Epidemiology for Public Health

Moyses Szklo

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HISTORICAL PAPER

AN EPIDEMIOLOGIC STUDY OF BLOOD PRESSURE LEVELS IN A BIRACIAL COMMUNITY IN THE SOUTHERN UNITED STATES [1,2]

By

GEORGE W. COMSTOCK [3]

(Received for publication December 15, 1956)

INTRODUCTON

A recent symposium on the epidemiology of hypertension (1) may well prove to be of great importance in the understanding of this disorder, not so much for the considerable body of information made available therein, but more for the deficiencies in present knowledge which were disclosed. These deficiencies were excellently summarized by Clark and Morsell (2) as follows: "(1) There are no consistent standards for blood pressure measurement; (2) there are no established criteria for defining hypertension; (3) none of the existing studies is based on a scientific sample of the population of the country or any subdivision of it; and (4) although the various studies leave no doubt that hypertension is a health problem of great magnitude which varies according to age, sex and race, they do not answer the question as to the actual extent of this problem."

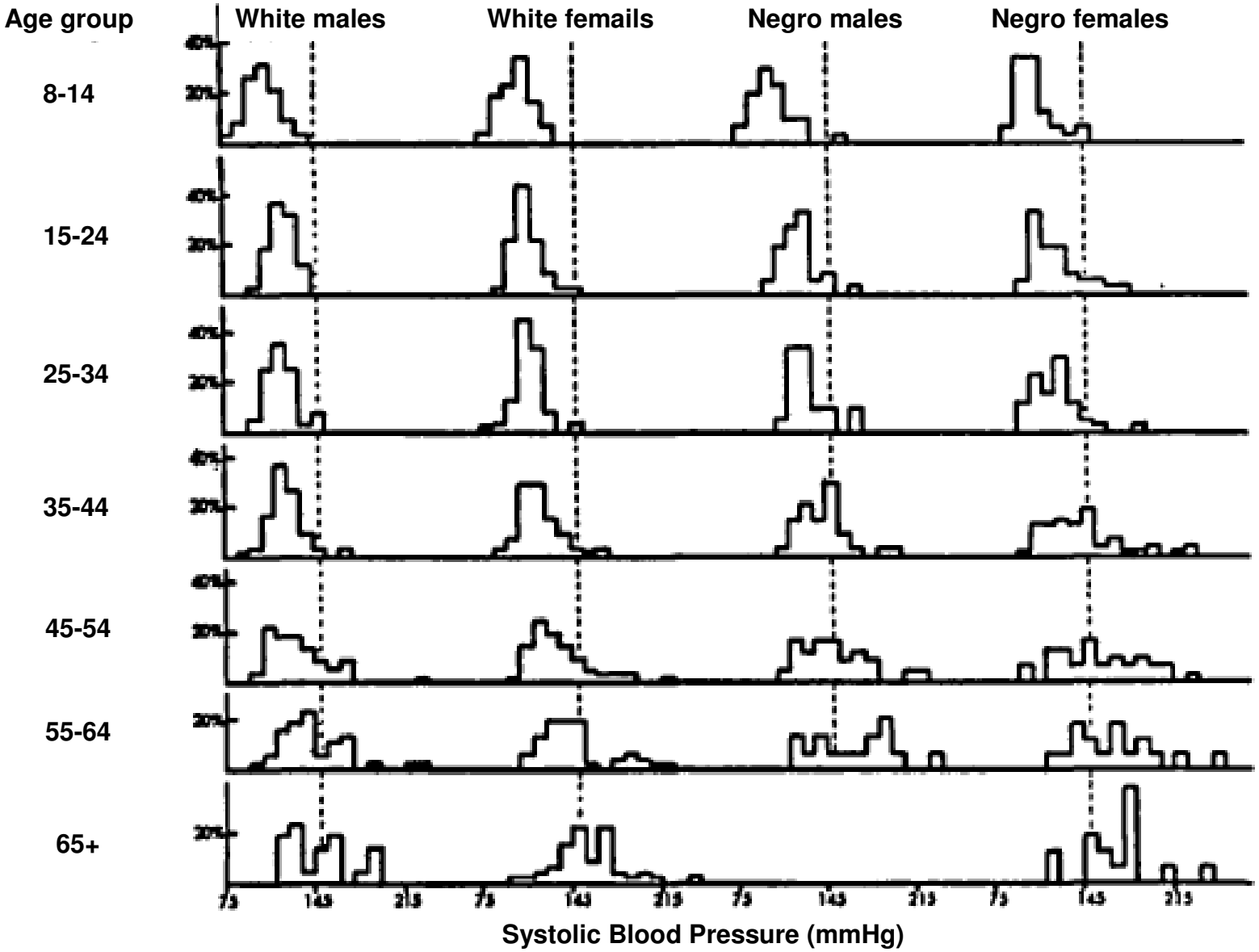
Although it is perfectly proper to refer to the epidemiology of hypertension, it should be realized that there are serious difficulties in this approach, largely due to the unfortunate fact that there is no general agreement on a definition of hypertension or hypertensive disease.

[1] From the Tuberculosis Program, U. S. Public Health Service, Department of Health, Education and Welfare, Washington, D. C.

[2] This study was made possible by the facilities of the Muscogee County Tuberculosis Study, an enterprise supported by the Georgia State Department, Muscogee County Health Department, and the United States Public Health Service. It is an abridgement of a thesis submitted by the author to the School of Hygiene and Public Health, The Johns Hopkins University, in partial fulfillment of the requirements for the degree of Doctor of Public Health.

[3] The author acknowledges with gratitude the very considerable assistance given by the entire staff of the Muscogee County Tuberculosis Study. He is especially indebted to the following individuals for assistance with particular phases of the study and analysis: Miss Olga Michaelson for the general supervision of the field study; Dr. Carroll E. Palmer, Tuber-

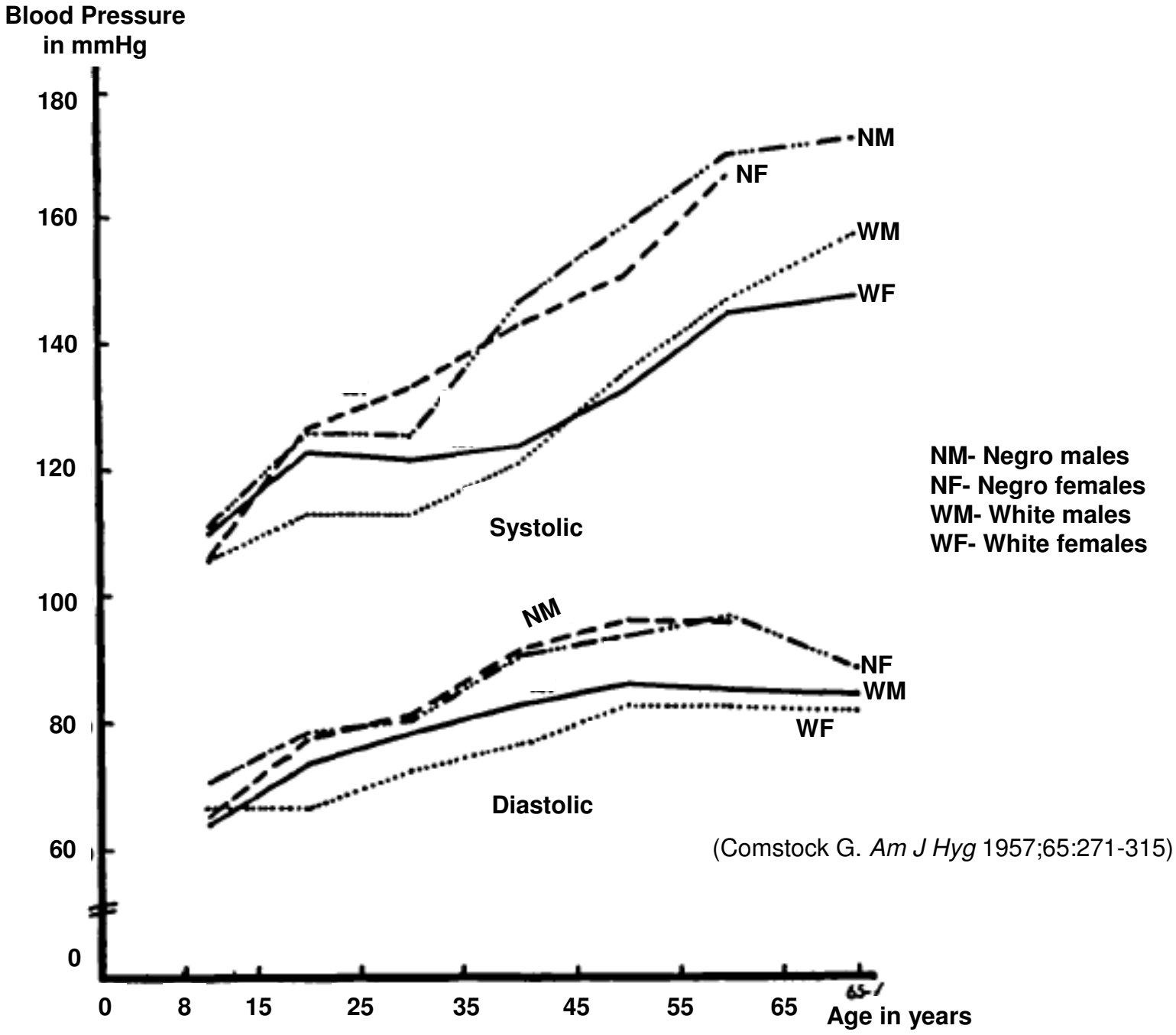
(Comstock G. Am J Hyg 1957;65:271-315)



Frequency distributions of systolic blood pressure by race, sex and age

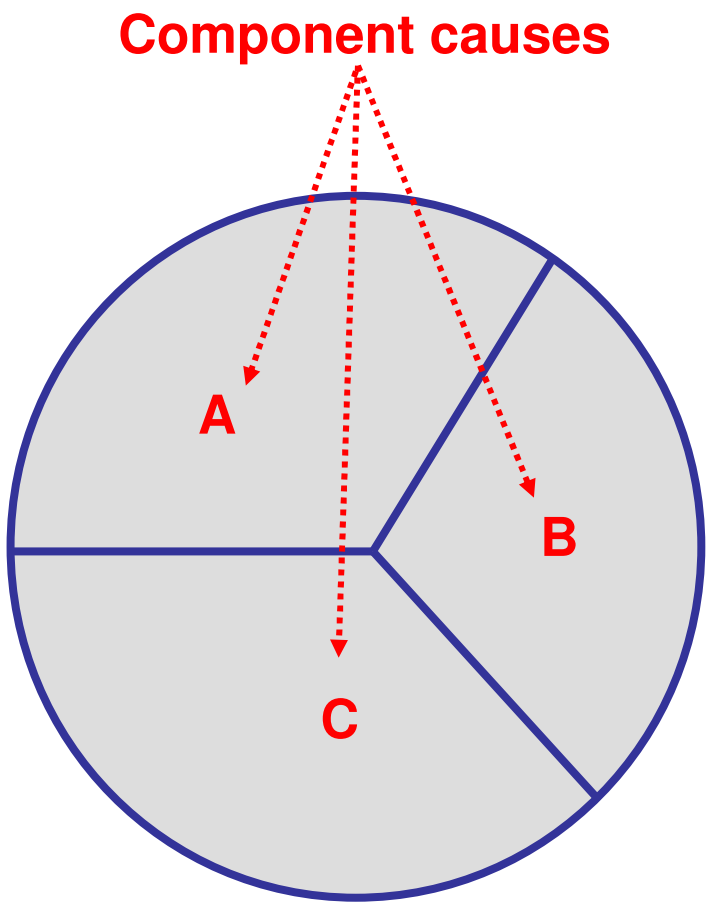
(Comstock G. *Am J Hyg* 1957;65:271-315)

"I submitted the paper for publication to the Journal of the American Medical Association. The journal was hesitant to publish the report because the editor was not certain of the scientific value of the case-control approach. However, shortly after the receipt of the paper by Levin and his colleagues, Wynder and Graham submitted a paper to JAMA reporting essentially the same results as those from Levin's study. The second author, Evarts Graham, was a surgeon with an international reputation as an innovator. It was thus difficult for the JAMA Editor to dismiss Wynder and Graham paper. Hence, both Levin et al, and Wynder and Graham papers were published in the same issue of the Journal of the American Medical Association. Doll and Hill's paper appeared a few months later."



(Comstock G. *Am J Hyg* 1957;65:271-315)

Mean systolic and diastolic blood pressure by race, sex and age



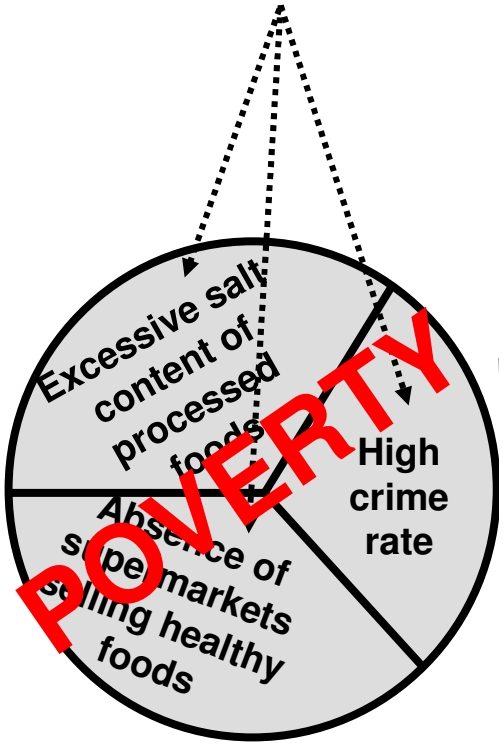
Sufficient Cause

<u>Sufficient cause</u>: a set of minimal conditions and events ("component causes") that inevitably produce disease (Rothman K. *Modern Epidemiology*. Boston, Toronto: Little Brown and Company,1986)

m1

STROKE PREVENTION

Distal component causes



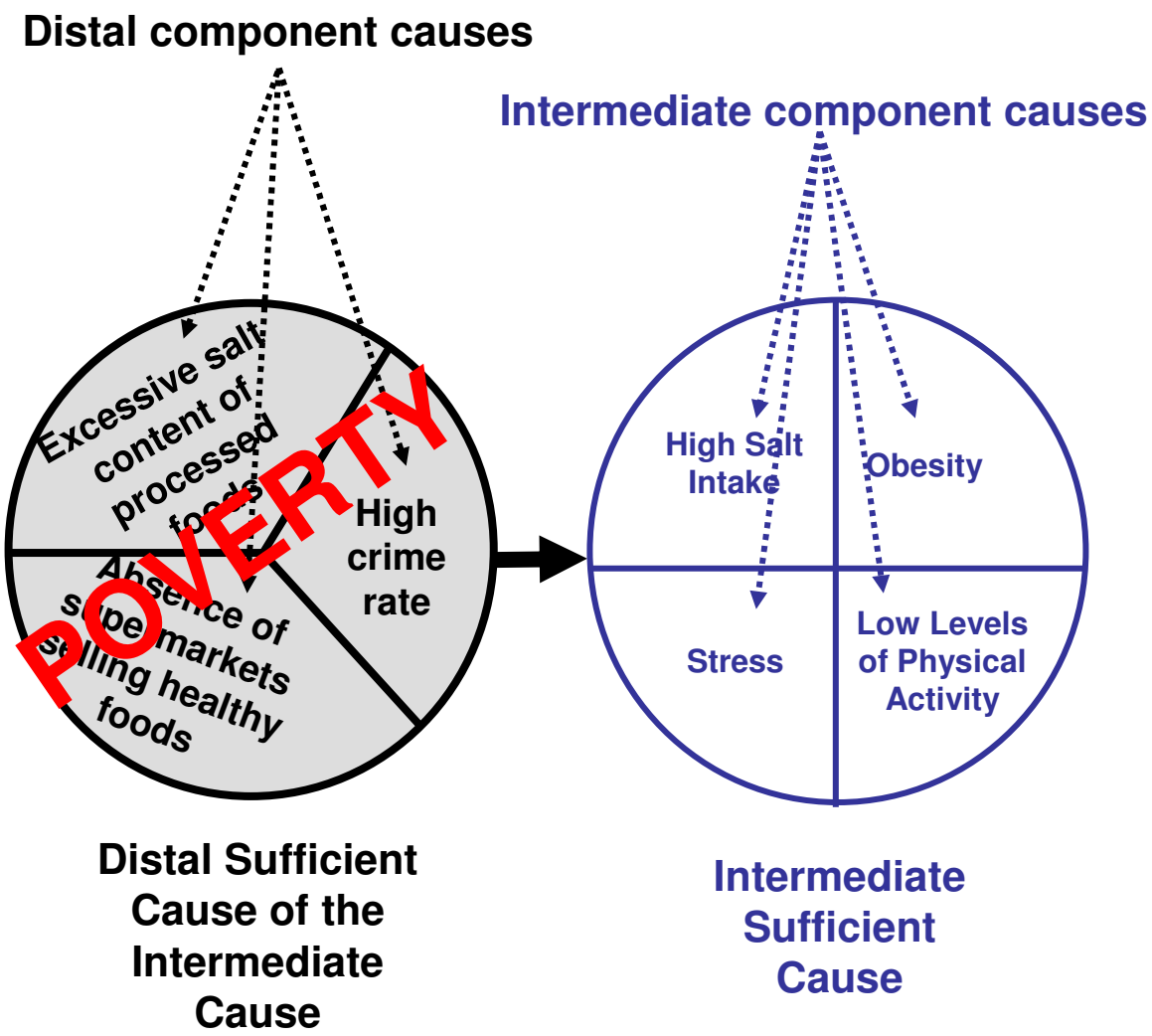
Distal Sufficient Cause of the Intermediate Cause

