Lecture 6: Measures of Disease Impact

Lecture prepared by Dr. Hailey Banack, PhD

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Review
Measures of Effect

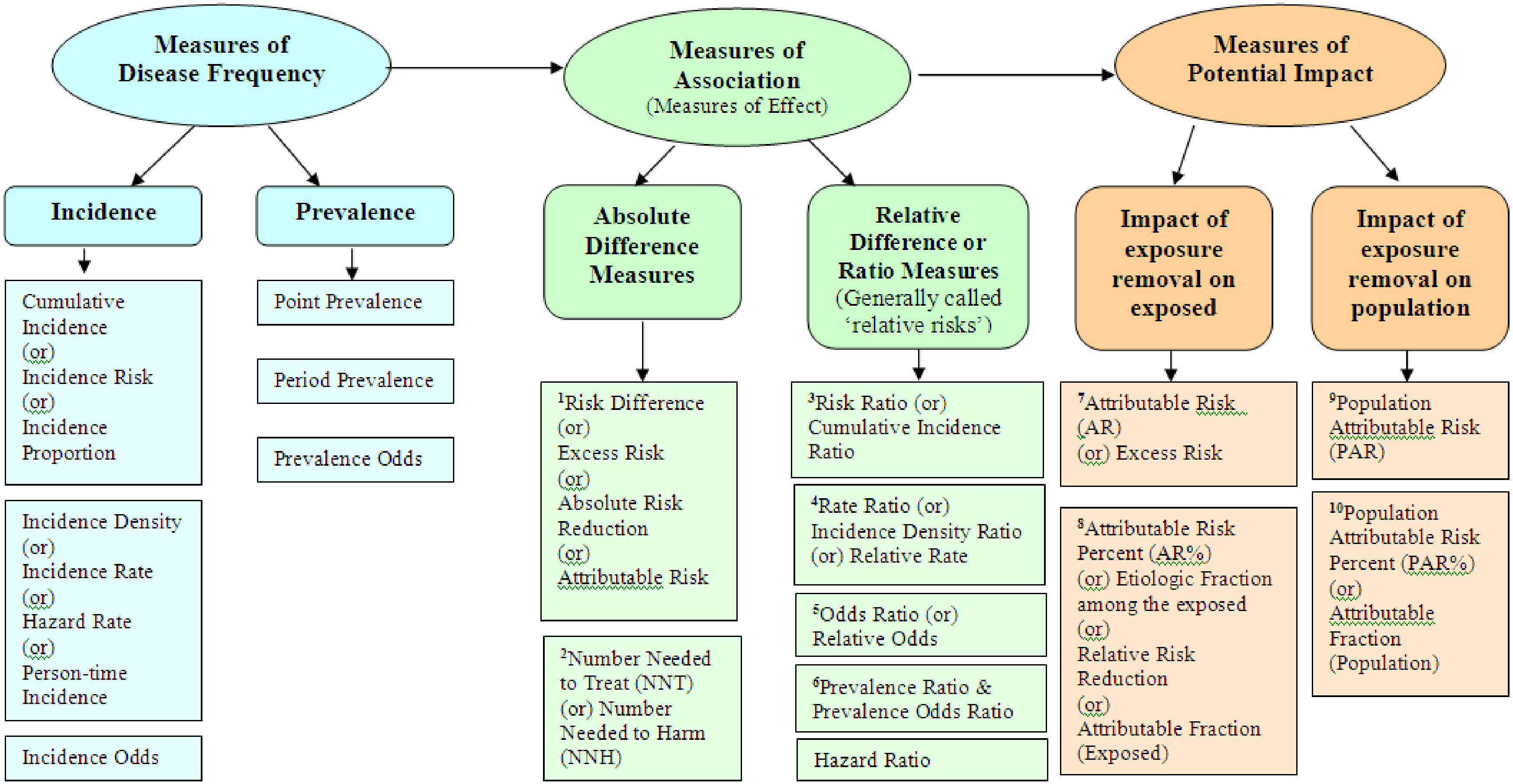
Risk Ratio:	$[a / (a + b)] \ / \ [c / (c + d)]$
Risk Difference:	$[a / (a + b)] - c / (c + d)$
Rate Ratio:	$[a / PT_e] \ / \ [c / PT_0]$
Rate Difference:	$[a / PT_e] - [c / PT_0]$

Odds Ratios

Odds Ratio: *[a * d] / [b * c]*

- If a disease/outcome is rare (<10%) , the odds ratio will be approximately the same as the risk ratio
- Odds are odd and hard to understand
  - Usually people understand odds by equating it with risk
- BUT, when the outcome is common, odds $\neq$ risk

Overview of Measurement in Epidemiology



Measures of Disease Frequency

Incidence

Cumulative Incidence (or) Incidence Risk (or) Incidence Proportion

Incidence Density (or) Incidence Rate (or) Hazard Rate (or) Person-time Incidence

Incidence Odds

Prevalence

Point Prevalence

Period Prevalence

Prevalence Odds

Measures of Association (Measures of Effect)

Absolute Difference Measures

[1]Risk Difference (or) Excess Risk (or) Absolute Risk Reduction (or) Attributable Risk

[2]Number Needed to Treat (NNT) (or) Number Needed to Harm (NNH)

Relative Difference or Ratio Measures (Generally called 'relative risks')

[3]Risk Ratio (or) Cumulative Incidence Ratio

[4]Rate Ratio (or) Incidence Density Ratio (or) Relative Rate

[5]Odds Ratio (or) Relative Odds

[6]Prevalence Ratio & Prevalence Odds Ratio

Hazard Ratio

Measures of Potential Impact

Impact of exposure removal on exposed

[7]Attributable Risk (AR) (or) Excess Risk

[8]Attributable Risk Percent (AR%) (or) Etiologic Fraction among the exposed (or) Relative Risk Reduction (or) Attributable Fraction (Exposed)

Impact of exposure removal on population

[9]Population Attributable Risk (PAR)

[10]Population Attributable Risk Percent (PAR%) (or) Attributable Fraction (Population)

Source: Pai, 2007

Attributable Risk

"How much of the disease that occurs can be attributed to a certain exposure?"

