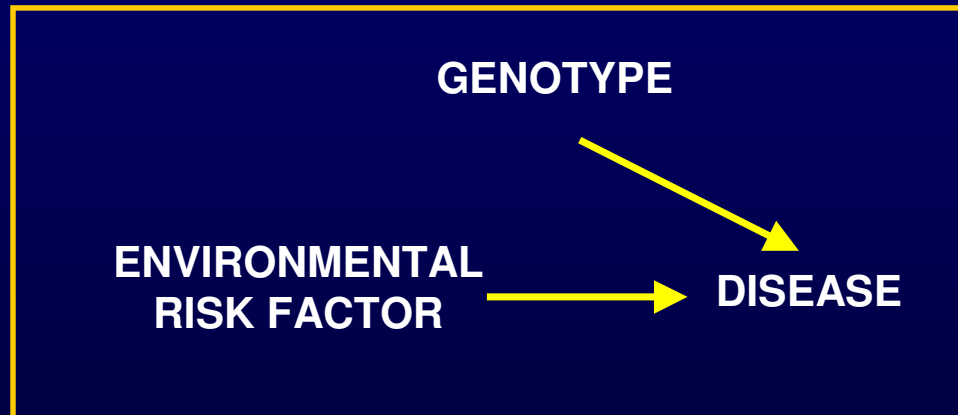


MODEL D: Both Genotype and Risk Factor Required to Increase Risk

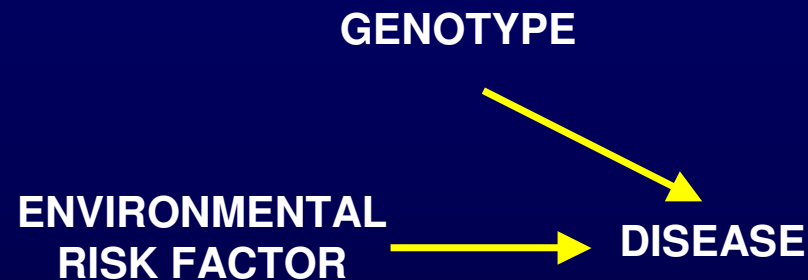


Relative Risks:			
High risk genotype		Low risk genotype	
Exposed	Unexposed	Exposed	Unexposed
+	1	1	1

MODEL E: Genotype and Risk Factor Each Affect Risk, and Combined Effect Greater than Additive



MODEL E: Genotype and Risk Factor Each Affect Risk, and Combined Effect Greater Than Additive



Relative Risks:			
High risk genotype		Low risk genotype	
Exposed	Unexposed	Exposed	Unexposed
+++	+	+	1