Slide 7

m1 Neste exemplo, eu resolvi expandir o modelo de Rothman através da introdução do elemento de temporalidade. Eu tambem distinguo neste exemplo os diferentes tipos de causas suficientes, isto é, distais, intermediárias e proximais

mszklo; 12/4/2006

m2

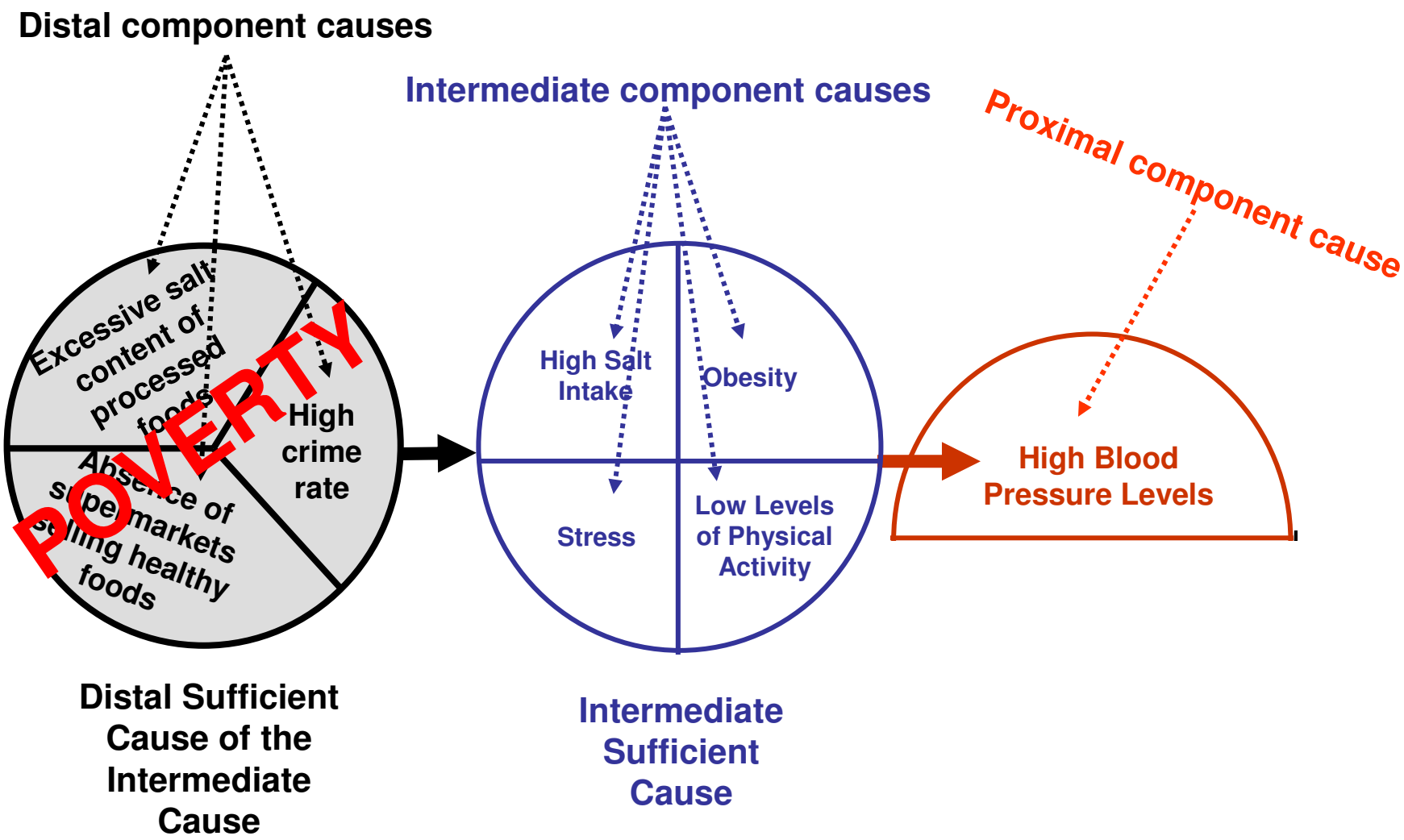

Distal component causes
Intermediate component causes
Excessive salt content of processed foods
High crime rate
Absence of supermarkets selling healthy foods
POVERTY
High Salt Intake
Obesity
Stress
Low Levels of Physical Activity
Distal Sufficient Cause of the Intermediate Cause
Intermediate Sufficient Cause

Slide 8

m2 Neste exemplo, eu resolvi expandir o modelo de Rothman através da introdução do elemento de temporalidade. Eu tambem distinguo neste exemplo os diferentes tipos de causas suficientes, isto é, distais, intermediárias e proximais

mszklo; 12/4/2006

m3

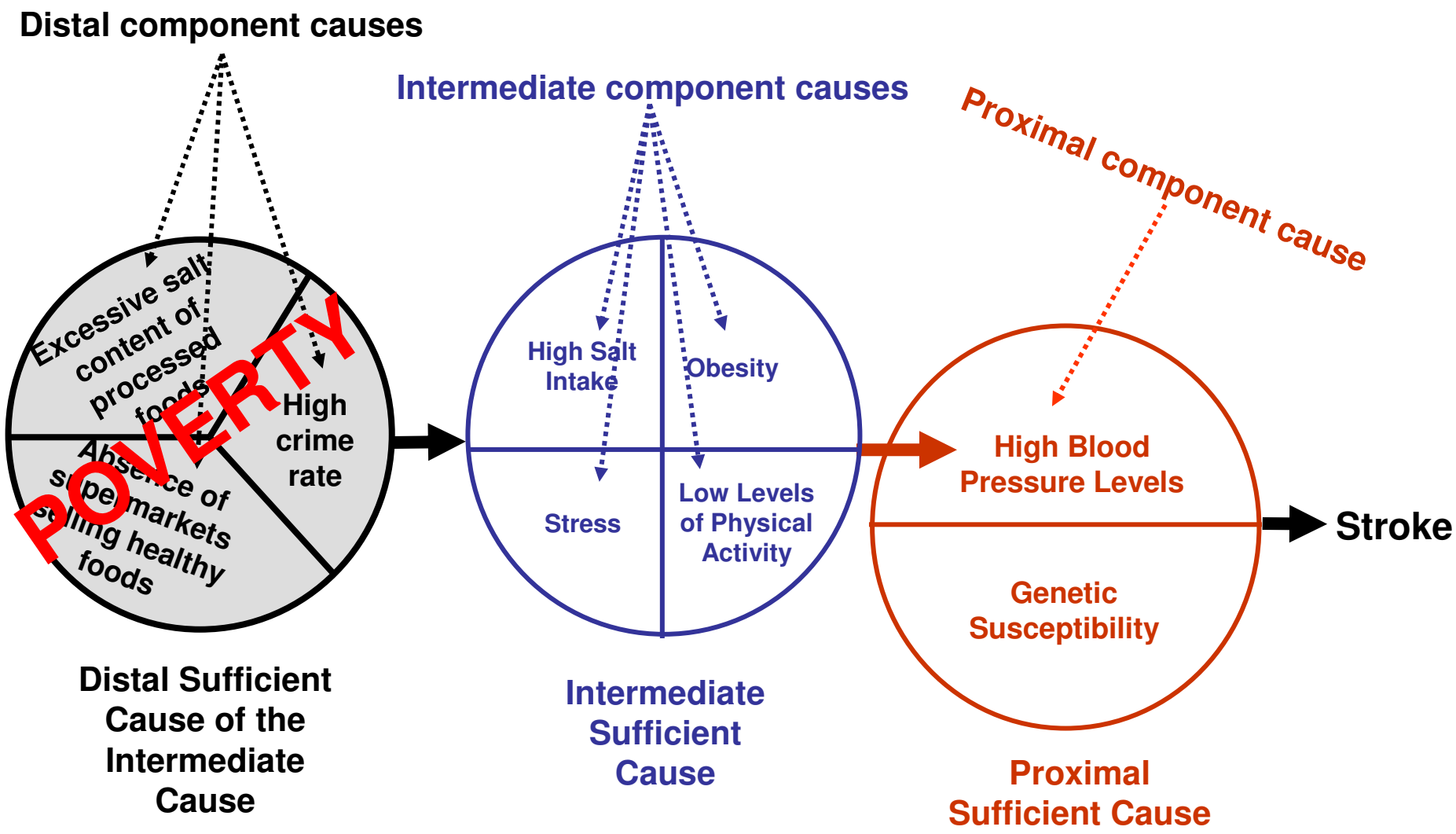

Distal component causes
Intermediate component causes
Proximal component cause
Excessive salt content of processed foods
High crime rate
Absence of supermarkets selling healthy foods
POVERTY
High Salt Intake
Obesity
Stress
Low Levels of Physical Activity
High Blood Pressure Levels
Distal Sufficient Cause of the Intermediate Cause
Intermediate Sufficient Cause

Slide 9

m3 Neste exemplo, eu resolvi expandir o modelo de Rothman através da introdução do elemento de temporalidade. Eu tambem distinguo neste exemplo os diferentes tipos de causas suficientes, isto é, distais, intermediárias e proximais

mszklo; 12/4/2006

m14

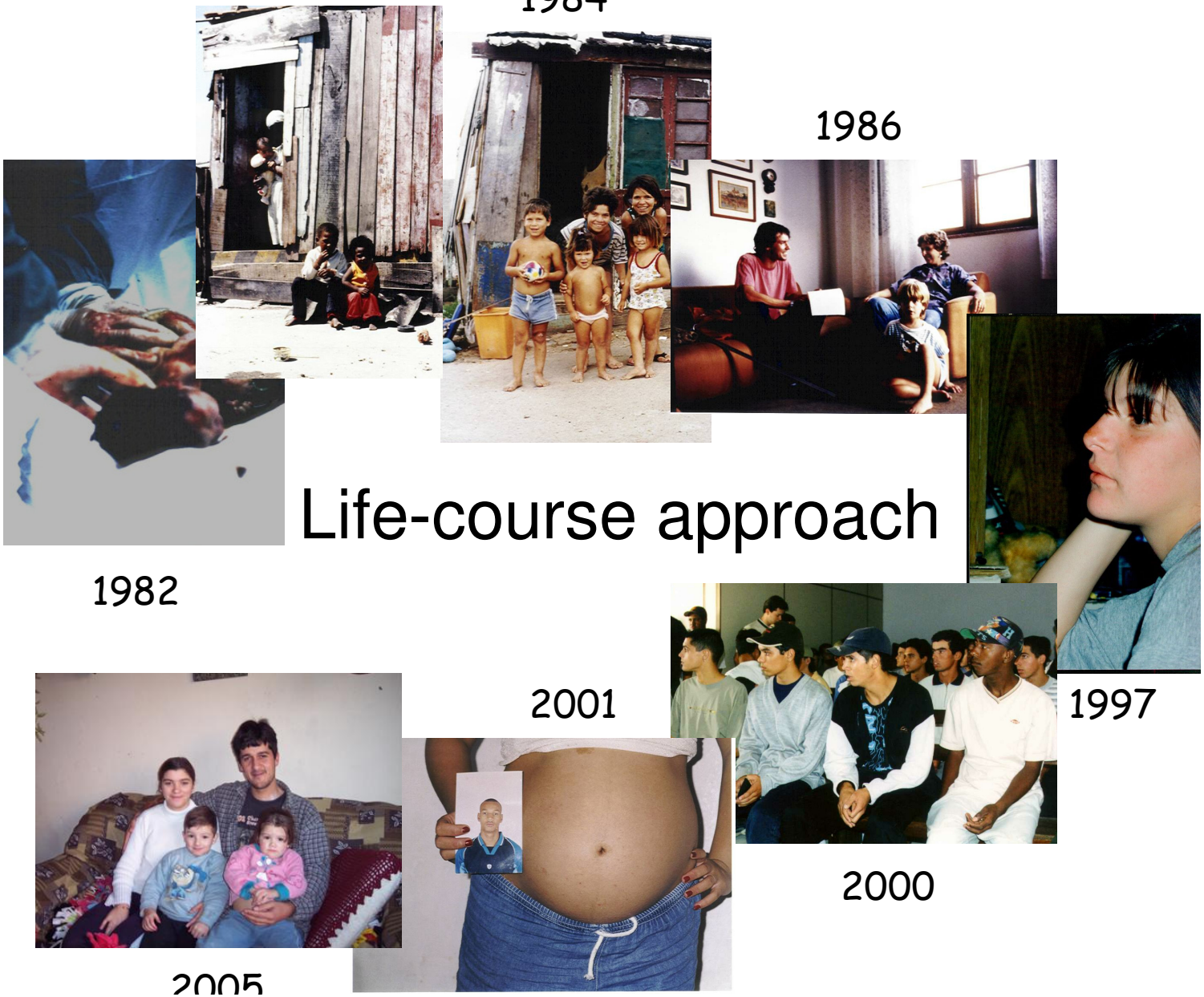

Distal component causes
Intermediate component causes
Proximal component cause
Excessive salt content of processed foods
High crime rate
Absence of supermarkets selling healthy foods
POVERTY
High Salt Intake
Obesity
Stress
Low Levels of Physical Activity
High Blood Pressure Levels
Genetic Susceptibility
Stroke
Distal Sufficient Cause of the Intermediate Cause
Intermediate Sufficient Cause
Proximal Sufficient Cause

Slide 10

m14 Neste exemplo, eu resolvi expandir o modelo de Rothman através da introdução do elemento de temporalidade. Eu tambem distinguo neste exemplo os diferentes tipos de causas suficientes, isto é, distais, intermediárias e proximais

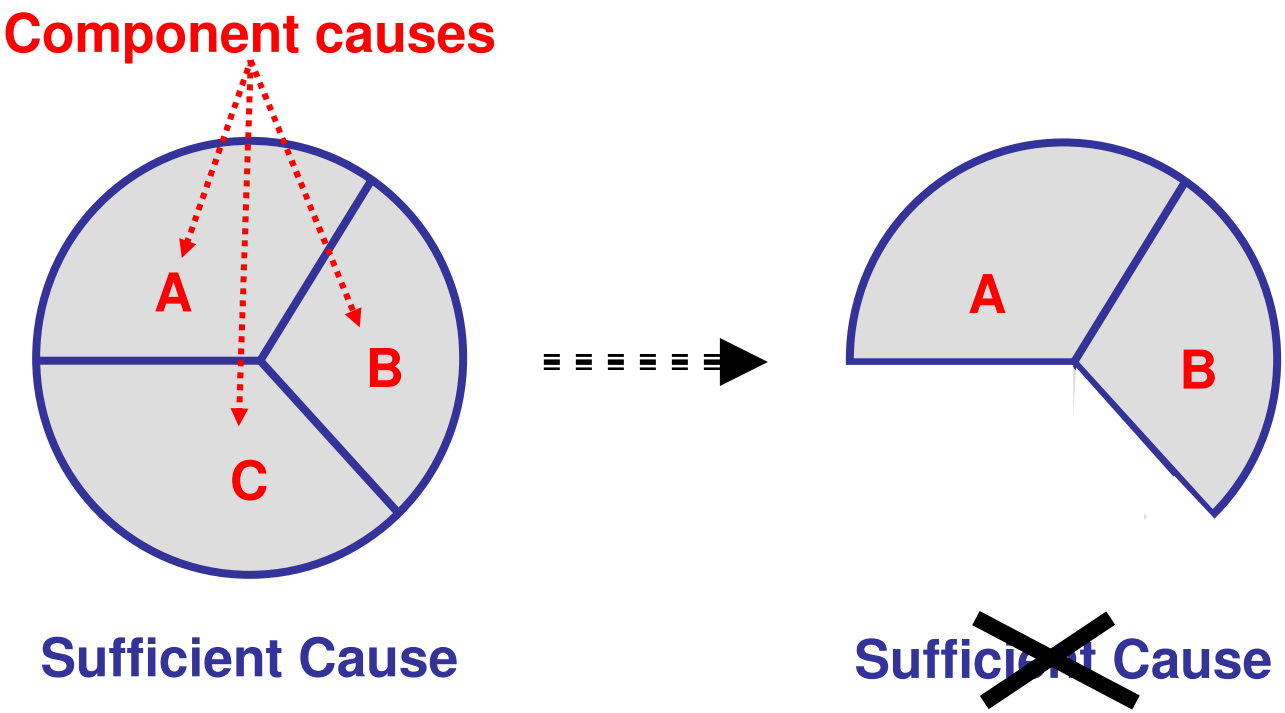
mszklo; 12/4/2006

THE PELOTAS STUDY



• Prevention or cessation of a single risk factor results in a disease risk decrease, as it eliminates all sufficient causes of which the risk factor is a component cause

• Common exposures are often related to rare outcomes in the same populations (e.g., Helicobacter pylori and gastric cancer)



(Ref. on sufficient cause: Rothman K. *Modern Epidemiology*. Boston, Toronto: Little Brown and Company,1986)

Epidemiology

Principles and Methods

Brian MacMahon, M.D., Ph.D., D.P.H.
Thomas F. Pugh, M.D., M.P.H.
Department of Epidemiology
Harvard University School of Public Health

Little, Brown and Company
Boston

serum of a specific virus. Thus the association with the virus is currently considered the direct one and that with serum indirect. Further studies might in due course reveal what specific attributes or molecular components of the virus might be considered more direct causal factors. Knowledge of causal mechanisms is not refined to the degree that makes it possible to state that *this* is the ultimate direct association and that no other associations intervene.