- Differs from the absolute and relative effect measures
  - Tells us the strength of a relationship between exposure and outcome
  - Useful for etiologic/causal questions

Types of Attributable Risk

Attributable risk in the exposed

- Attributable risk (AR)
- Attributable fraction (AF), attributable risk percent (AR%)

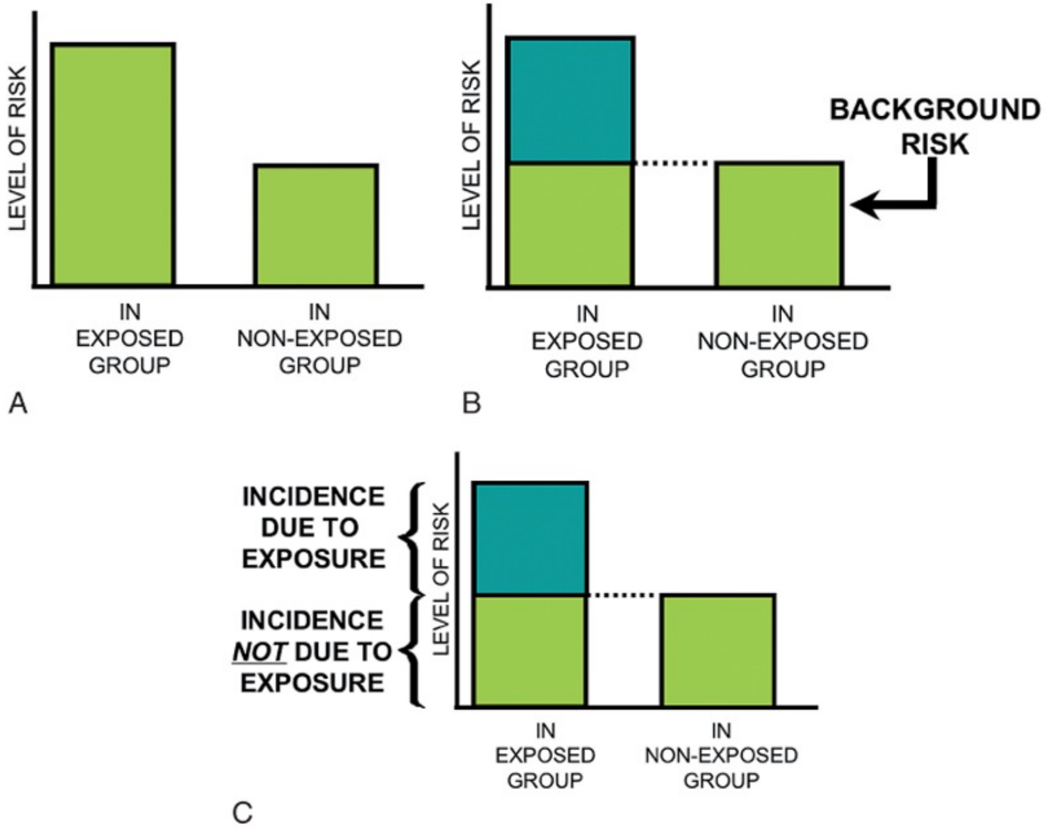
Attributable risk in the total population

- Population attributable risk (PAR)
- Population attributable fraction (PAF), population attributable risk percent (PAR%)

Measures of Potential Impact

- AR and PAR tell us the impact of removing the exposure
- Consider:
  - Exposure= smoking, Outcome= lung cancer
  - What is the impact of removing smoking on the risk of lung cancer among smokers?
  - What is the impact of removing smoking on the risk of lung cancer in the population?

Background Risk



Gordis: Epidemiology, 4th Edition.
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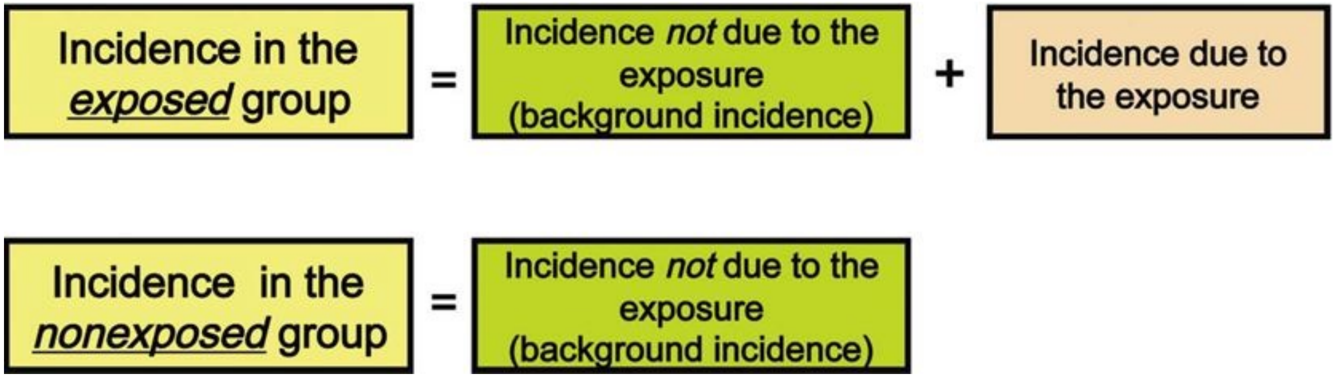
- Both exposed and unexposed people have the same level of background risk
- Risk in exposed group is due to both background risk and exposure

Attributable Risk



Incidence in the ***exposed*** group = Incidence *not* due to the exposure (background incidence) + Incidence due to the exposure

Incidence in the ***nonexposed*** group = Incidence *not* due to the exposure (background incidence)

Attributable risk (AR) = $I_e - I_o$

=(Incidence in exposed group)- (Incidence in unexposed group)

Attributable Risk

- Conceptually and mathematically, attributable risk = risk difference
    - Absolute effect of exposure removal
    - Difference in risk of disease between groups
    - “Assuming *X* is a cause of *Y*, by eliminating X, [AR] cases of *Y* would be eliminated amongst those exposed to *X*.”

	SIDS (D+)	No SIDS (D-)	Row total (Margins)
Prone (E+)	9	837	846
Non-prone (E-)	6	1755	1761
Column total (Margins)	15	2592	2607

Cumulative incidence among exposed (prone) = 9/846= 0.0106

Cumulative incidence among unexposed = 6/1761= 0.0034

Attributable Risk = 0.0106-0.0034= 0.0072

If prone babies were made to sleep on their back, then 7 SIDS cases would be averted for every 1000 babies that sleep prone

	SIDS (D+)	No SIDS (D-)	Row total (Margins)
Prone (E+)	a	b	a+b
Non-prone (E-)	c	d	c+d

Cumulative incidence among exposed (prone) = a/(a+b) = 0.0106

Cumulative incidence among unexposed = c/(c+d) = 0.0034

*Recall: cumulative incidence is another term for risk

Attributable risk = $I_e – I_o$ = [a/(a+b)] - [(c/c+d)]

Risk difference = [a/(a+b)] - [(c/c+d)]

Relative Risk vs. Attributable Risk

- **Relative risk (RR)**
  - Provides a measure of the strength of an association between an exposure and outcome
  - Helps to evaluate whether there is a causal relationship between exposure and outcome
  - Magnitude of relative risk does not predict magnitude of attributable risk

- **Attributable risk (AR)**
  - Provides a measure of the public health impact of an exposure on the exposed group: if the exposure where removed, how much of the disease burden will be reduced?
  - Assumes the exposure is causal
  - Attributable risks for different risk factors do not add up to 100%

Attributable Fraction

What proportion of the risk in the exposed group is due to the exposure?