Patterns of Risk in Different Models

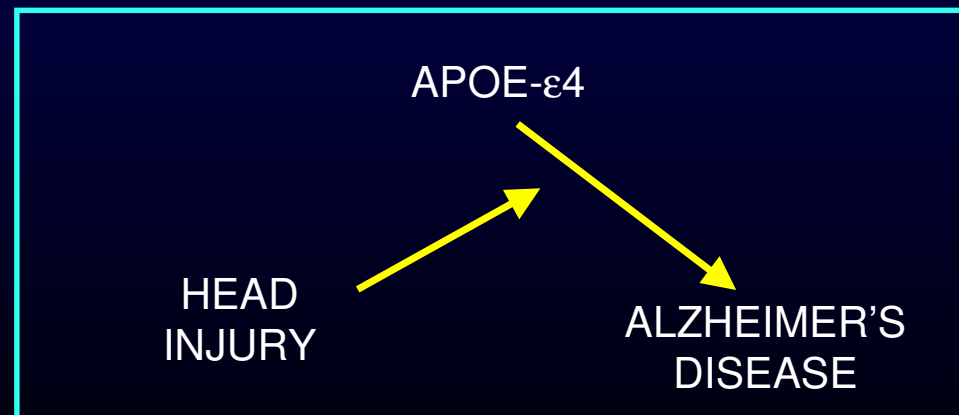
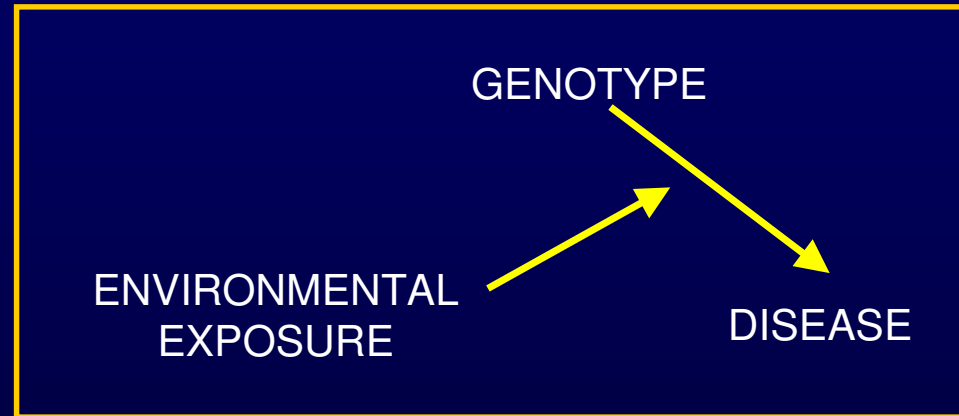
Model	Genotype Present		Genotype Absent	
	Exposure Present	Exposure Absent	Exposure Present	Exposure Absent
A. Genotype increases expression of exposure	+	1	+	1
B. Genotype exacerbates effect of exposure	++	1	+	1
C. Exposure exacerbates effect of genotype	++	+	1	1
D. Both genotype and exposure required	+	1	1	1
E. Genotype and exposure each affect risk; combined effect greater than additive	++	+	+	1

Effects of Head Injury and APOE ϵ 4 on Alzheimer's Disease: Evidence of Interaction?

	≥ 1 APOE ϵ 4 allele		0 APOE ϵ 4 alleles	
	Head injury	No head injury	Head injury	No head injury
AD cases	7	48	6	52
Controls	1	35	9	78
Odds Ratio	10.2	2.0	1.0	1.0
(95% CI)	(1.2-89.0)	(1.1-3.5)	(0.3-3.2)	(reference)

Mayeux R, et al. *Neurology* 1995;45:555-557.

MODEL C: Exposure Exacerbates Effect of Genotype



Limitations

- ┆ Many other models are possible
 - Only risk *raising* effects included (protective effects not considered)
 - Only *synergistic* models included (antagonism not considered, e.g., genotype suppresses effect of exposure)
- ┆ Variation in *response* to risk factors not considered

Estrogen use, APOE, and cognitive decline

	≥1 APOE-ε4 allele (N=667)		0 APOE-ε4 alleles (N=1969)	
	Current estrogen user	Never used estrogen	Current estrogen user	Never used estrogen
% cognitively impaired	18%	18%	8%	15%
Adjusted RR	1.3	1.0	0.6	1.0
95% CI	0.74-2.42	reference	0.36-0.99	reference

Yaffe K, et al. *Neurology* 2000;54:1949-1953.

Case-Only Methods for Testing Gene-Environment Interaction

Association between genotype and exposure ***within cases only*** indicates gene-environment interaction:

- Only tests for interaction on a *multiplicative* scale
- Assumes genotype and exposure occur independently in the population (i.e., individuals with genotype are not more likely to be exposed than those without genotype)

	Exposed	Unexposed
Genotype present	a	b
Genotype absent	c	d

$$OR_{ge} = ad/bc$$

Importance of Understanding Gene-Environment Interaction

- 1 Increased accuracy and precision in the detection of both genetic and environmental effects
- 1 Refinement of public health recommendations (screening, intervention)