The practical significance of causal associations in the development of preventive programs does not necessarily depend on the degree of directness. First, more direct associations may not yet have been identified and so there may be no choice but to make use of obviously indirect associations in preventive programs. For example, knowledge of the association of freedom from scurvy with diets containing fresh fruits and vegetables was put to practical use hundreds of years before the identification of vitamin C, and prevention of smallpox antedates modern virology by almost 200 years. Second, more direct causes, although known, may not be susceptible to economical alteration, whereas the indirect ones may be. For example, preventive measures against serum hepatitis are directed against poor syringe hygiene and not specifically toward removal of the hepatitis virus. And decades after the discovery of the microorganisms associated with enteric disease, preventive measures are still directed, at least in the United States and Europe, primarily toward the provision of clean water and food, rather than against specific microorganisms.

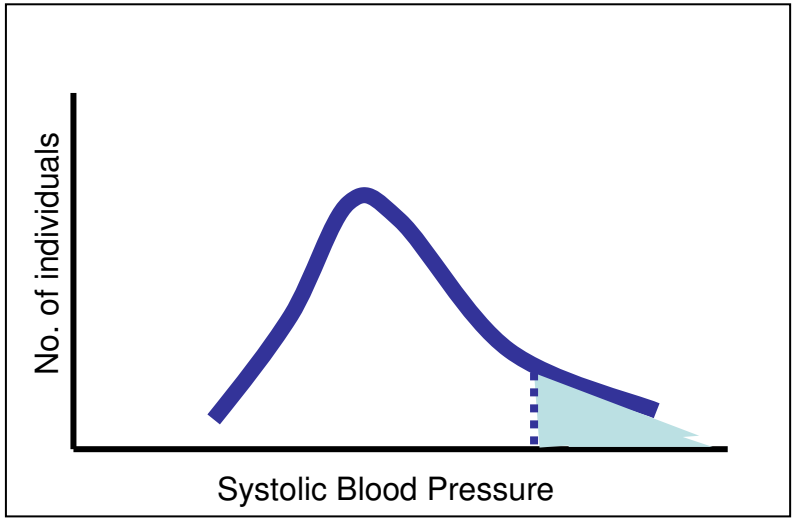
THE WEB OF CAUSATION

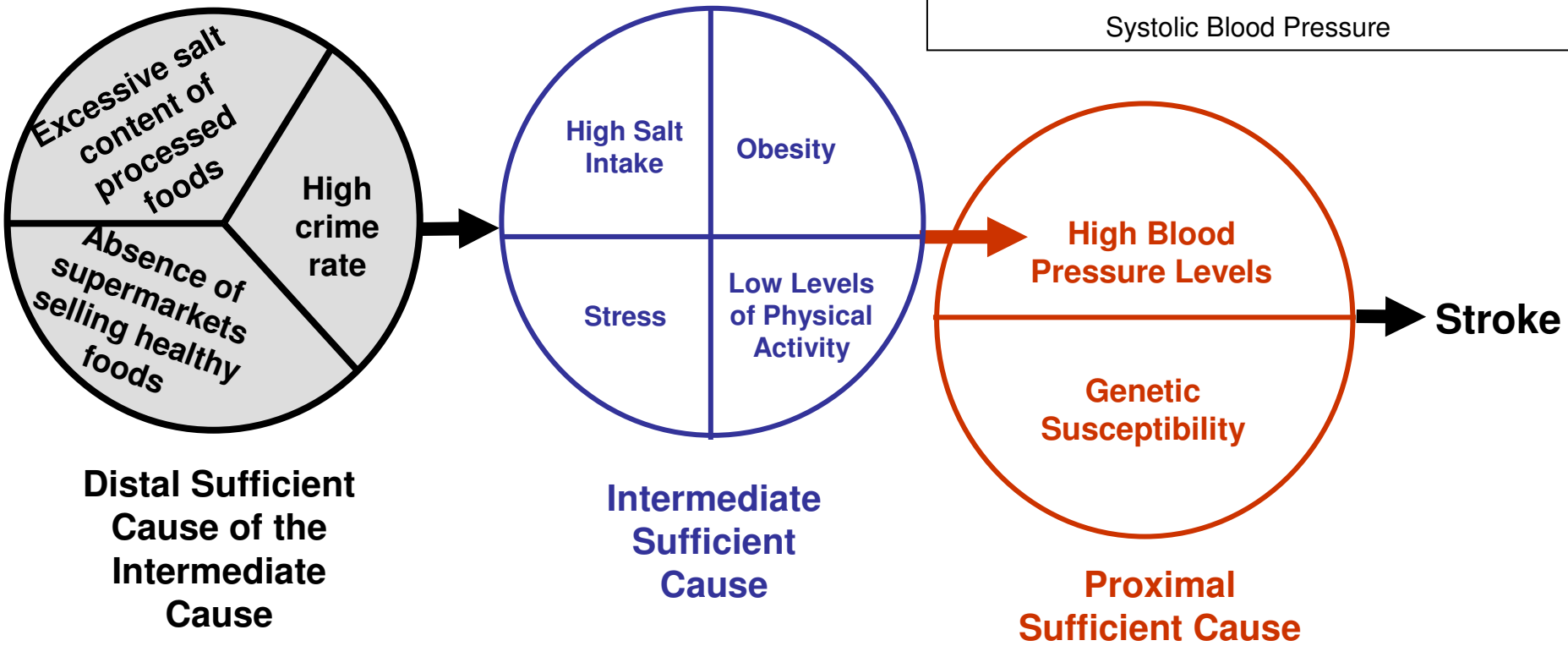
We have discussed the types of association that may exist between two categories of events. In fact, effects are not dependent on single causes. The concept of chains of causation, although useful has the defect of oversimplification. In Figure 2 are shown some of the components that enter into the causal association between treatment for syphilis and serum hepatitis. When

Rose G, Int J Epidemiol 1985;14:32-38

m15

High risk strategy: identification, treatment and control of **all** patients with hypertension





Slide 15

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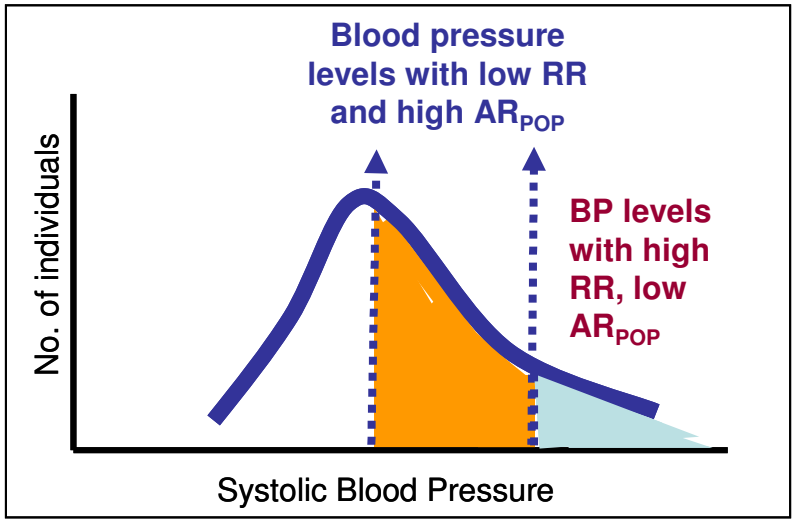
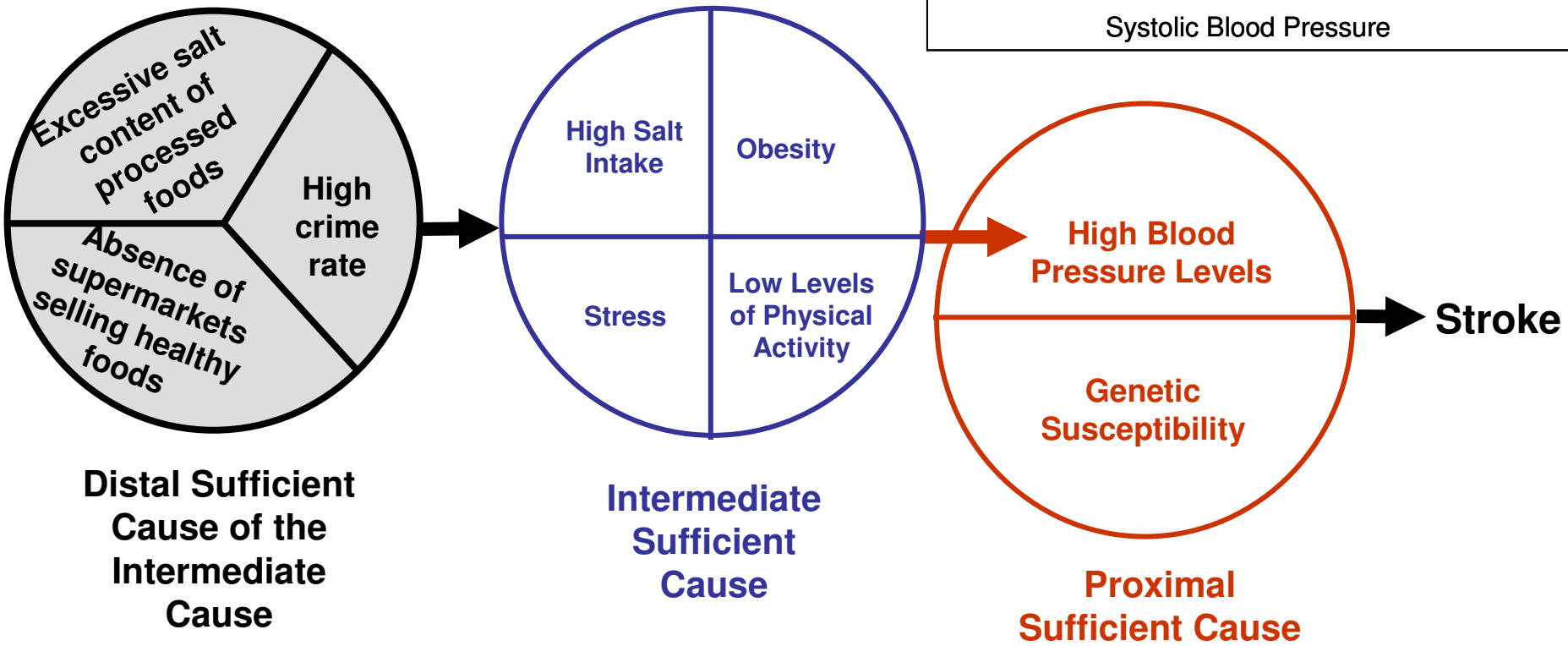
mszklo; 12/4/2006

m16

High risk strategy: identification, treatment and control of **all** patients with hypertension





$$\text{Population Attributable Risk} = \frac{\text{Risk Factor } \mathbf{Pr}\text{evalence } (\mathbf{Re}\text{lative Risk} - 1.0)}{\text{Risk Factor } \mathbf{Pr}\text{evalence } (\mathbf{Re}\text{lative Risk} - 1.0) + 1.0}$$

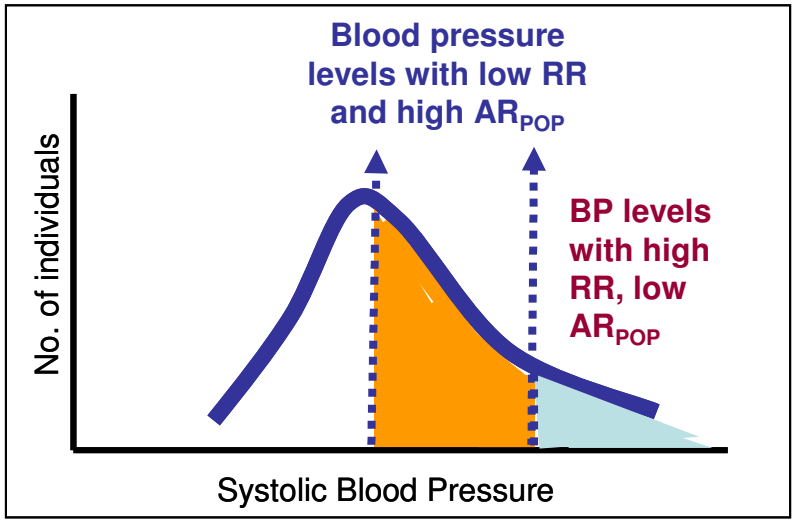
Slide 16

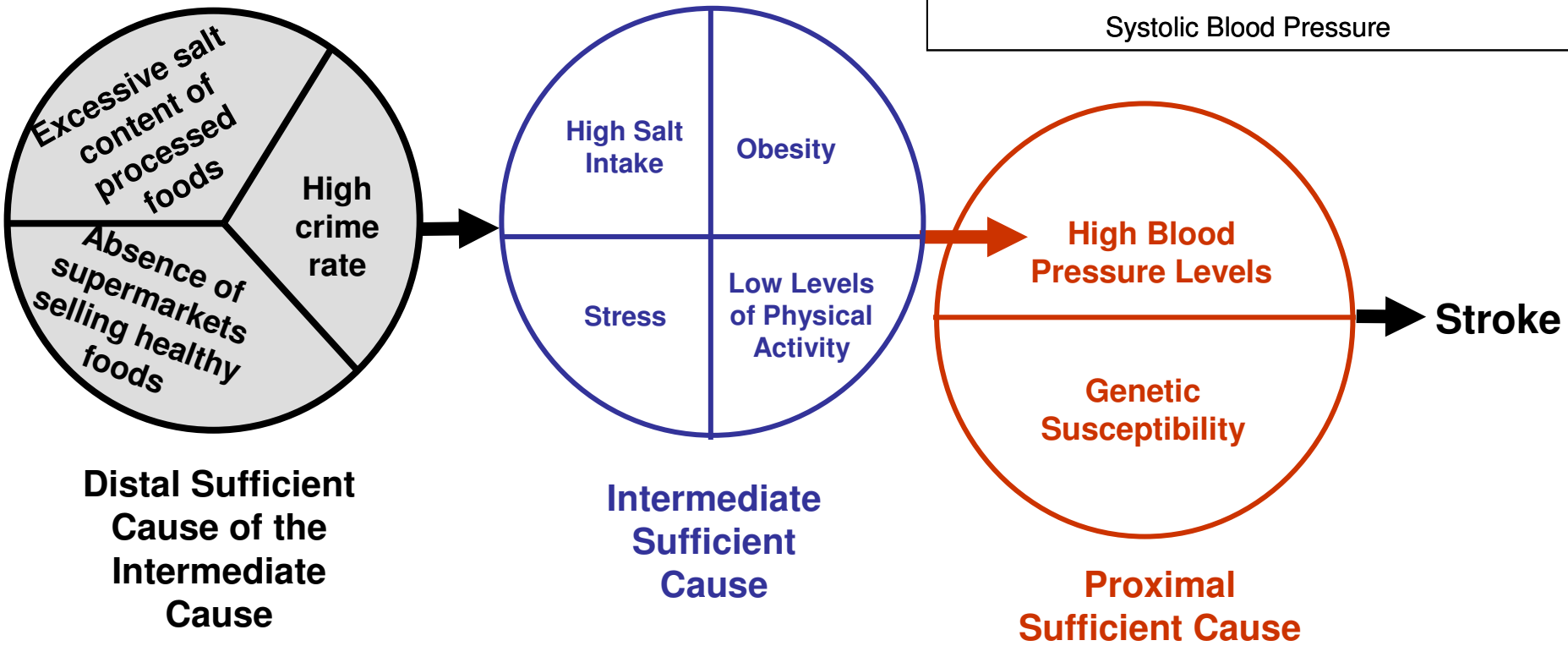
m16 Neste exemplo, eu resolvi expandir o modelo de Rothman através da introdução do elemento de temporalidade. Eu tambem distinguo neste exemplo os diferentes tipos de causas suficientes, isto é, distais, intermediárias e proximais

mszklo; 12/4/2006

m32

High risk strategy: identification, treatment and control of **all** patients with hypertension → ⇓ stroke incidence ~ 15% (Law MR, et al. *Br Med J* 1991;302:819-24)