Attributable fraction (%) = $(I_e - I_o / I_e) * 100$

$$= \frac{\text{(Incidence in exposed group)} - \text{(Incidence in unexposed group)}}{\text{(Incidence in exposed group)}}$$

“the proportion by which the incidence rate of the outcome among those exposed would be reduced if the exposure were eliminated”

[Porta, 2008]

SIDS example

Among exposed babies (prone sleepers) what proportion of cases of SIDS are due to prone sleeping position?

$$AF\% = (I_e - I_o) / I_e \times 100$$

$$AF\% = (AR) / I_e \times 100$$

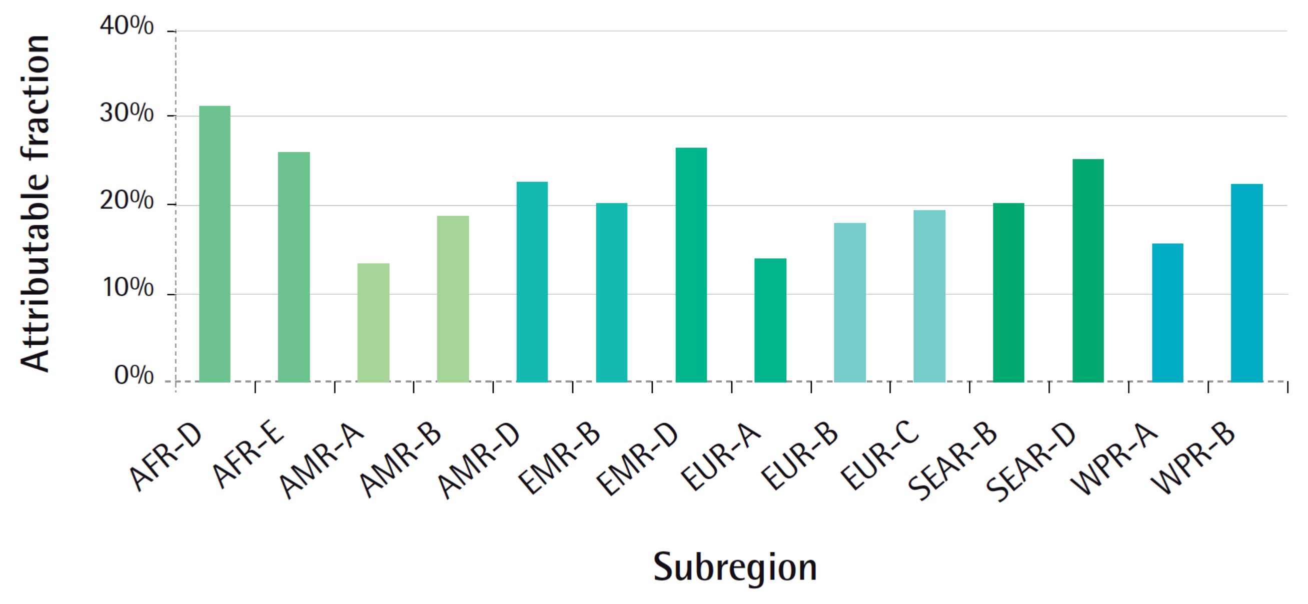
$= [(I_e - I_o) / I_e] \times 100$

$= (0.0072) / (0.0106) \times 100$

$= 67.9\%$

Environment and Health

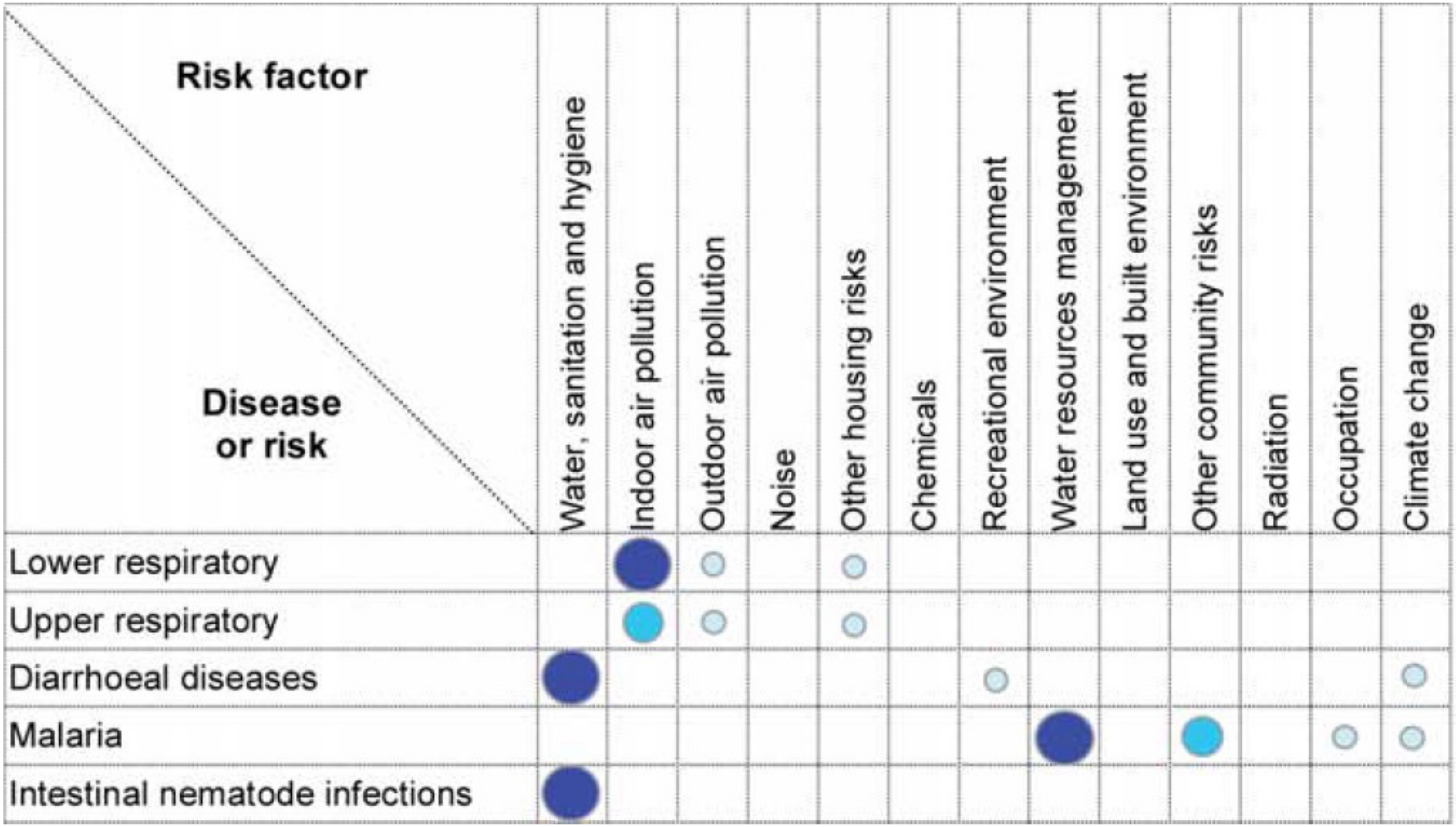
Globally, an estimated 23% of all deaths (premature mortality) is attributable to environmental factors (WHO)



Environmental disease burden, by WHO subregion [a]

http://www.who.int/quantifying_ehimpacts/publications/preventingdisease.pdf

Environmental Attributable Fractions



Risk factor / Disease or risk	Water, sanitation and hygiene	Indoor air pollution	Outdoor air pollution	Noise	Other housing risks	Chemicals	Recreational environment	Water resources management	Land use and built environment	Other community risks	Radiation	Occupation	Climate change
Lower respiratory		⬤	○		○								
Upper respiratory		●	○		○								
Diarrhoeal diseases	⬤						○						○
Malaria								⬤		●		○	○
Intestinal nematode infections	⬤												

Alternate Formula

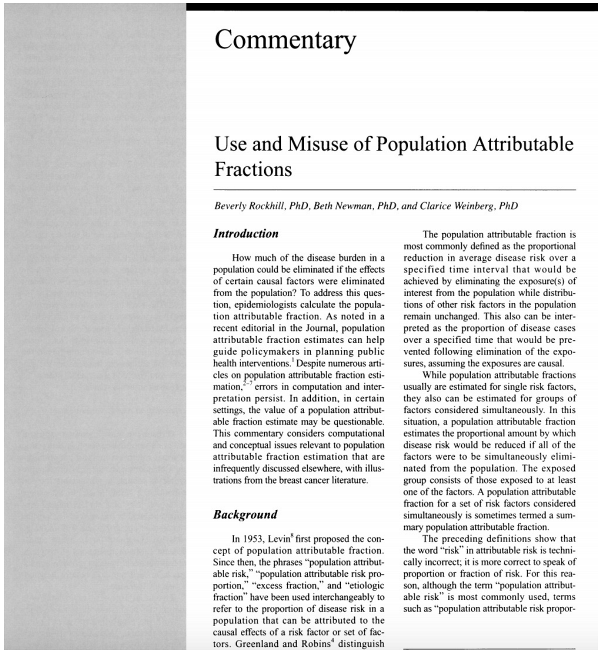
Can also calculate attributable fraction using the RR with this alternate formula :

$$AF\% = \frac{[(RR-1)\,]}{[RR]}$$

The advantage of this formula is that you don’t need to know the incidence in the exposed and unexposed group

Population Attributable Risk (PAR)

Proportion of disease risk in the population that can be attributed to the causal effects of a risk factor or set of factors



Commentary

Use and Misuse of Population Attributable Fractions

Beverly Rockhill, PhD, Beth Newman, PhD, and Clarice Weinberg, PhD

Introduction

How much of the disease burden in a population could be eliminated if the effects of certain causal factors were eliminated from the population? To address this question, epidemiologists calculate the population attributable fraction. As noted in a recent editorial in the Journal, population attributable fraction estimates can help guide policymakers in planning public health interventions.[1] Despite numerous articles on population attributable fraction estimation,[2–7] errors in computation and interpretation persist. In addition, in certain settings, the value of a population attributable fraction estimate may be questionable. This commentary considers computational and conceptual issues relevant to population attributable fraction estimation that are infrequently discussed elsewhere, with illustrations from the breast cancer literature.

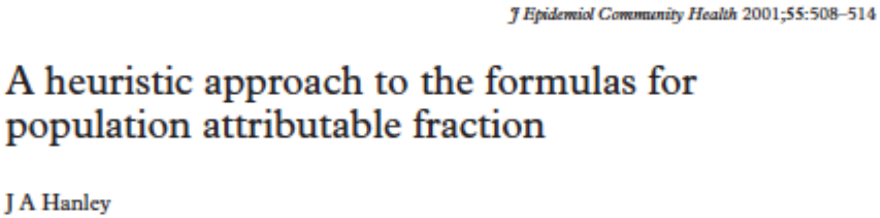
Background

In 1953, Levin[8] first proposed the concept of population attributable fraction. Since then, the phrases "population attributable risk," "population attributable risk proportion," "excess fraction," and "etiologic fraction" have been used interchangeably to refer to the proportion of disease risk in a population that can be attributed to the causal effects of a risk factor or set of factors. Greenland and Robins[4] distinguish

The population attributable fraction is most commonly defined as the proportional reduction in average disease risk over a specified time interval that would be achieved by eliminating the exposure(s) of interest from the population while distributions of other risk factors in the population remain unchanged. This also can be interpreted as the proportion of disease cases over a specified time that would be prevented following elimination of the exposures, assuming the exposures are causal.

While population attributable fractions usually are estimated for single risk factors, they also can be estimated for groups of factors considered simultaneously. In this situation, a population attributable fraction estimates the proportional amount by which disease risk would be reduced if all of the factors were to be simultaneously eliminated from the population. The exposed group consists of those exposed to at least one of the factors. A population attributable fraction for a set of risk factors considered simultaneously is sometimes termed a summary population attributable fraction.

The preceding definitions show that the word "risk" in attributable risk is technically incorrect; it is more correct to speak of proportion or fraction of risk. For this reason, although the term "population attributable risk" is most commonly used, terms such as "population attributable risk propor-

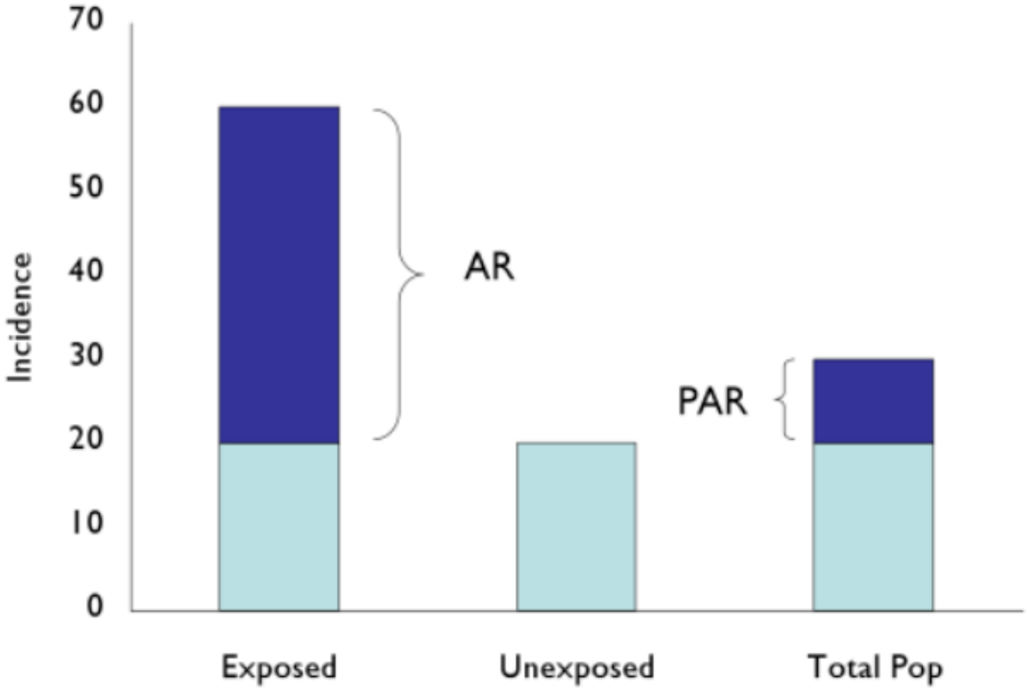


J Epidemiol Community Health 2001;55:508–514

A heuristic approach to the formulas for population attributable fraction

J A Hanley

Population Attributable Risk (PAR)



- *What would be the impact of removing an exposure on the total population?*
- *E.g., smoking cessation intervention or policy*

PAR: The excess number of cases in the population due to exposure

Harper, 2011

Indoor Smoking Bans

- *PAR can answer the question: What would be the impact of banning indoor smoke exposure on population levels of lung cancer?*

Utility of PAR

- To determine which exposures have the most relevance to the health of a community
- Can estimate PAR for a single risk factor or for several factors simultaneously
- If the exposure was removed from the population, then how much of the disease in the population will be avoided?