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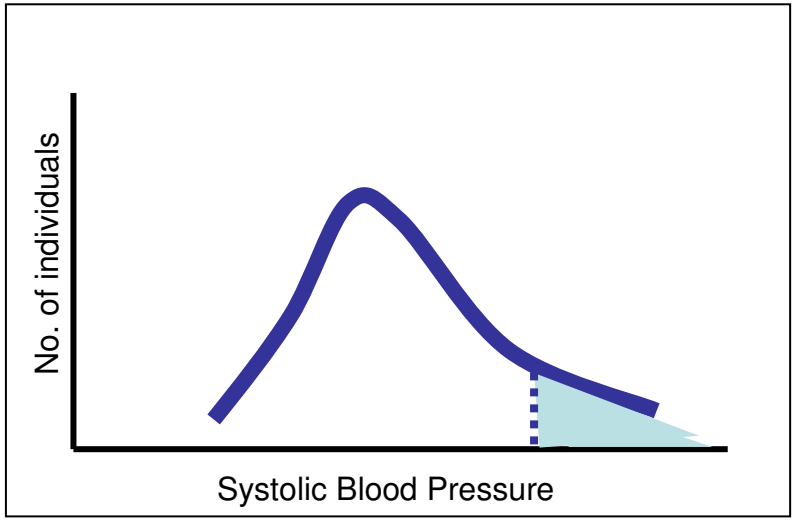
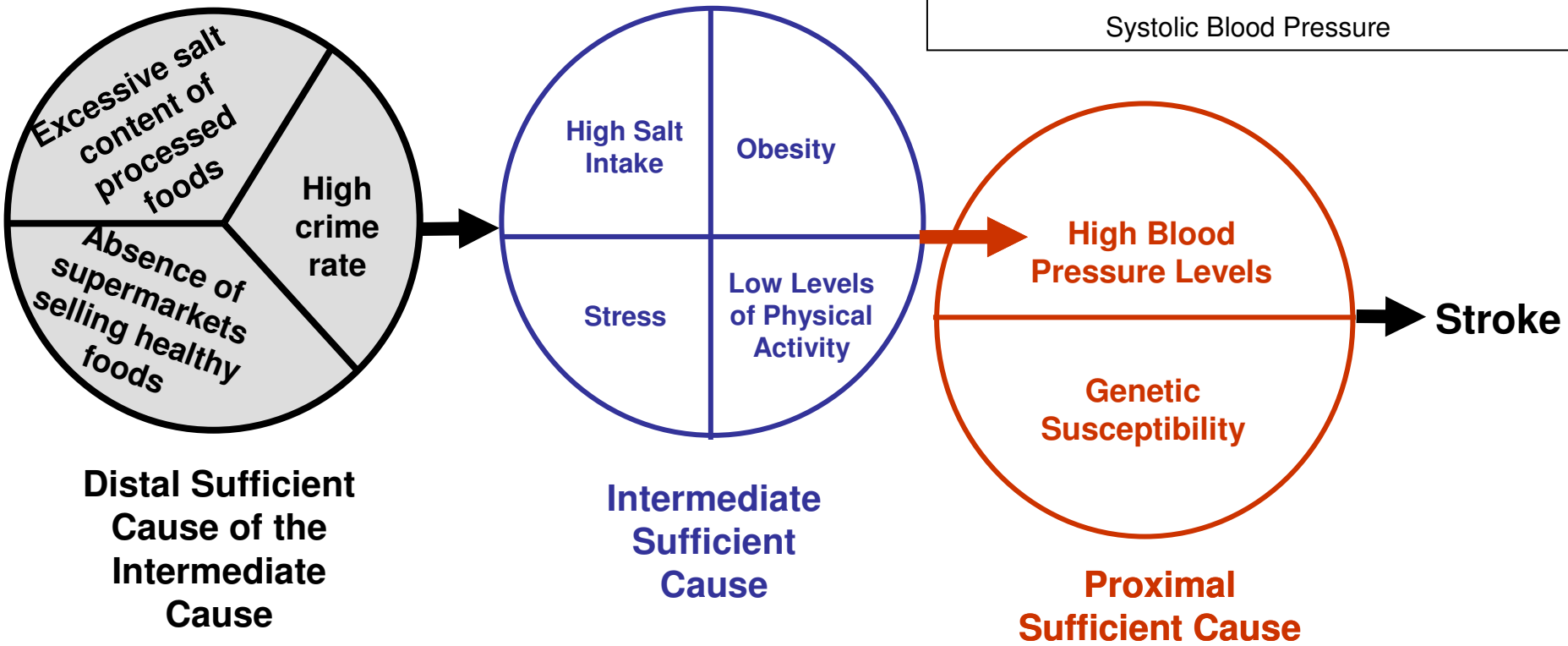
mszklo; 12/4/2006

m18

Population-wide strategy: ⇓ per capita salt intake





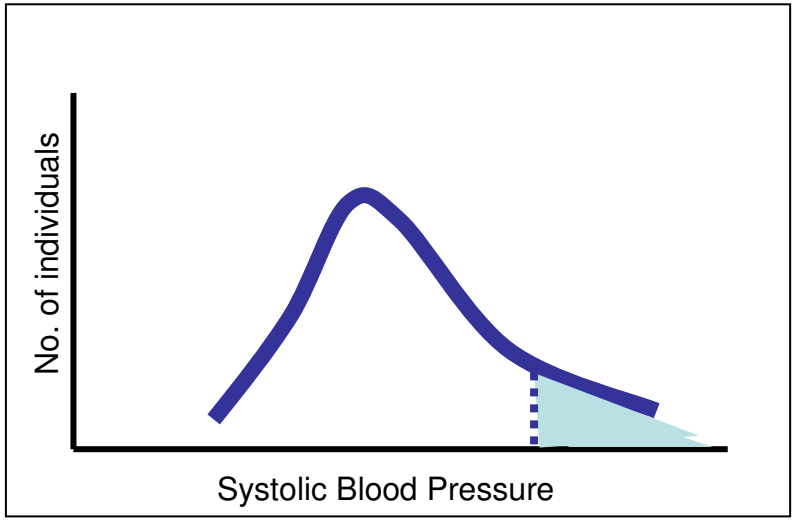
Slide 18

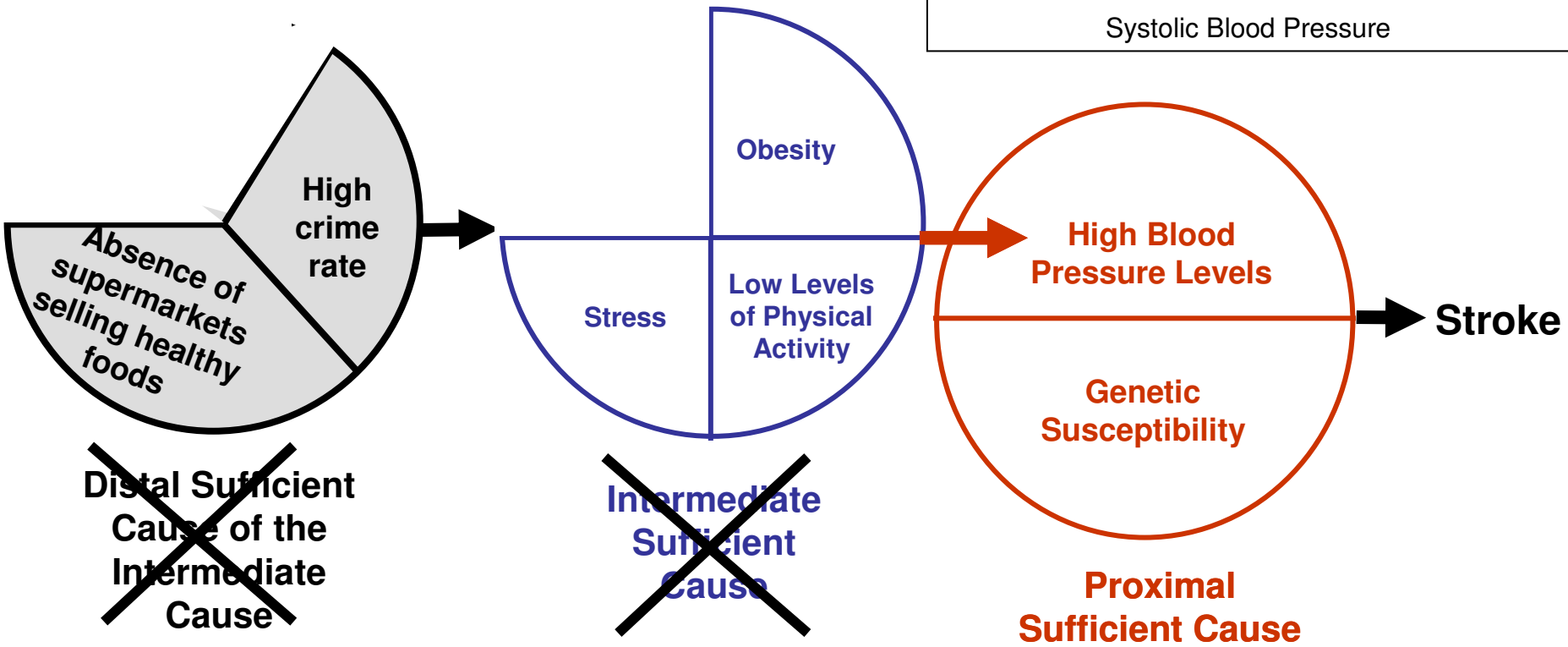
m18 Neste exemplo, eu resolvi expandir o modelo de Rothman através da introdução do elemento de temporalidade. Eu tambem distinguo neste exemplo os diferentes tipos de causas suficientes, isto é, distais, intermediárias e proximais

mszklo; 12/4/2006

m37

Population-wide strategy: ⇓ per capita salt intake





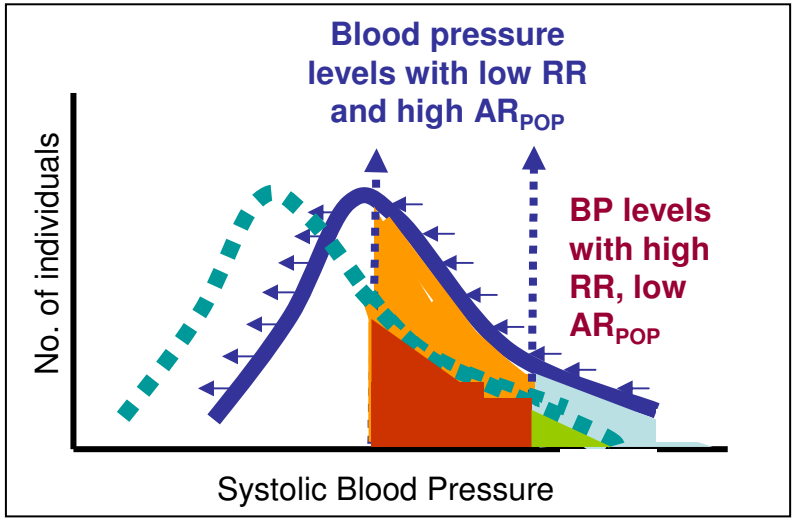
Slide 19

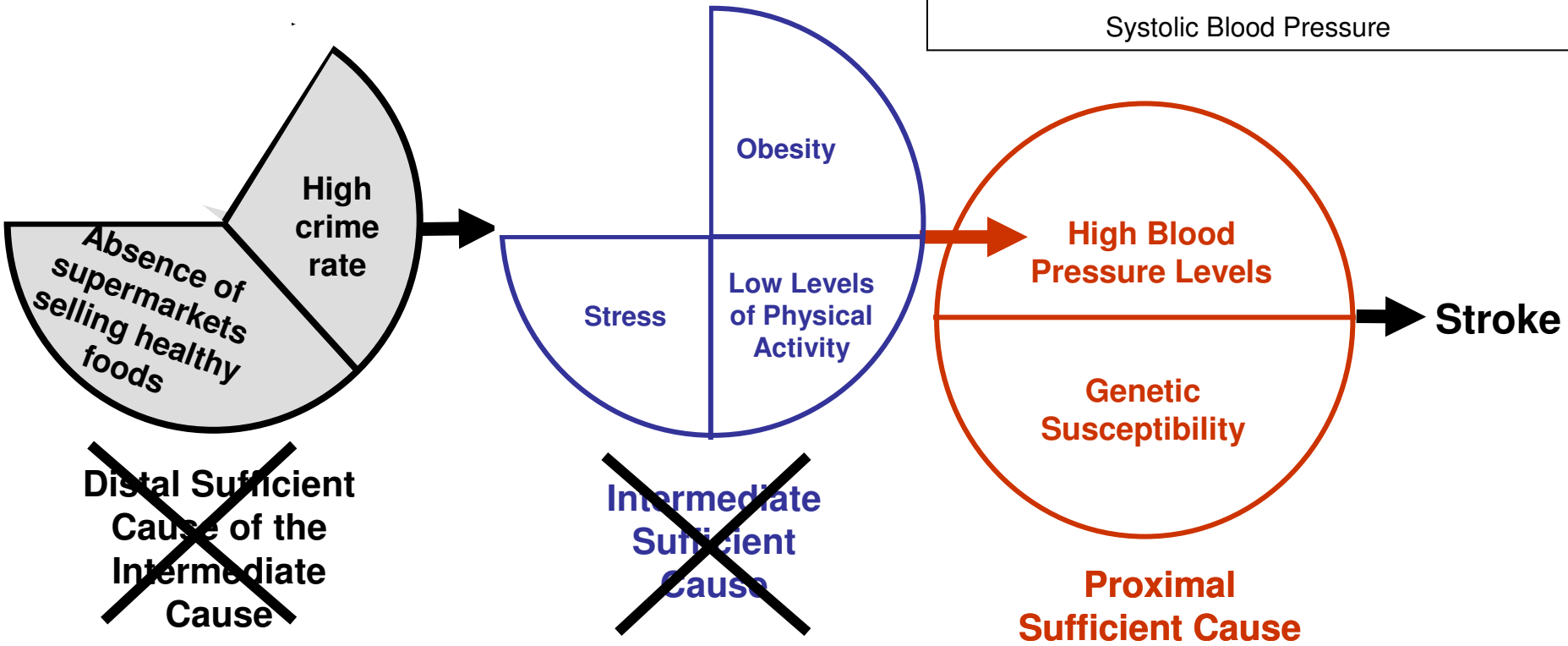
m37 Neste exemplo, eu resolvi expandir o modelo de Rothman através da introdução do elemento de temporalidade. Eu tambem distinguo neste exemplo os diferentes tipos de causas suficientes, isto é, distais, intermediárias e proximais

mszklo; 12/4/2006

m33

Population-wide strategy: ⇓ per capita salt intake





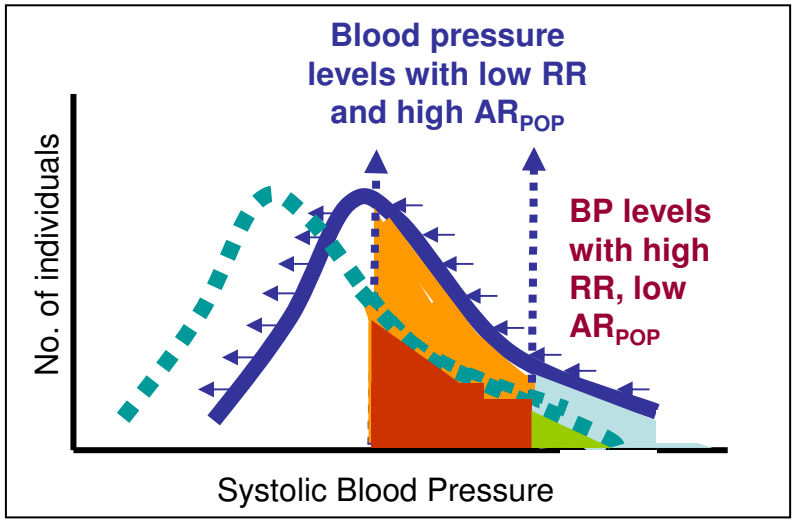
Slide 20

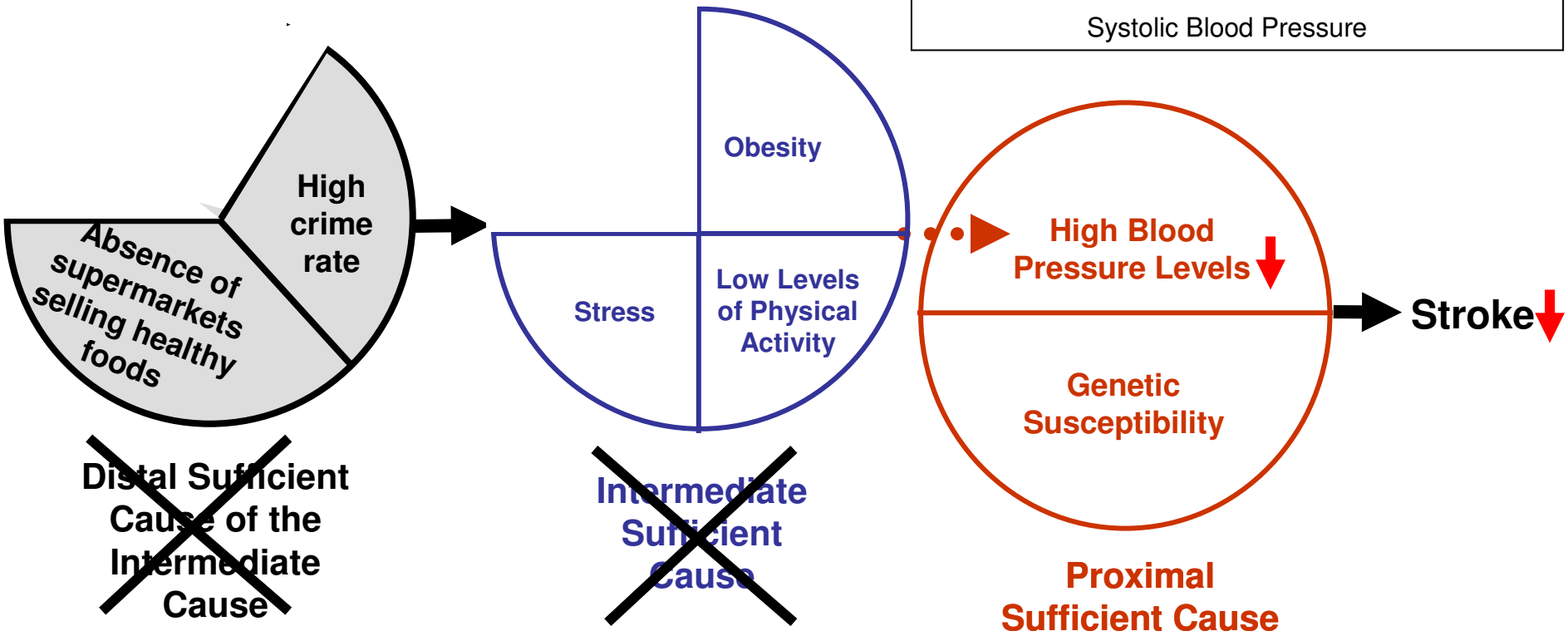
m33 Neste exemplo, eu resolvi expandir o modelo de Rothman através da introdução do elemento de temporalidade. Eu tambem distinguo neste exemplo os diferentes tipos de causas suficientes, isto é, distais, intermediárias e proximais

mszklo; 12/4/2006

m39

Population-wide strategy: ⇓ per capita salt intake= 33% → ⇓ stroke incidence ~ 22% (Law MR, et al. *Br Med J* 1991;302:819-24)