Population Attributable Risk (PAR) = $I_t - I_o$

=(Incidence in total population)- (Incidence in unexposed group)

Population Attributable Risk Percent

Population Attributable Risk (%) = $(I_t - I_o / I_t) * 100$

$$= 100 * \frac{[(\text{Incidence in total population}) - (\text{Incidence in unexposed group})]}{(\text{Incidence in total population})}$$

- What proportion of the disease incidence in a total population (including both exposed and unexposed people) can be attributed to a specific exposure?
- If smoking were eliminated, what proportion of the incidence of lung cancer in the total population (which consists of both smokers and nonsmokers) would be prevented?

SIDS Example

	SIDS (D+)	No SIDS (D-)	Row total (Margins)
Prone (E+)	9	837	846
Non-prone (E-)	6	1755	1761
Column total (Margins)	15	2592	2607

PAR = I_t-I_0 = (15/2607) - (6/1761) = 0.0023= 2.3 per 1000

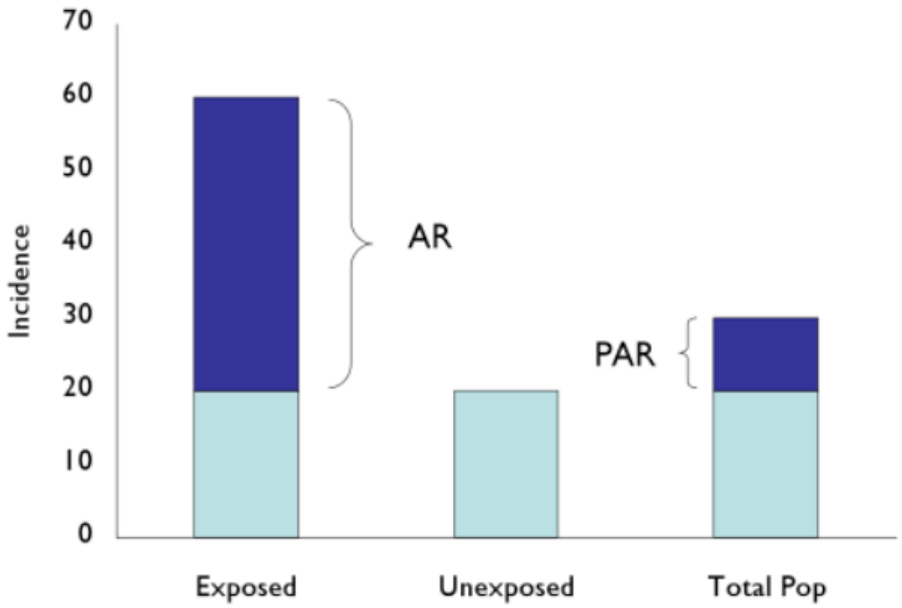
PAR% = 0.0023/0.0058 x 100 = 0.41%

Interpretation: Making all babies sleep on their back would eliminate 41% of all cases of SIDS in the population.

AR vs. PAR

The AR% in the SIDS example was 68% and the PAR% was 41%

The impact of removing an exposure on the exposed group is greater than the impact of removing the exposure from the population



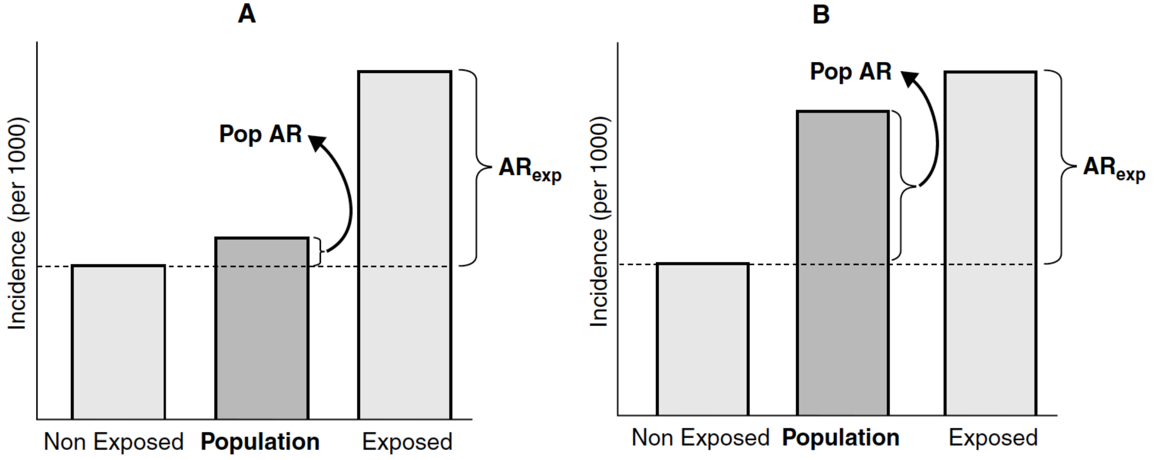
Relative Risk vs. Population Attributable Fraction

- **Relative risk**
  - Provides a measure of the strength of an association between an exposure and a disease
  - Helps to evaluate the causal relationship between an exposure and a disease
  - Magnitude of relative risk does not predict magnitude of attributable risk

- **PAR%**
  - Provides a measure of the public health impact of an exposure on the entire population
  - Assumes the exposure is causal (and also that exposure can be completely removed)
  - A strong RR may not translate to a large PAR% if the exposure is not widely prevalent in the population
  - Conversely, a weak RR may have a big PAR% if the exposure is very common (e.g. smoking, obesity, air pollution)