Slide 21

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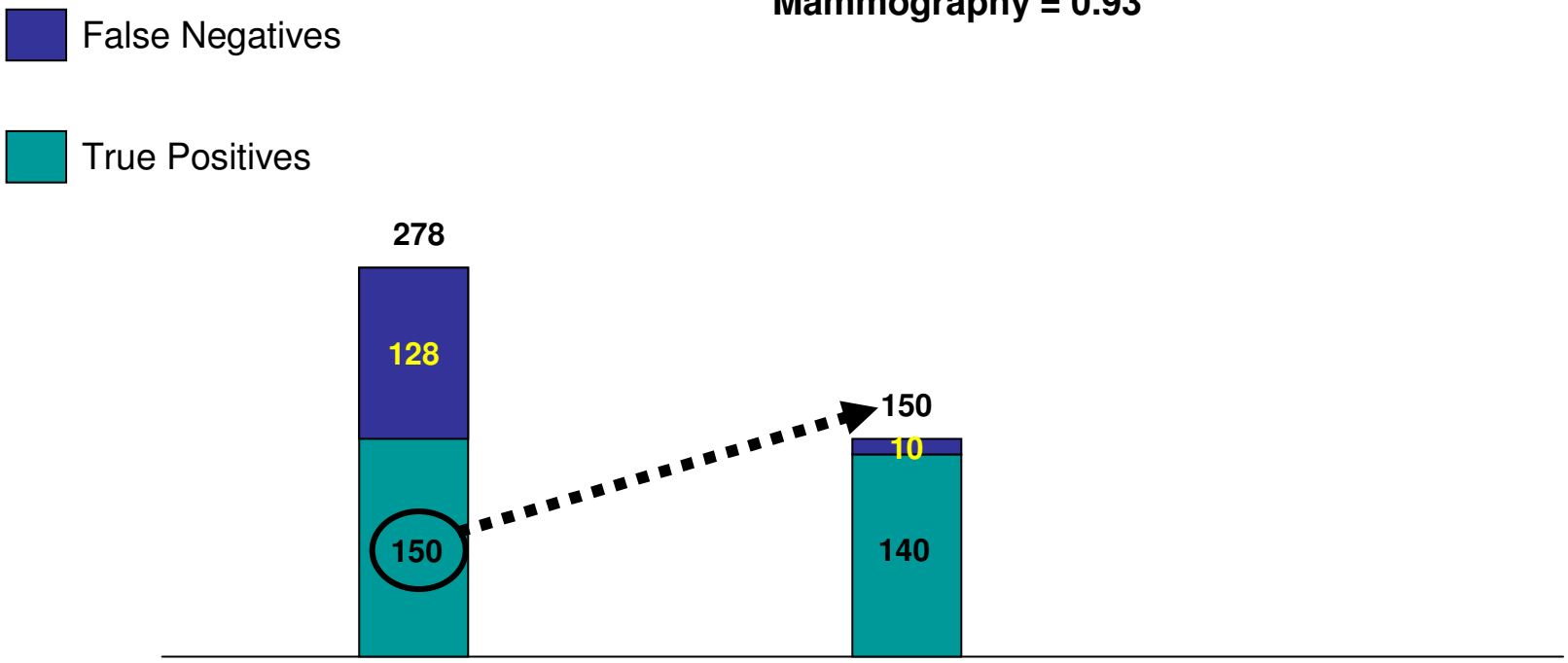
mszklo; 12/4/2006

m9

SENSITIVITY OF A HIGH RISK SCREENING PROGRAM FOR INCIDENT BREAST CANCER CASES DURING ONE YEAR IN A TARGET POPULATION OF 100 000 WOMEN¶

•Average yearly incidence in S. Paulo, 1998-2000 ≅ 278/100 000§

1st Phase: Sensitivity of Family History of Breast Cancer = 0.54*; 2nd Phase: Sensitivity of Mammography = 0.93**



1st Phase: Sensitivity of Family History = 0.54*

2nd Phase: Sensitivity of Mammography = 0.93**

High Risk Screening → Program Sensitivity= 0.54 × 0.93 = 0.50

§Câncer no Brasil- Dados do Registro de Câncer de Base Populacional. Disponível em http://www.inca.gov.br/vigilancia/ CONPREV-INCA-MS e IBGE-MP

¶Szklo M. *J Gen Intern Med* 1990; 5(Suppl):S47-S49

*Hartmann et al, *New Eng J Med* 2005;353:229-37

**Mushlin et al, *Am J Prev Med* 1998;14:143-53

Slide 22

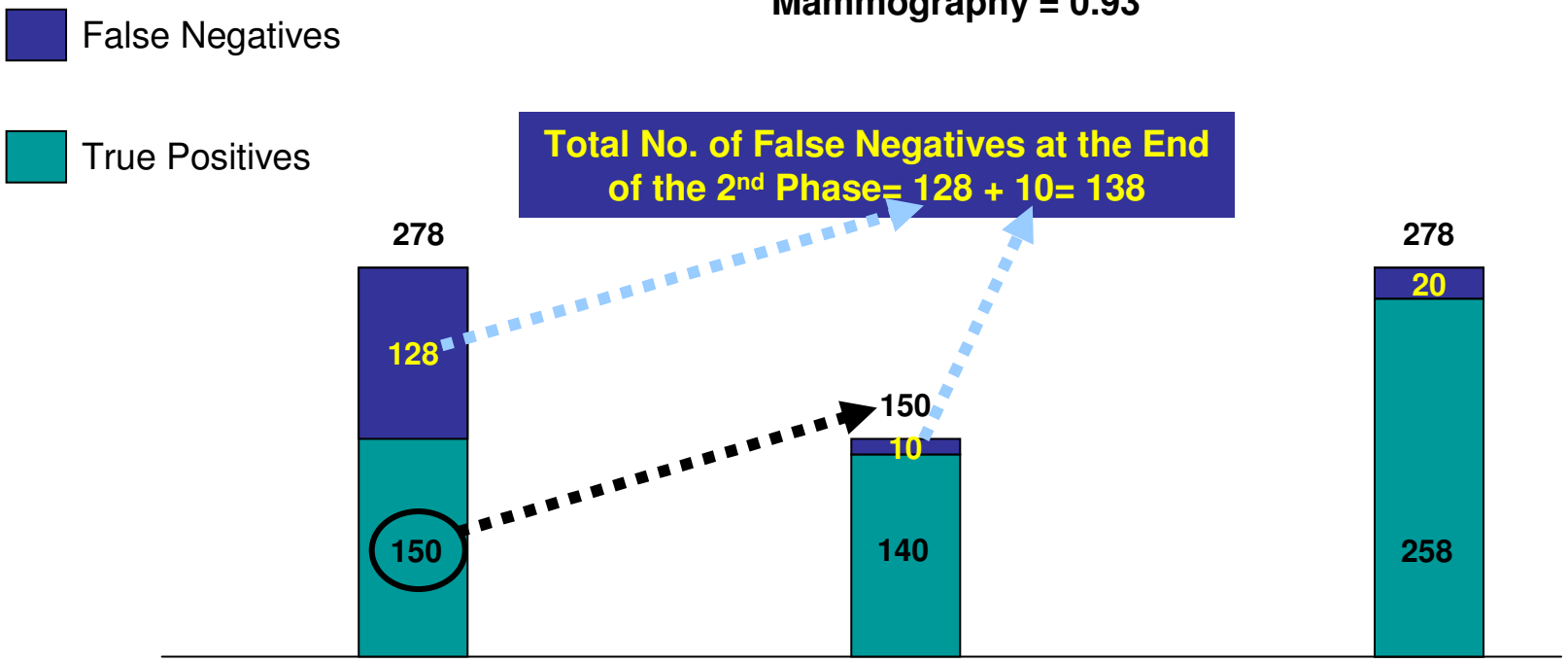
m9 A estratégia de alto risco tambem é inferior à estratégia populacional do ponto de vista de efetividade de um programa de rastreamento.
mszklo; 12/4/2006

m10

SENSITIVITY OF A HIGH RISK SCREENING PROGRAM FOR INCIDENT BREAST CANCER CASES DURING ONE YEAR IN A TARGET POPULATION OF 100 000 WOMEN¶

- **Average yearly incidence in S. Paulo, 1998-2000 ≅ 278/100 000§**

1st Phase: Sensitivity of Family History of Breast Cancer = 0.54*; 2nd Phase: Sensitivity of Mammography = 0.93**



1st Phase: Sensitivity of Family History = 0.54*

2nd Phase: Sensitivity of Mammography = 0.93**

High Risk Screening → Program Sensitivity= 0.54 × 0.93 = 0.50

Total Target Population-Wide Screening: Sensitivity of Mammography= 0.93

§Câncer no Brasil- Dados do Registro de Câncer de Base Populacional. Disponível em http://www.inca.gov.br/vigilancia/ CONPREV-INCA-MS e IBGE-MP

¶Szklo M. *J Gen Intern Med* 1990; 5(Suppl):S47-S49
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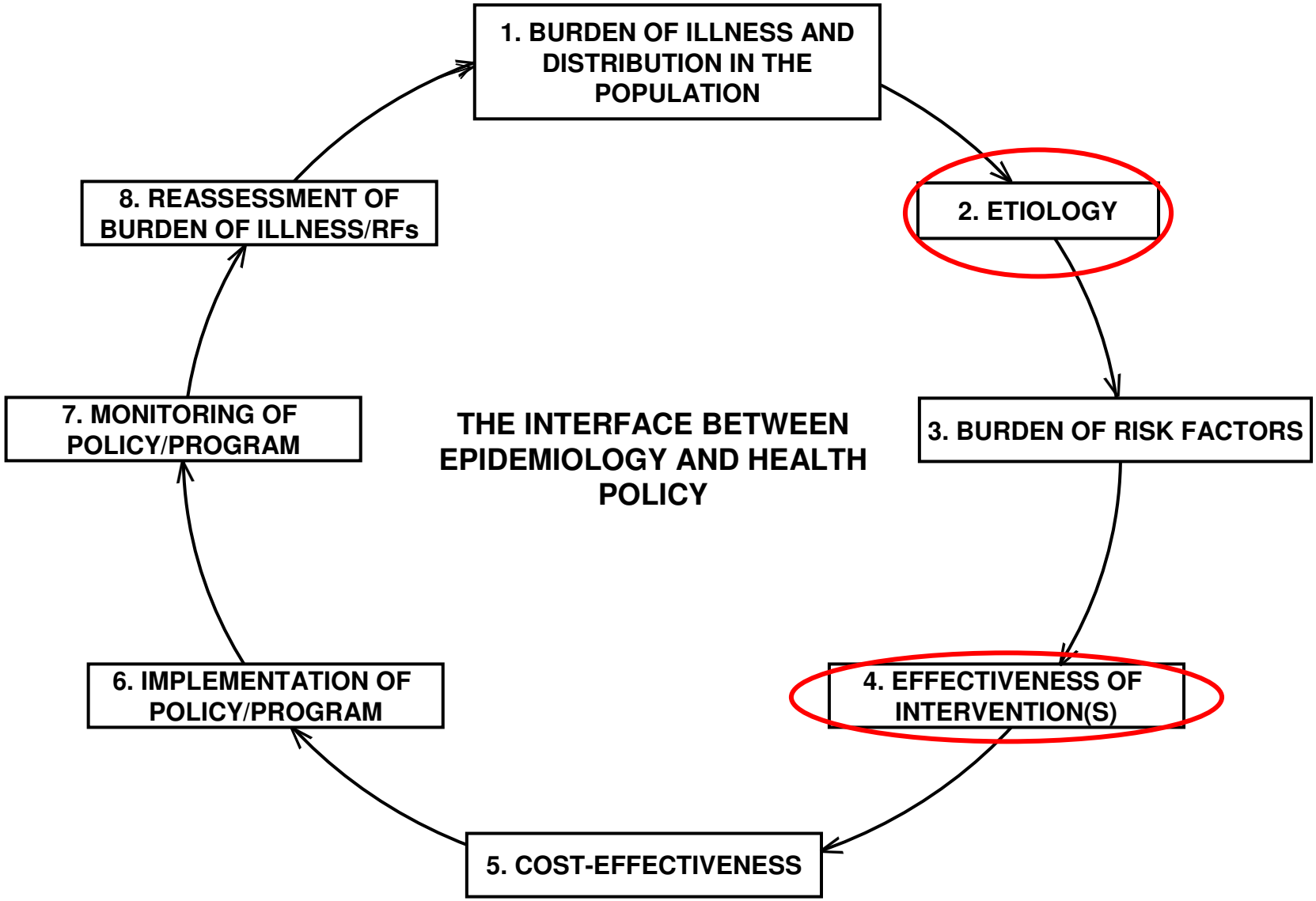
Slide 23

m10 A estratégia de alto risco tambem é inferior à estratégia populacional do ponto de vista de efetividade de um programa de rastreamento.
mszklo; 12/4/2006

EPIDEMIOLOGY IS RELEVANT TO ALL ASPECTS RELATED TO HEALTH POLICY AND PROGRAMS

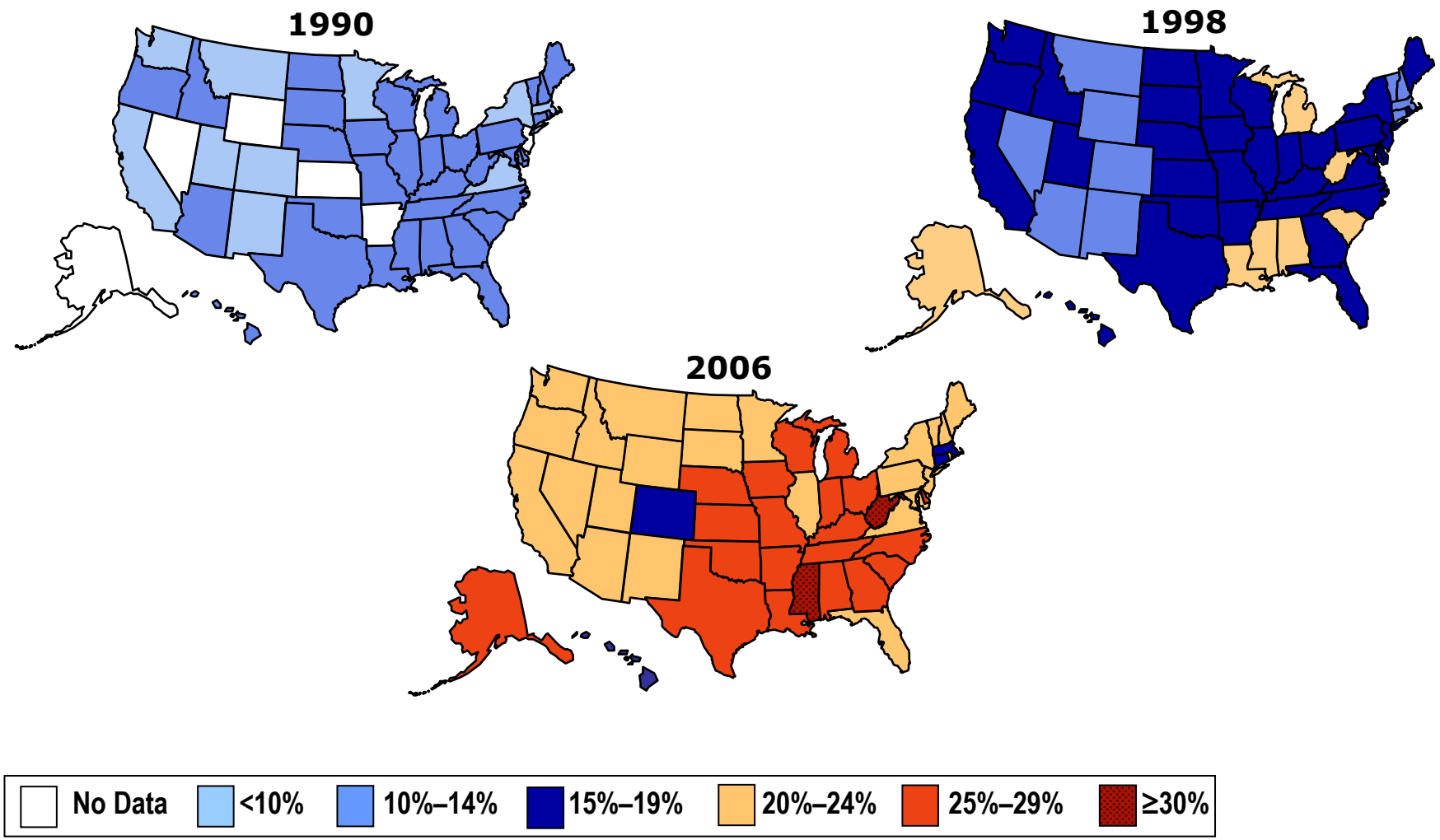


Modified from: Tugwell et al, *J Chronic Dis* 38 (4)