PAR and Exposure Prevalence

The population is composed of exposed and unexposed individuals

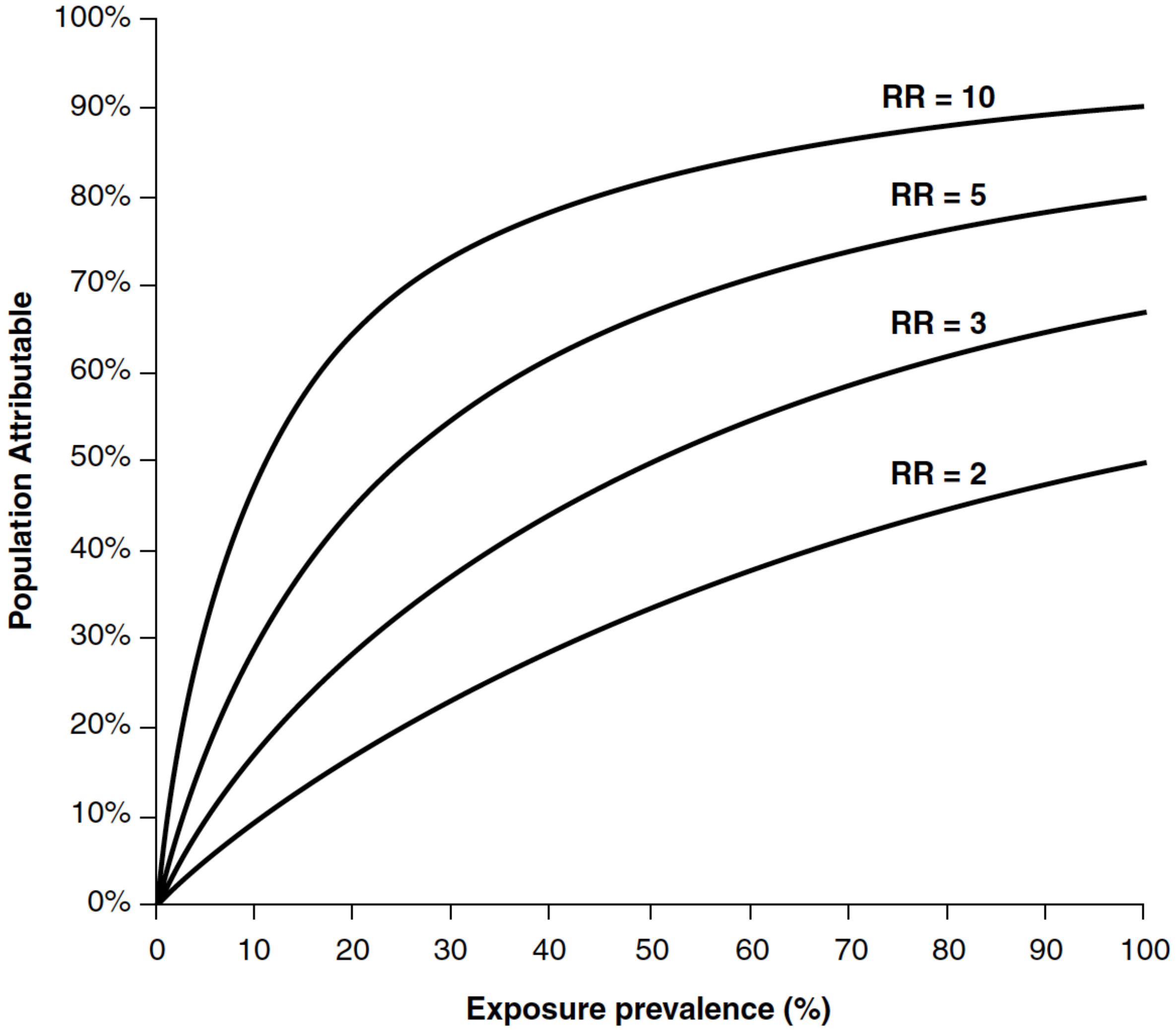


For a fixed value of relative risk, the PAR is very dependent on prevalence of exposure

The incidence in the population is similar to the incidence in the unexposed when the exposure is rare

The incidence in the population is closer the incidence in the exposed when the exposure is common

Szklo & Nieto. Epidemiology: Beyond the basics. 2nd Edition, 2007



For all values of the relative risk, the PAR% increases as exposure prevalence increases

Szklo & Nieto. Epidemiology: Beyond the basics. 2^{nd} Edition, 2007

Alternative Formula: PAR%

This alternative formula for the PAR% makes it clear how it is dependent on exposure prevalence :

$$\text{PAR\%} = \frac{[P_{exp}\,(RR-1)\,]}{[P_{exp}\,(RR-1)+1]} * 100$$

Where P_{exp} = Prevalence of exposure in the **population**

So, if P_{exp} is large, then even if the RR is small, it will still work out to a large PAR%

*Important Note: Several authors have emphasized the importance of using crude RR values (**not confounder** adjusted RR values)