Obesity Trends* Among U.S. Adults

BRFSS, 1990, 1998, 2006

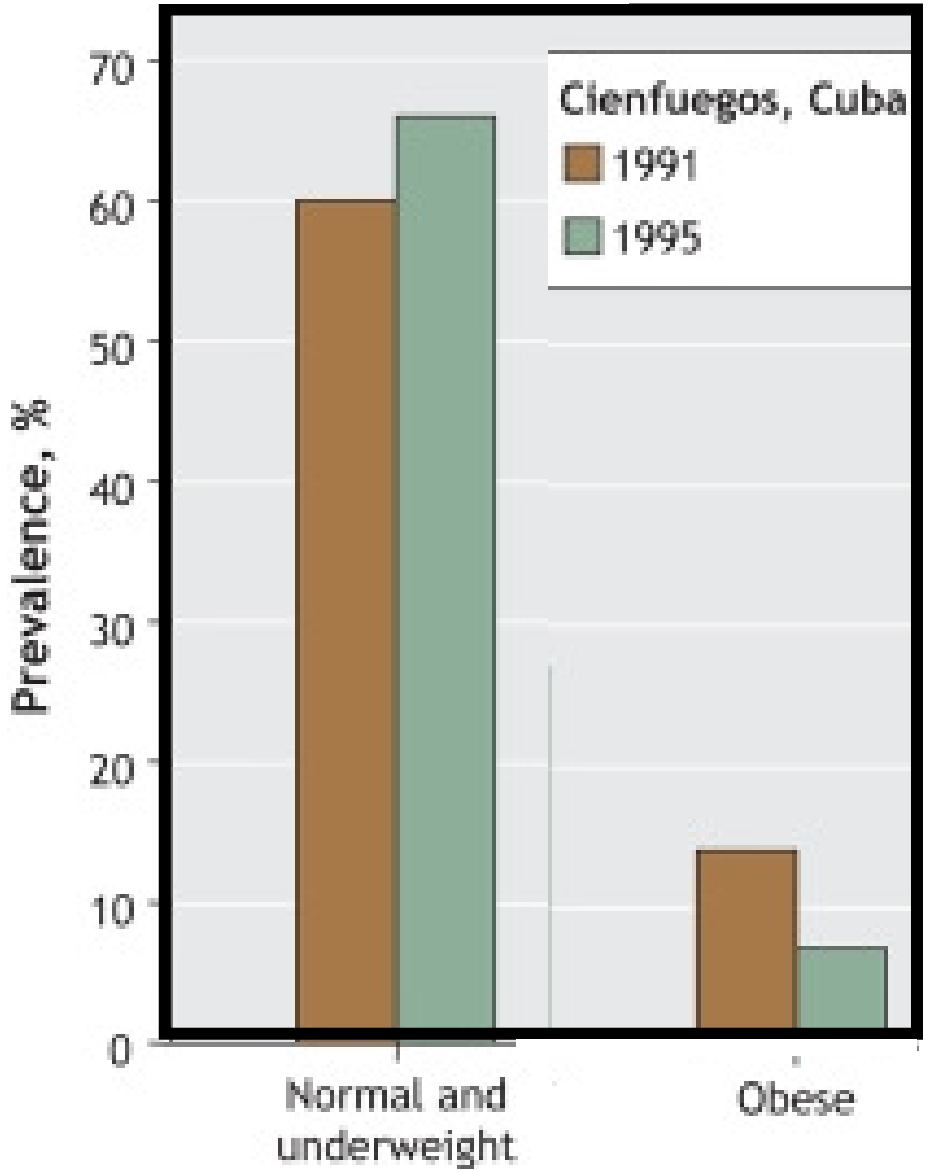
(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



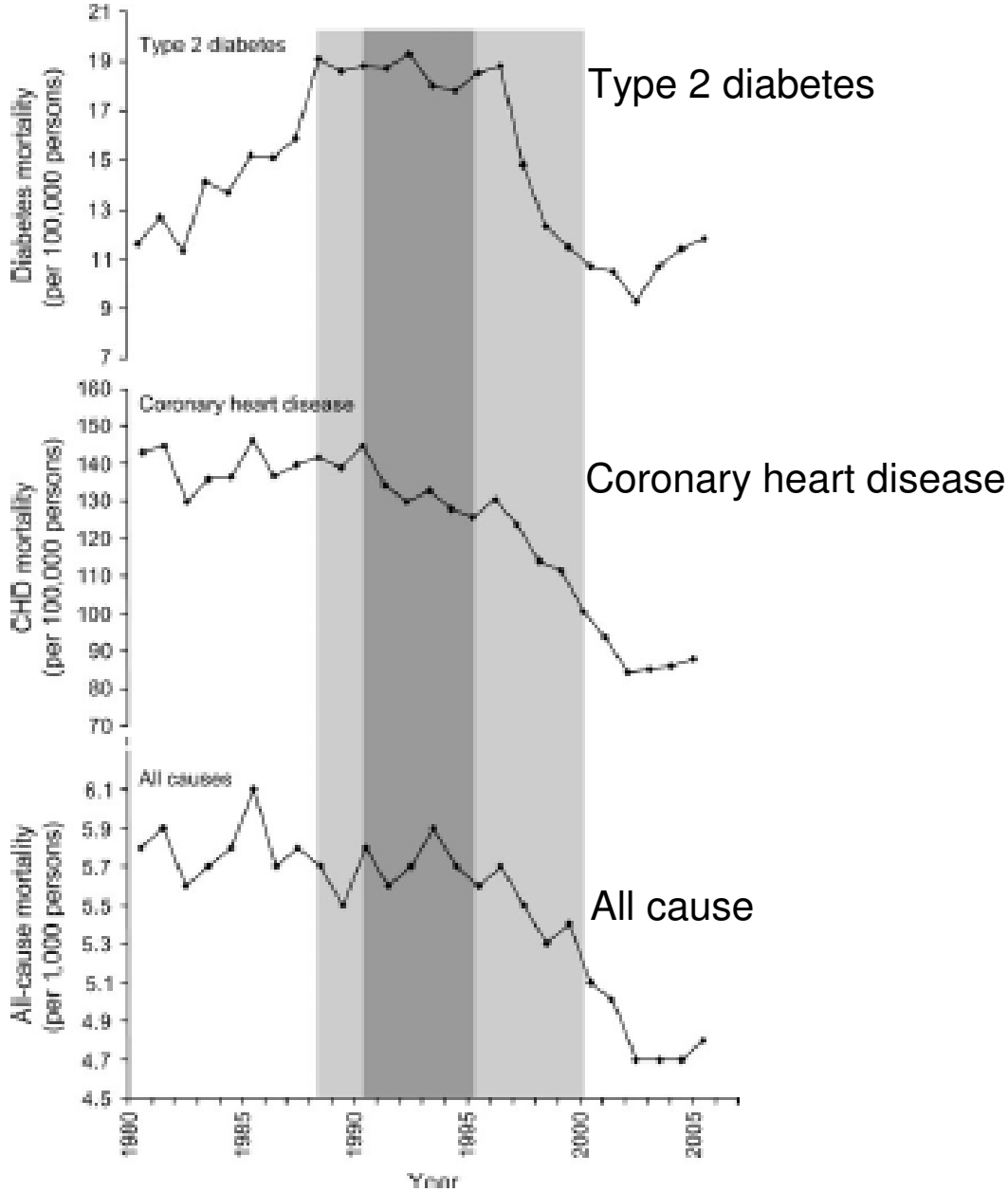
Body Mass Index and Prevalence of Overweight + Obesity, Ages 20 Years and Older, Brazil, 1975 and 2003

Characteristic	Men		Women	
	1975	2003	1975	2003
Total sample, No.	57 179	44 097	62 709	49 232
BMI ≥ 25, %	**18.0**	**41.0**	**27.3**	**39.8**

(Monteiro CA, et al. Income-specific trends in obesity in Brazil: 1975-2003. *Am J Pub Hlth* 2007;97:1808-1812)



Change in obesity prevalence in Cienfuegos, Cuba, between 1991 and 1995 (Modified from: Franco M, et al. *CMAJ* 2008;178:1032-1034)



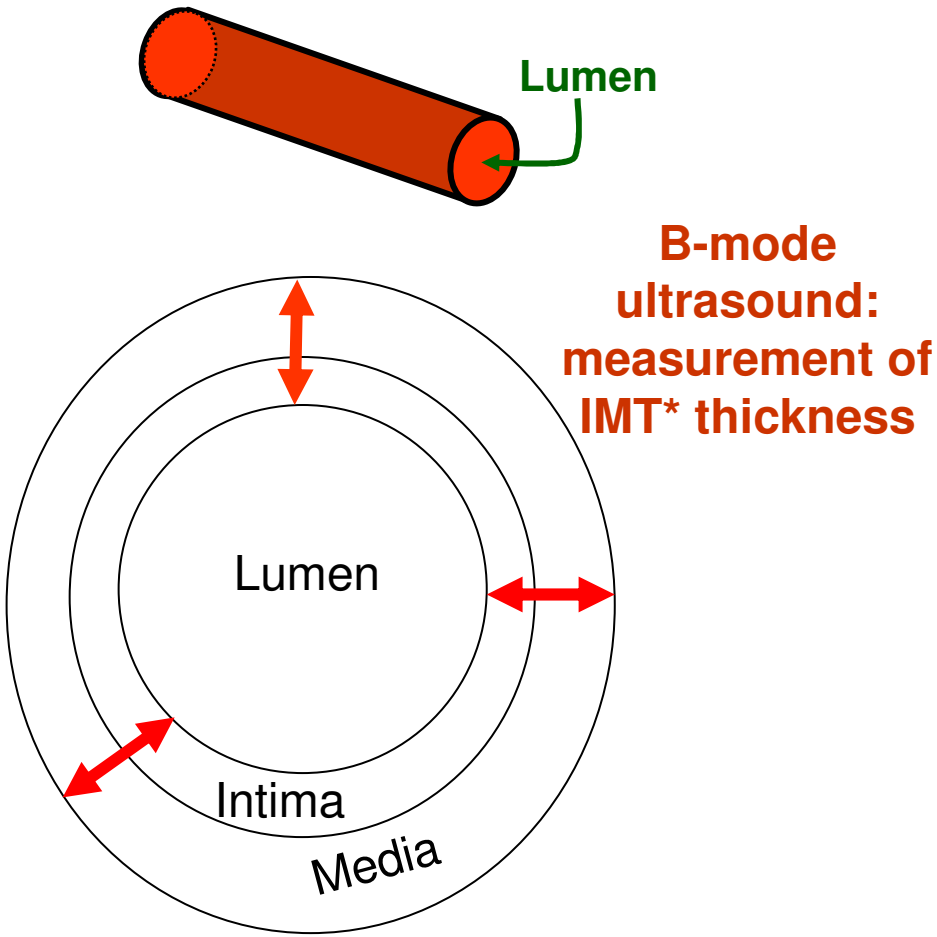
Trends in age-adjusted mortality from type 2 diabetes, coronary heart disease, and all cause mortality. The shaded zones coincide with the economic crisis (1989-2000) and the most severe years of the crisis (1991-1995) (Modified from Franco M, et al. *Am J Epidemiol* 2007;166:1374-1380)

Low Density Lipoprotein (LDL) Equivalent

‘Which concentration of LDL would replicate the magnitude of the relationship of a given risk factor to each phase of the natural history of atherosclerosis?’

(Sharrett et al, *Atherosclerosis* 2004;172:143-9)

Low Density Lipoprotein Equivalent (LDL_{eq})



*IMT: intimal-medial thickness

Atherosclerosis

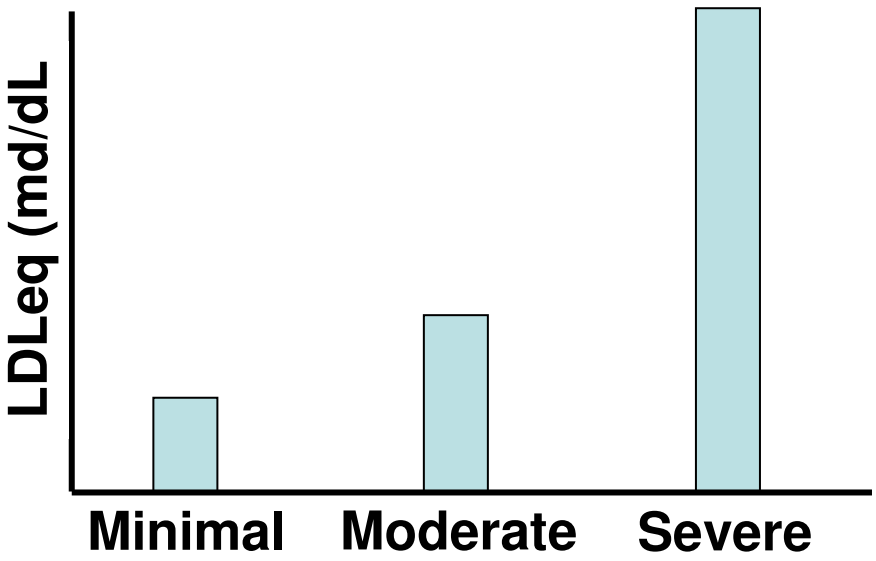
Minimal: IMT < 75th percentile with no clinical manifestations

Moderate: IMT ≥ 75th percentile with no clinical manifestations

Severe: Peripheral Arterial Disease (Ankle-Brachial Index <0.90)

(Sharrett et al, *Atherosclerosis* 2004;172:143-9)

LDL_{eq}: Serum LDL concentration that replicates the strength of the association of smoking with atherosclerosis



LDL_{eq} according to atherosclerosis severity level, adjusted for age, gender, center/ethnic background, LDL-cholesterol, diabetes and blood pressure.

(Sharrett et al, *Atherosclerosis* 2005)

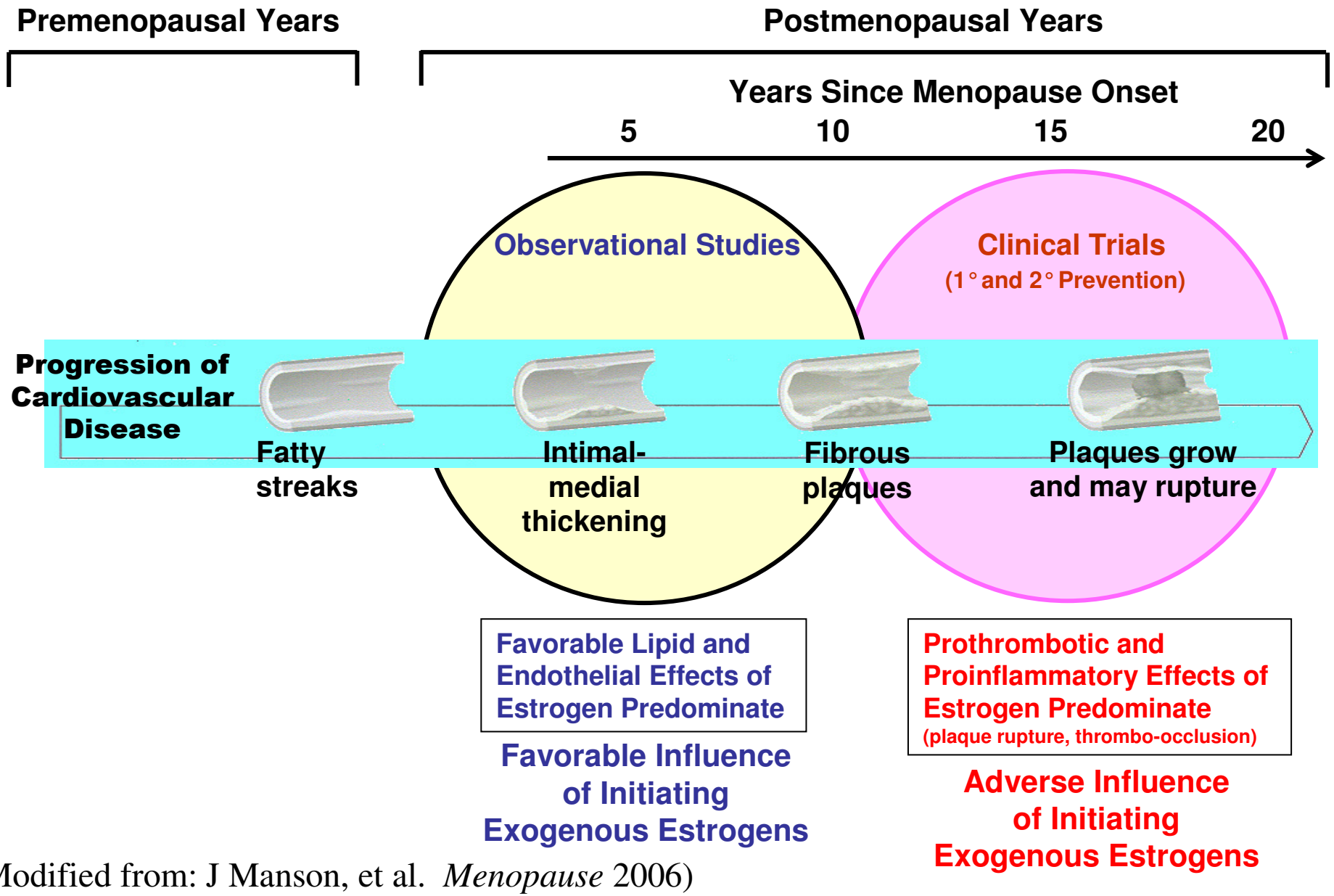
Age-, Field Center- and Race-Adjusted Average Annual CHD Incidence Rates/1000 Person-Years, Atherosclerosis Risk In Communities (ARIC) Study

Risk Factor	Rates	
	Women	Men
Smoking		
Current	5.3	11.5
Former	1.6	5.8
Never	1.3	4.7

(Chambless et al, *Am J Epidemiol* 1997;146:483-94)

Relation of Postmenopausal Hormone Therapy to Coronary Heart Disease in Observational Studies and in the Women's Health Initiative Estrogen-plus-progestin Trial

Timing of Hormone Therapy Initiation in Relation to Stage of Atherosclerosis: Observational Studies vs Clinical Trials



(Modified from: J Manson, et al. *Menopause* 2006)

Qualitative Gene-environment Interaction

One in 15,000 people may not properly metabolize phenylalanine, an essential amino acid found in aspartame.

Both the gene AND the environmental exposure are required for symptoms to occur.

PHENYLKETONURICS: CONTAINS PHENYLALANINE

Cumulative Incidence (%) and Relative Risks of Myocardial Infarction (MI) During a 7-Year Follow-up, According to Previous MI History and Presence of Type 2 Diabetes at Baseline

Diabetes	Previous MI	Relative Risk
Absent	No	1.0
	Yes	5.4
Present	No	1.0
	Yes	2.2

Negative Multiplicative Interaction

(Haffner et al, N Eng J Med 1998;339:229)

Cumulative Incidence (%) and Relative Risks of Myocardial Infarction (MI) During a 7-Year Follow-up, According to Previous MI History and Presence of Type 2 Diabetes at Baseline

Diabetes	Previous MI	Incidence (%)	Relative Risk	AR* (absolute difference)
Absent	No	3.5	1.0	Reference
	Yes	18.8	5.4	15.3%
Present	No	20.2	1.0	Reference
	Yes	45.0	2.2	24.8%

Negative Multiplicative Interaction

Positive Additive Interaction

(Haffner et al, N Eng J Med 1998;339:229)

NHLBI SNP Genotyping and Association Projects

- Enhancing Development of Genome-wide Association Methods (ENDGAME)
- SNP Health Association REsource (SHARe)
- Genome-wide Association: SNP Typing for Association with Multiple Phenotypes from Existing Epidemiologic Data (STAMPEED)
- Candidate-gene Association Resource (CARE)
- Resequencing and Genotyping Centers (RS&G)

SNP Health Association Resource (SHARe)

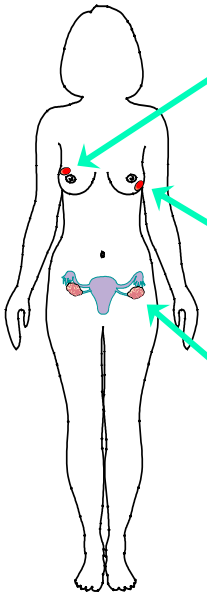
- Create a resource of genome-wide SNP typing and multiple phenotypes for gene finding and replication
- Competitive selection of one genotyping center contract for 500k SNP typing (Affymetrix)
- Delivery of genotyping data to NCBI for merge with bioinformatically recoded phenotype data
- 3 Studies selected by NHLBI

Candidate-gene Association REsource (CARE)

- Funds genotyping center to genotype candidate genes and single genome-wide association study and merge data with std phenotypes
- Creates 50,000 person cohort with genotyping of 1,000+ candidate genes (10-20 SNPs per gene)
- Conducts a 1m SNP chip GWAS on combined African American Cohort (~7,500)

Life Time Associated Risks of Cancer

BRCA1



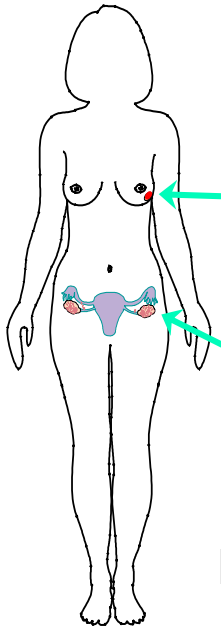
Breast cancer - often early age at onset (50%-85%)

Second primary breast cancer (40%-60%)

ovarian cancer (15%-45%)

Possible increased risk of other cancers (eg, prostate, colon)

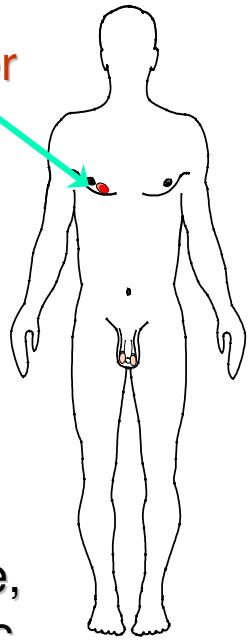
BRCA2



male breast cancer (6%)

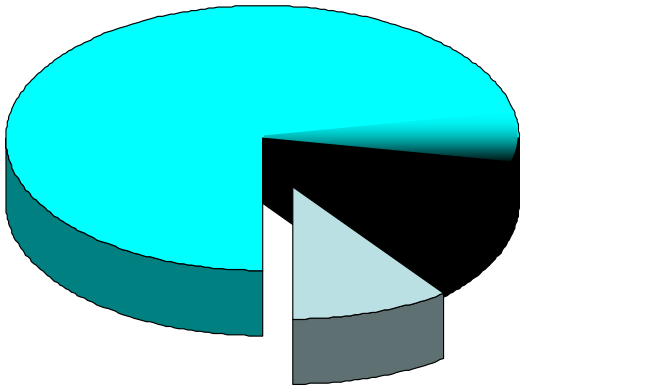
breast cancer (50%-85%)

ovarian cancer (10%-20%)



Increased risk of prostate, laryngeal, and pancreatic cancers (magnitude unknown)

How Much Breast Is Hereditary?



Breast Cancer

Sporadic

Hereditary

GENETIC INHERITANCE:

- **High Relative Risk**
- **Low Population Attributable Risk**

Example of a "small effect" and its impact on Levin's population attributable risk with varying prevalences of the risk factor

Relative risk (RR)	Prevalence of risk factor	Levin's population attributable risk* (%)
1.3	0.25	7
1.3	0.50	13
1.3	0.75	18

* [Exposure prevalence × (RR−1.0)] ÷ [Exposure prevalence × (RR−1.0) + 1.0].

No. of new cases of coronary heart disease (CHD) in the USA in 2004= 1.2 million

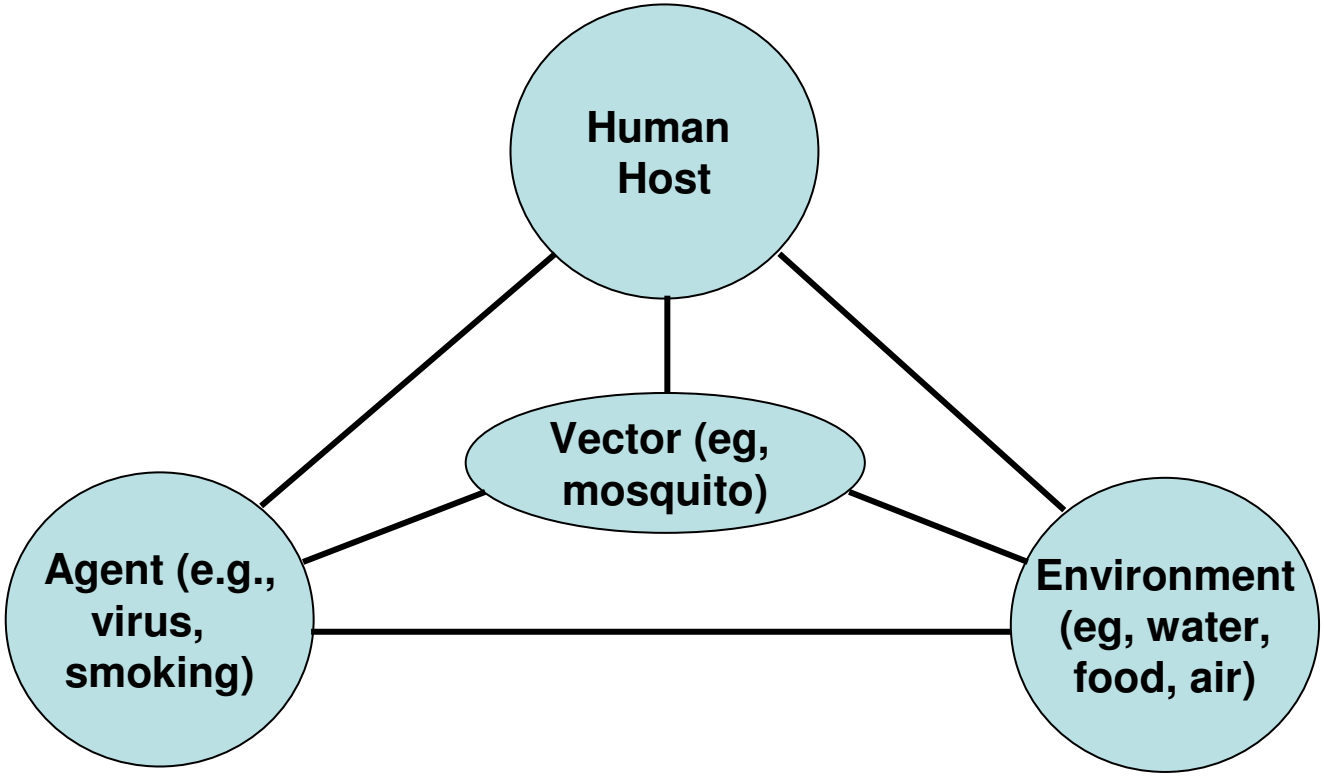
New cases of CHD attributed to ETS* in the USA= 0.13 x 1.2 million= 156,000

*Environmental Tobacco Smoking

(Szklo M. Evaluation of epidemiologic evidence for policy-making. Am J Epidemiol 2001; 154:S13-S17)

Primary Prevention Relies on the Triad of Risk Factors

THREE BASIC STRATEGIES



Primary Prevention Relies on the Triad of Risk Factors

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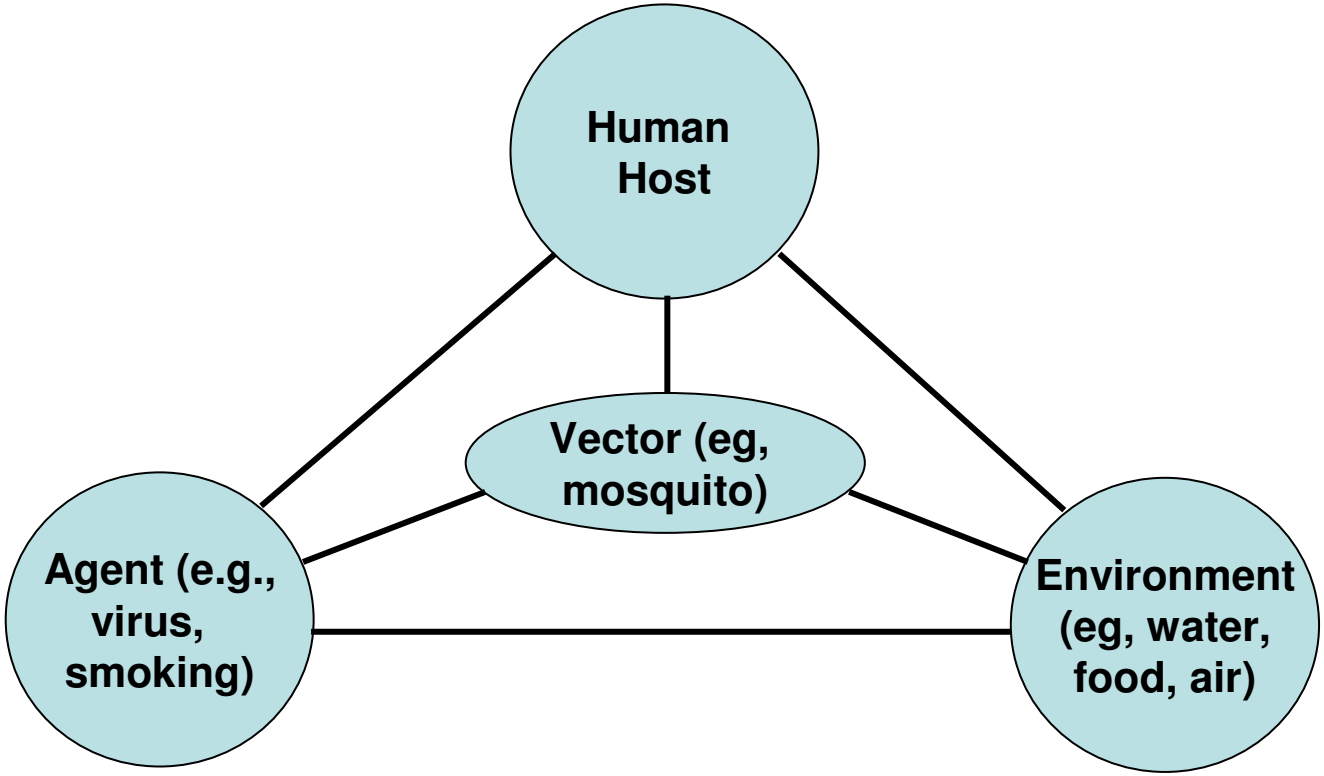
- Eliminate/decrease exposure to agent and/or the vector



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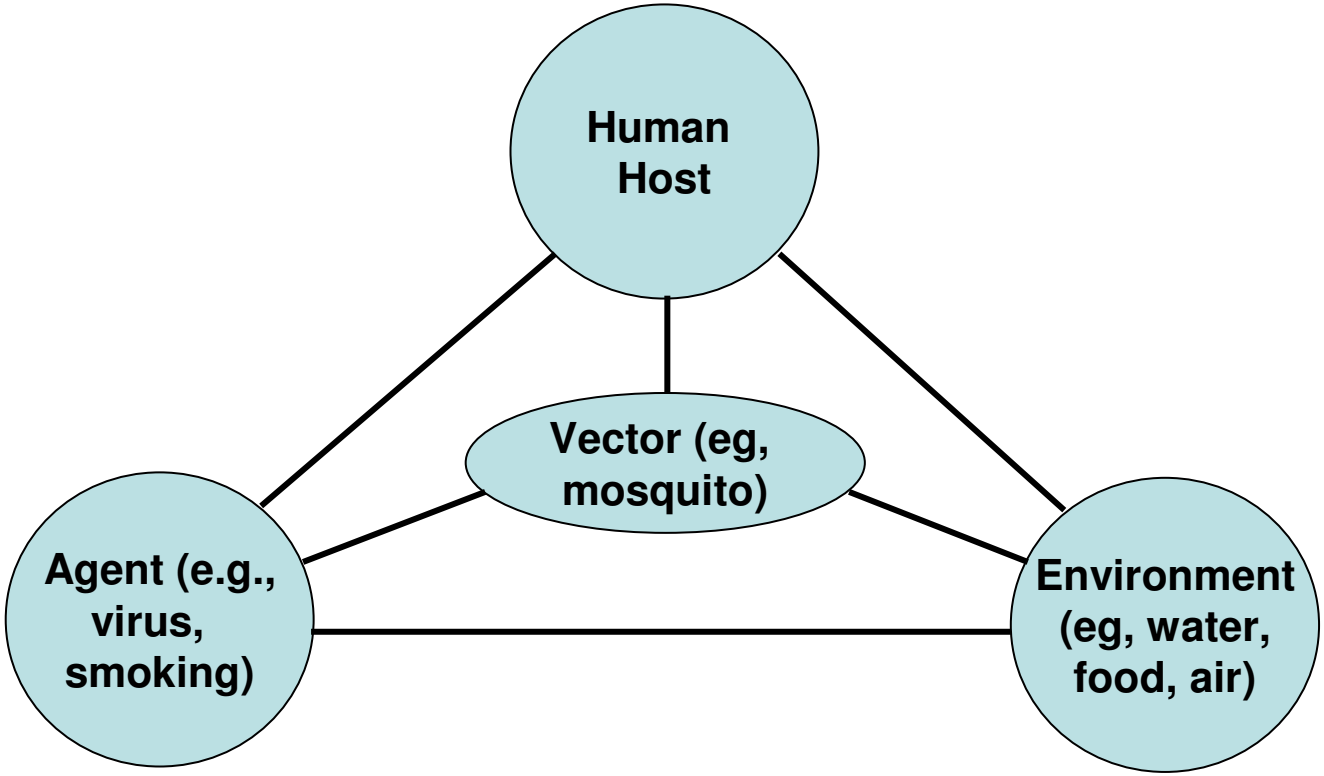
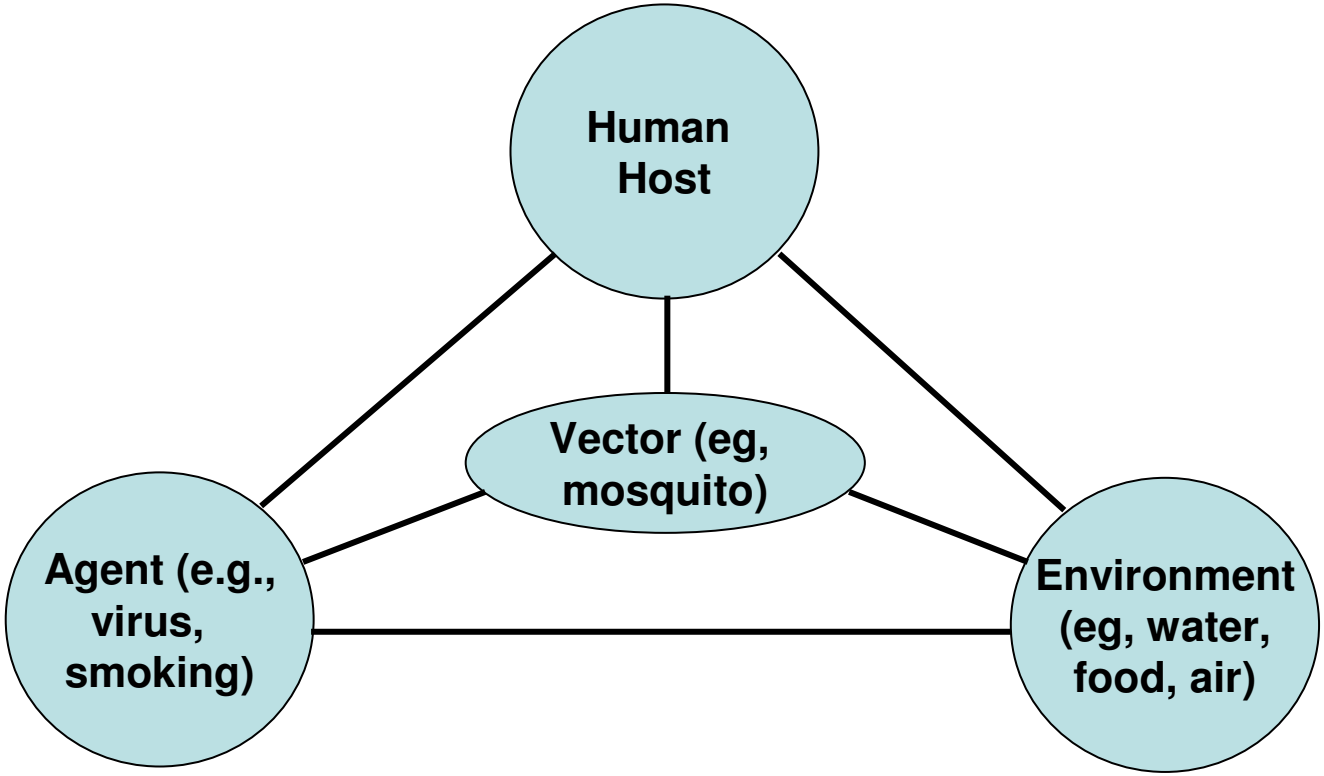
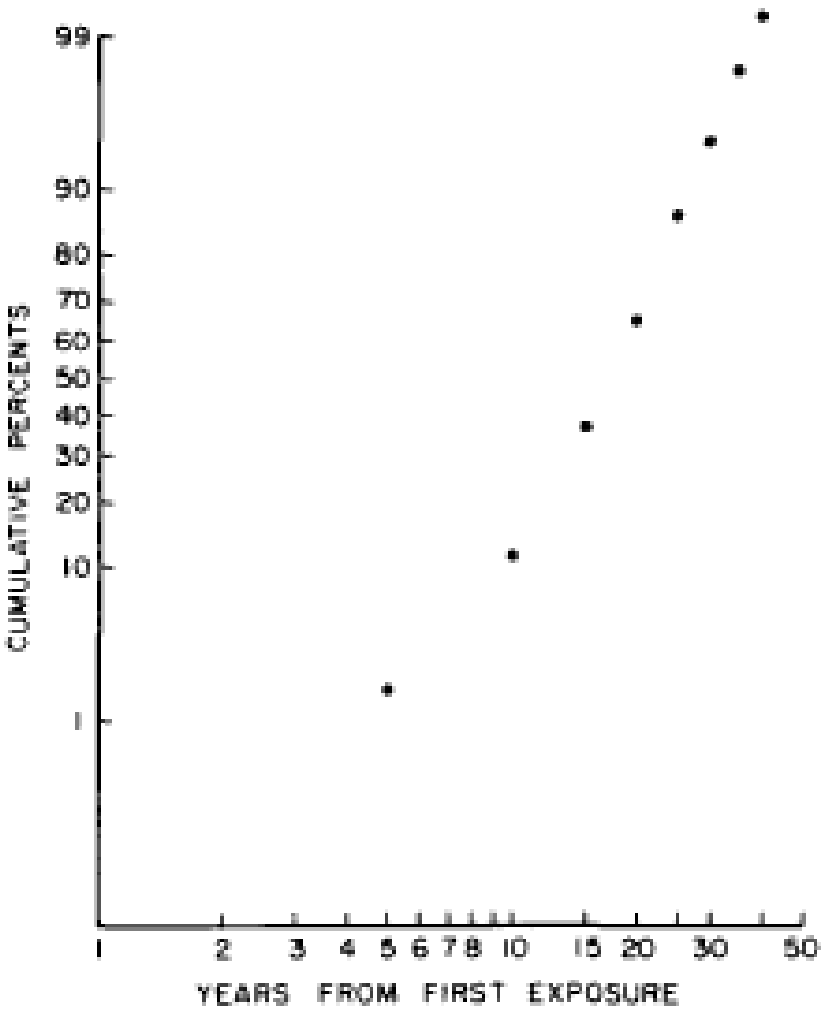