Estimating PAF for obesity

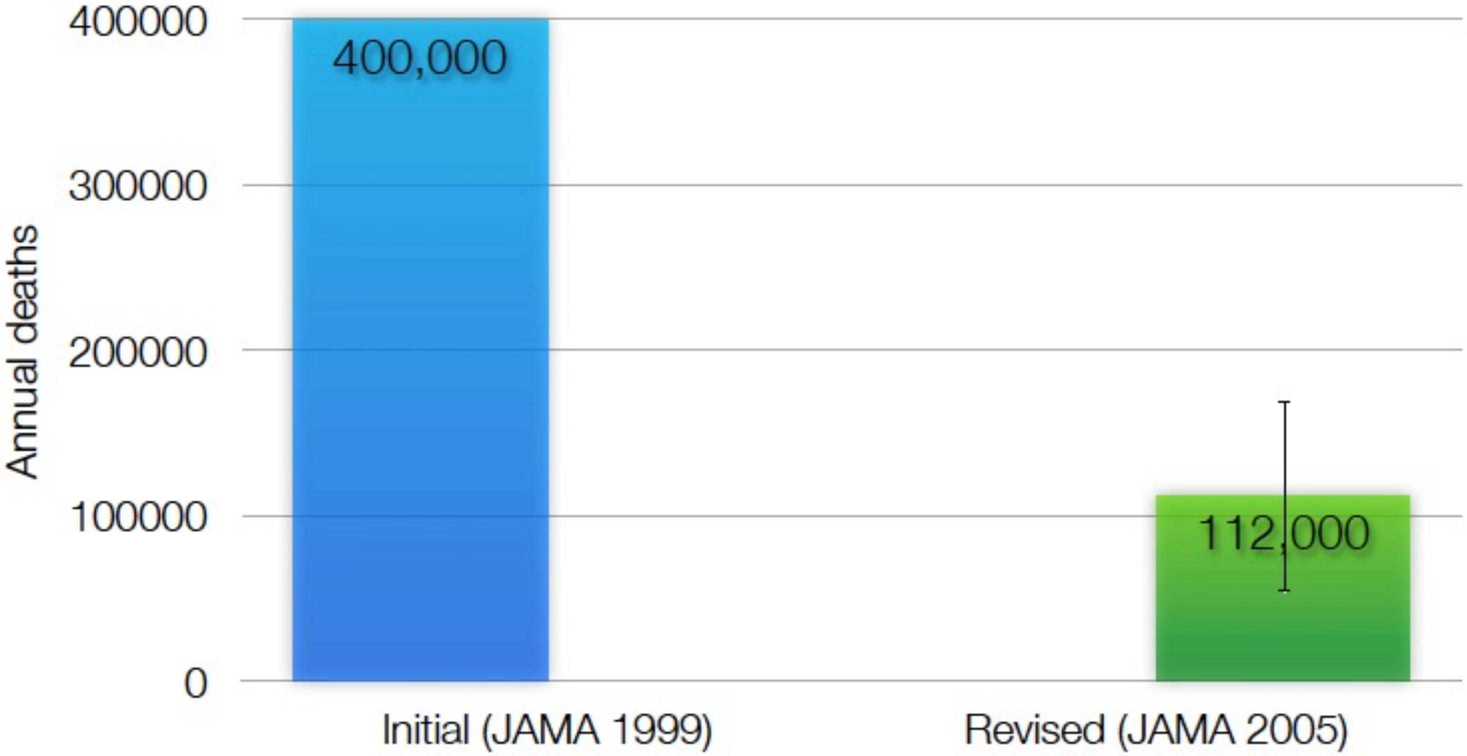
The New York Times

HEALTH

Data on Deaths From Obesity Is Inflated, U.S. Agency Says

By **GINA KOLATA** NOV. 24, 2004

“The Centers for Disease Control and Prevention says that its widely publicized estimate that 400,000 Americans die each year from being too fat is wrong and that it will submit a new, lower figure to the medical journal that published its original estimate last March.”



In calculating deaths in the United States attributable to overweight and obesity, Allison et al. adjusted their risk estimates for age, sex, and smoking but used an attributable risk formula for an unadjusted relative risk.

Cannot use adjusted risk ratios in the PAR% formula, you will get the wrong answer

(Flegal et al., 2004)

PAR% Example

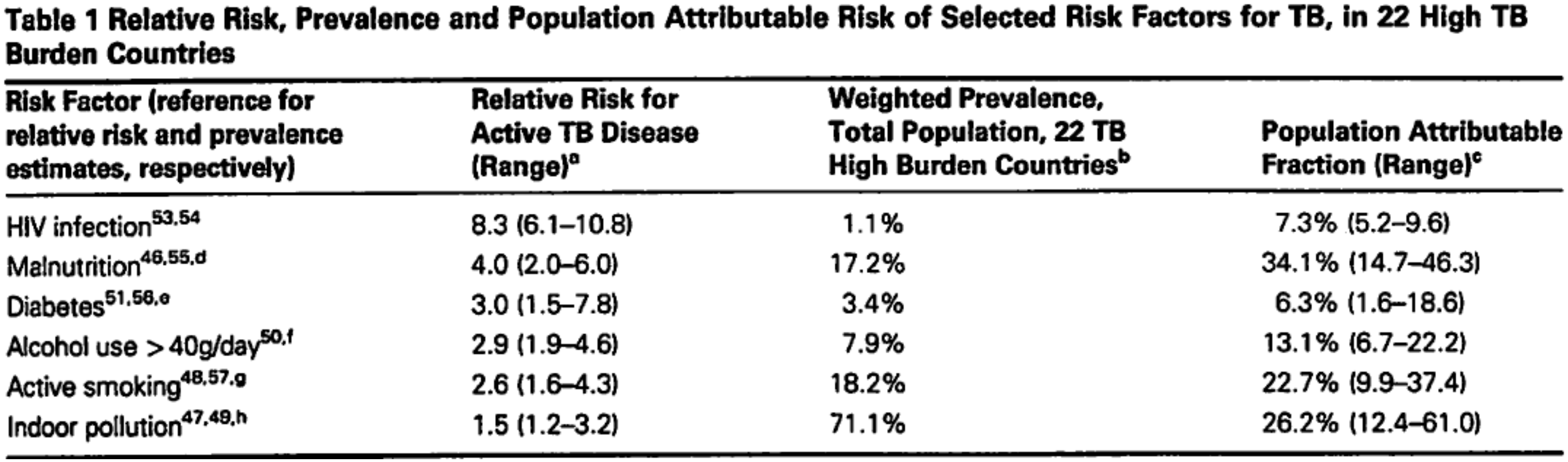


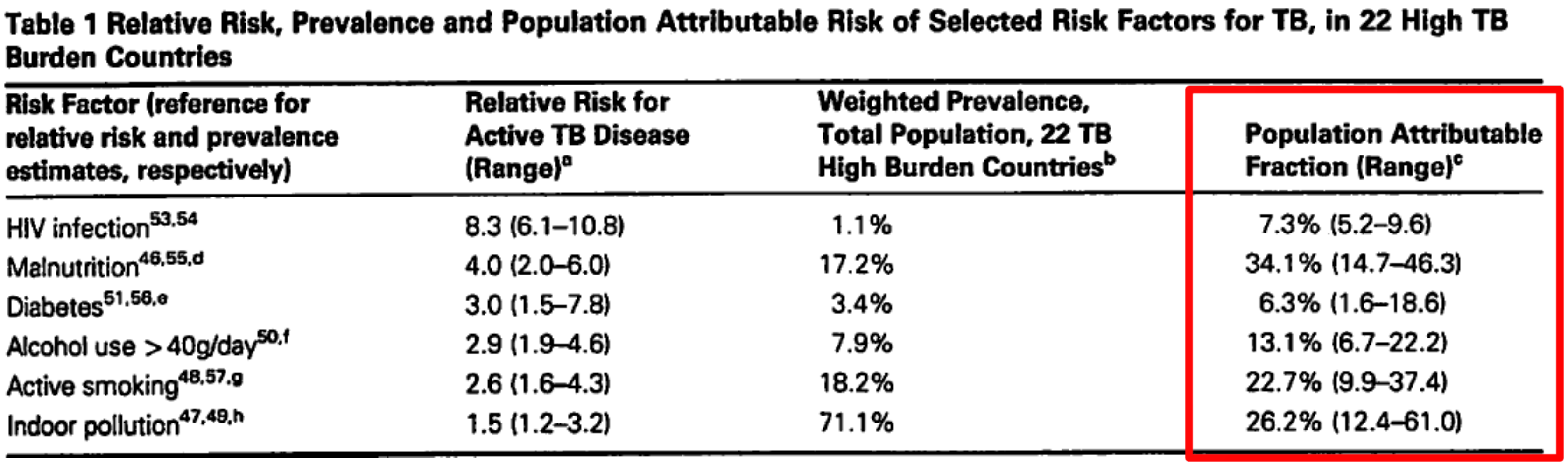
Table 1 Relative Risk, Prevalence and Population Attributable Risk of Selected Risk Factors for TB, in 22 High TB Burden Countries

Risk Factor (reference for relative risk and prevalence estimates, respectively)	Relative Risk for Active TB Disease (Range)[a]	Weighted Prevalence, Total Population, 22 TB High Burden Countries[b]	Population Attributable Fraction (Range)[c]
HIV infection[53,54]	8.3 (6.1–10.8)	1.1%	7.3% (5.2–9.6)
Malnutrition[46,55,d]	4.0 (2.0–6.0)	17.2%	34.1% (14.7–46.3)
Diabetes[51,56,e]	3.0 (1.5–7.8)	3.4%	6.3% (1.6–18.6)
Alcohol use >40g/day[50,f]	2.9 (1.9–4.6)	7.9%	13.1% (6.7–22.2)
Active smoking[48,57,g]	2.6 (1.6–4.3)	18.2%	22.7% (9.9–37.4)
Indoor pollution[47,49,h]	1.5 (1.2–3.2)	71.1%	26.2% (12.4–61.0)