Primary Prevention Relies on the Triad of Risk Factors

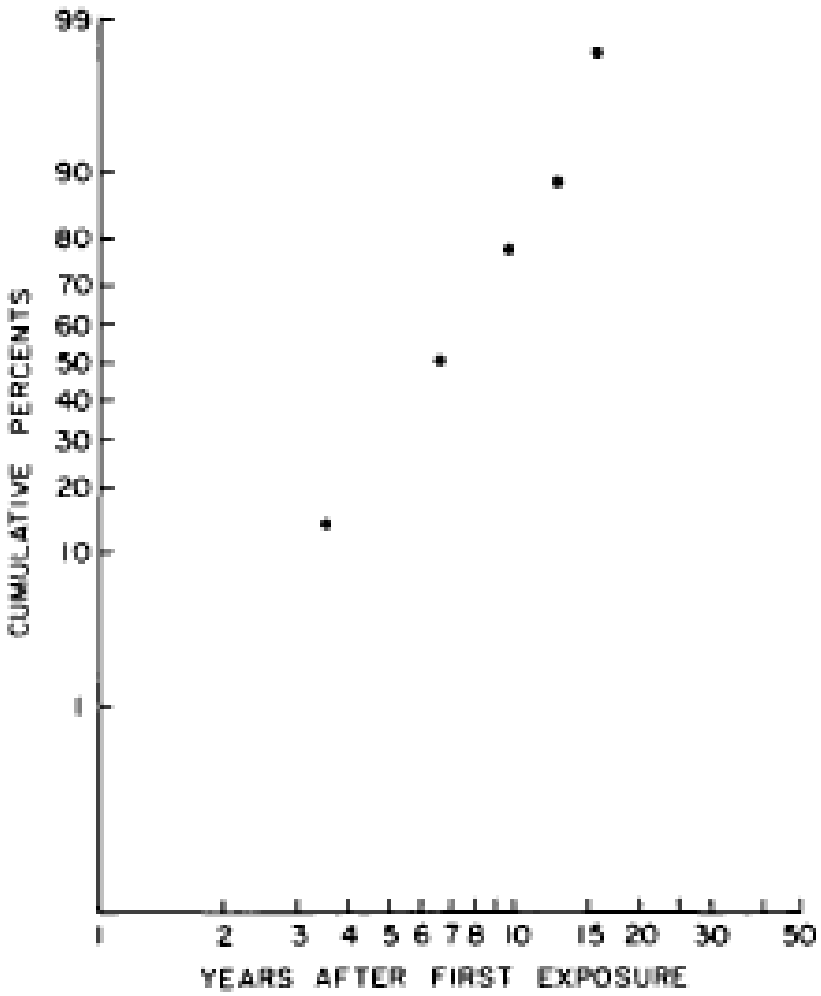
THREE BASIC STRATEGIES

- Eliminate/decrease exposure to agent and/or the vector
- Make environment hostile to agent
- Increase host resistance





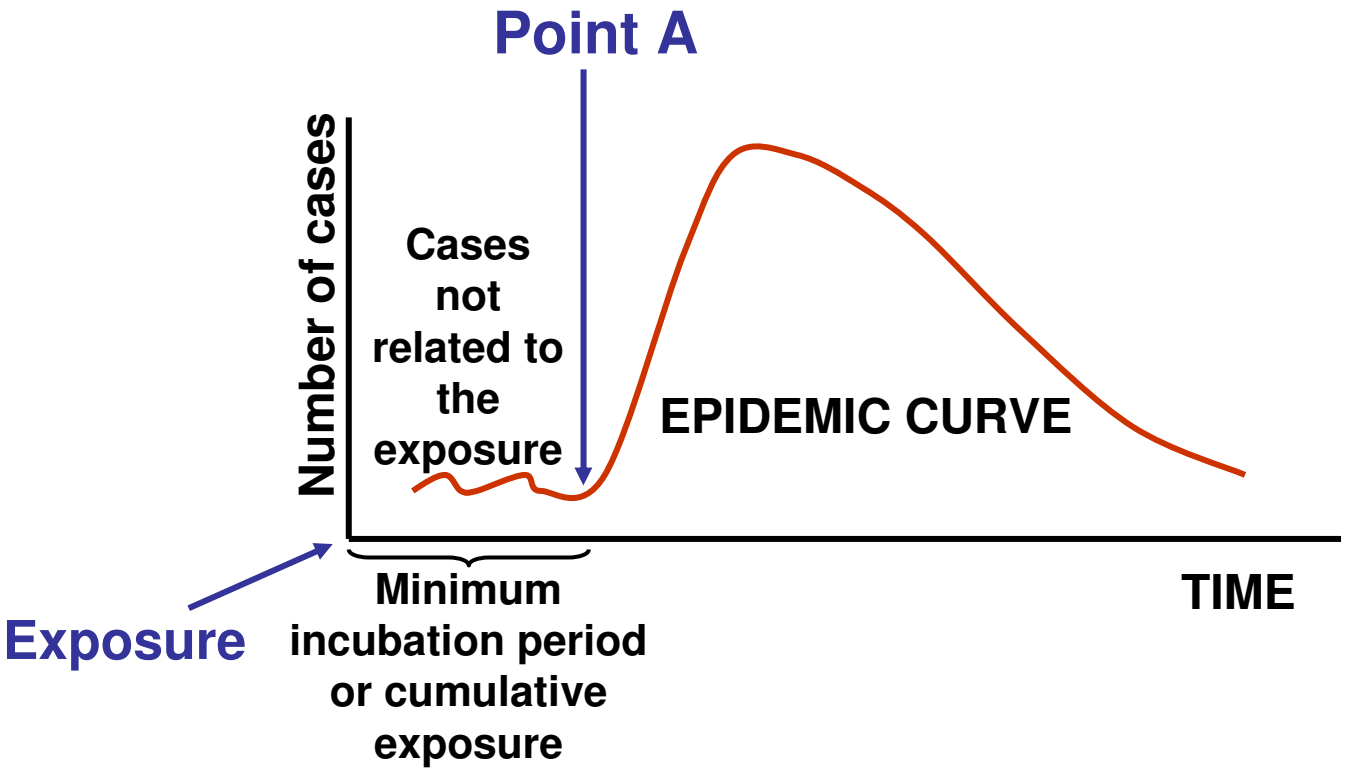
Bladder tumors in dyestuff workers (20)



Leukemia after radiotherapy for ankylosing spondylities (9)

(Armenian HK, Lilienfeld AM. Am J Epidemiol 1974;99:92-100)

Incubation Period and Associations



Epidemiology for Public Health

- Social Epidemiology/Population-wide (rather than high risk) approaches

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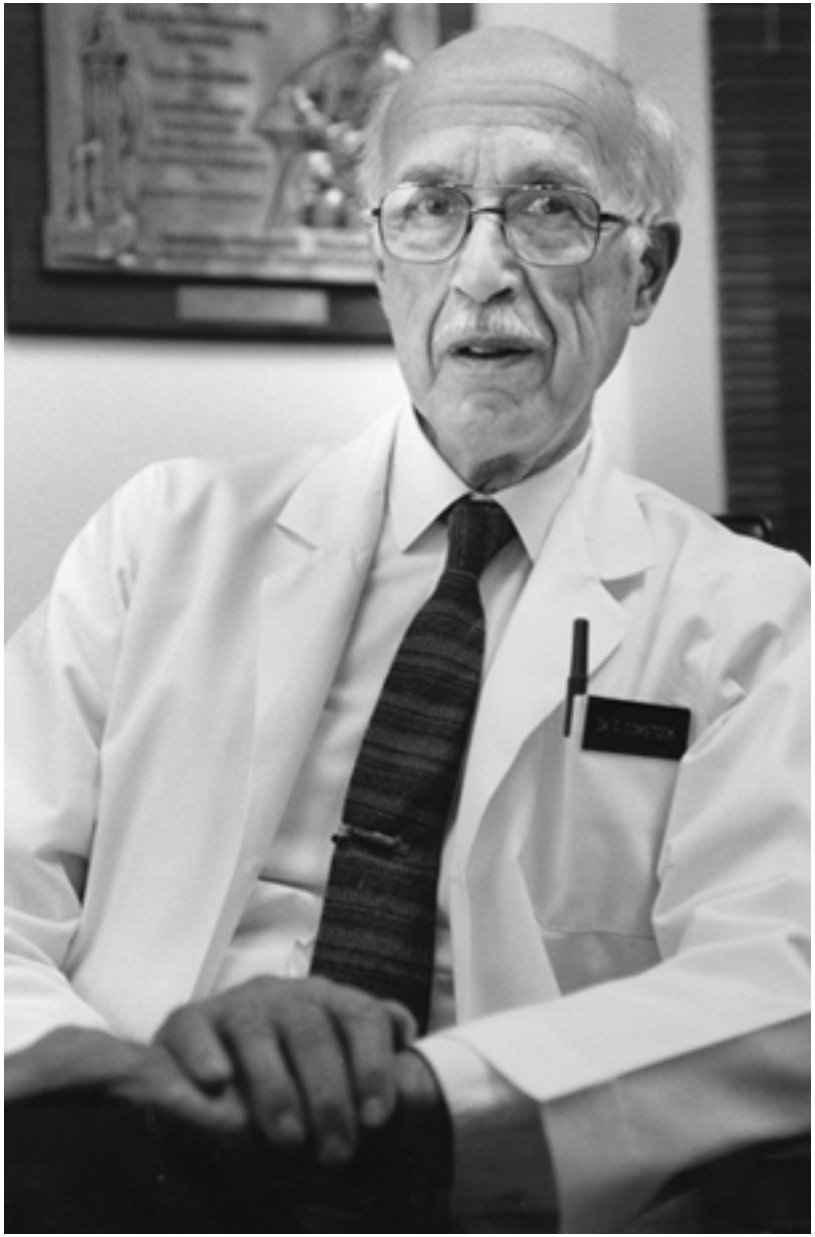
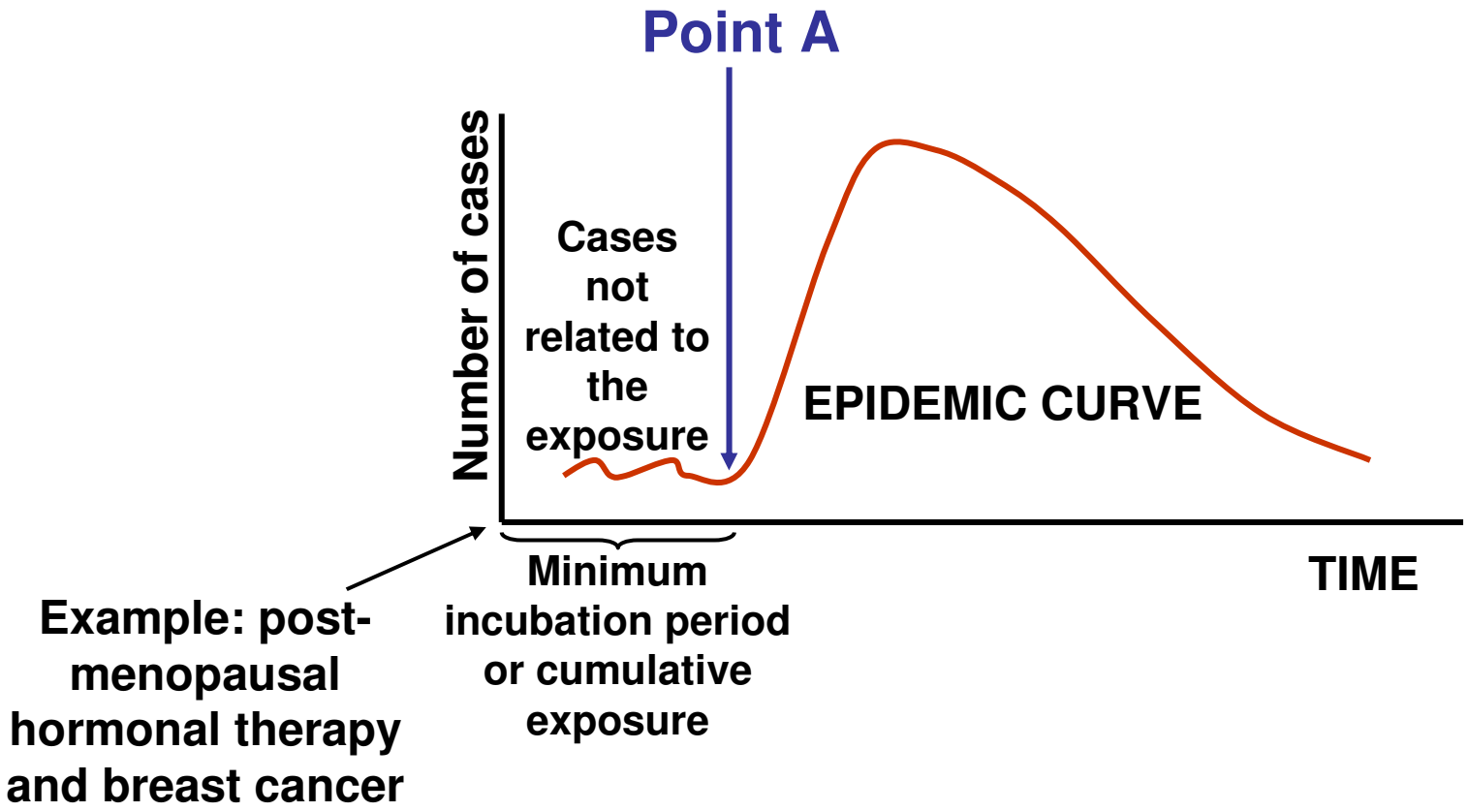
- Focus on application to Public Health (rather than on biologic mechanisms)
- Attributable risk – type measures of association (rather than ratio-based)
- Additive model for interaction (rather than multiplicative)
- **Confounded associations: unbiased, and useful for defining high risk groups**



"IF NOT APPLIED TO PREVENTION AND PUBLIC HEALTH, EPIDEMIOLOGY TENDS TO BE FAIRLY BORING..."
(Comstock, personal communication)

"Public Health Epidemiology"	"Academic Epidemiology"
Attributable risk-type measures	Relative risk- type measures
Additive model for interaction	Multiplicative model for interaction
Tends to population-wide approach	Tends to high risk approach
Confounded association ≠ Biased association	Confounded association ≈ Biased association
Focus on application	Focus on mechanisms

Incubation Period and Associations