Notice how the PAR% for TB is dependent on prevalence of exposure and RR

Lonnroth et al. Sem Resp Crit Care Med 2008

Adding PAR%



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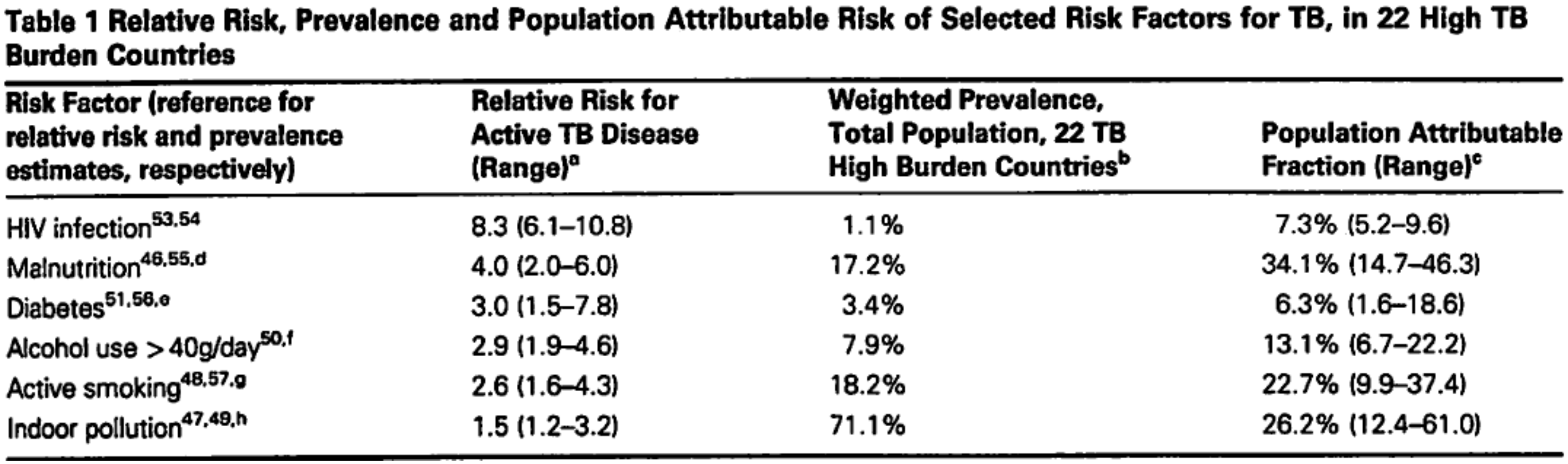
If you add up the PAR% they sum to more than 100%

How is that possible?

PAR% can sum to more than 100%

- Many diseases are caused by multiple risk factors, and individual risk factors may interact in their impact on overall risk of disease
- As a result, PAFs for individual risk factors often overlap and add up to more than 100 percent.
- If you want to estimate how the incidence of disease would change by eliminating multiple causes of disease, **you cannot just sum the PAR% calculated for each exposure**

X Wrong approach X



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Indoor pollution[47,49,h]	1.5 (1.2–3.2)	71.1%	26.2% (12.4–61.0)

Question: How much would the incidence of TB change if we eliminated HIV infection and malnutrition?

WRONG Answer: 7.3% + 34.1% =41.4%

X X Eliminating HIV and malnutrition, would eliminate 41.4% of all cases of TB in the population

Distributive Property

- PAF can be partitioned into exposure-category specific attributable fractions
- Can sum exposure-category specific attributable fractions to equal the PAF
- Note how this differs from adding exposure-category specific PAF to equal total PAF (i.e., the wrong approach as described on the previous slide)

Category specific attributable fractions

- Fraction of total disease risk in the population that would be eliminated if people only in that exposure category were shifted to the unexposed group

- Estimated as

$$pd_i\left(\frac{RR_i-1}{RR_i}\right)$$

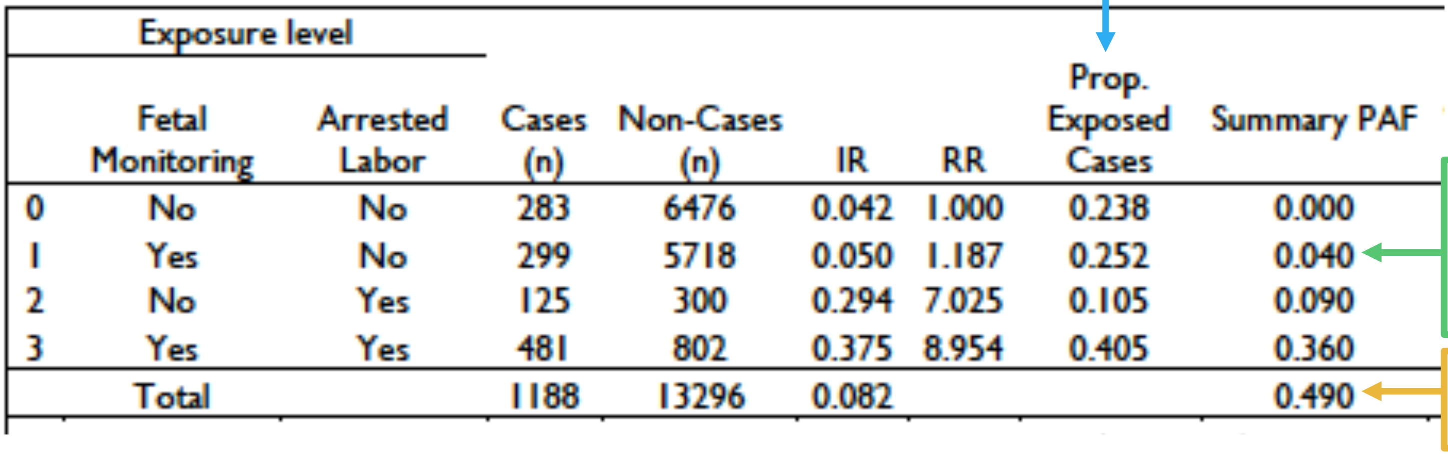
Where RR is the risk ratio for the exposed group and *pd* represents the proportion of total cases in the population arising from the exposure

Summing category specific attributable fractions

To get the PAF from the category specific attributable fractions:

$$\sum_i pd_i \left(\frac{RR_i - 1}{RR_i}\right),$$

Pd



Exposure level								
	Fetal Monitoring	Arrested Labor	Cases (n)	Non-Cases (n)	IR	RR	Prop. Exposed Cases	Summary PAF
0	No	No	283	6476	0.042	1.000	0.238	0.000
1	Yes	No	299	5718	0.050	1.187	0.252	0.040
2	No	Yes	125	300	0.294	7.025	0.105	0.090
3	Yes	Yes	481	802	0.375	8.954	0.405	0.360
	Total		1188	13296	0.082			0.490

Each row here represents category specific PAF

Sum of category specific PAF

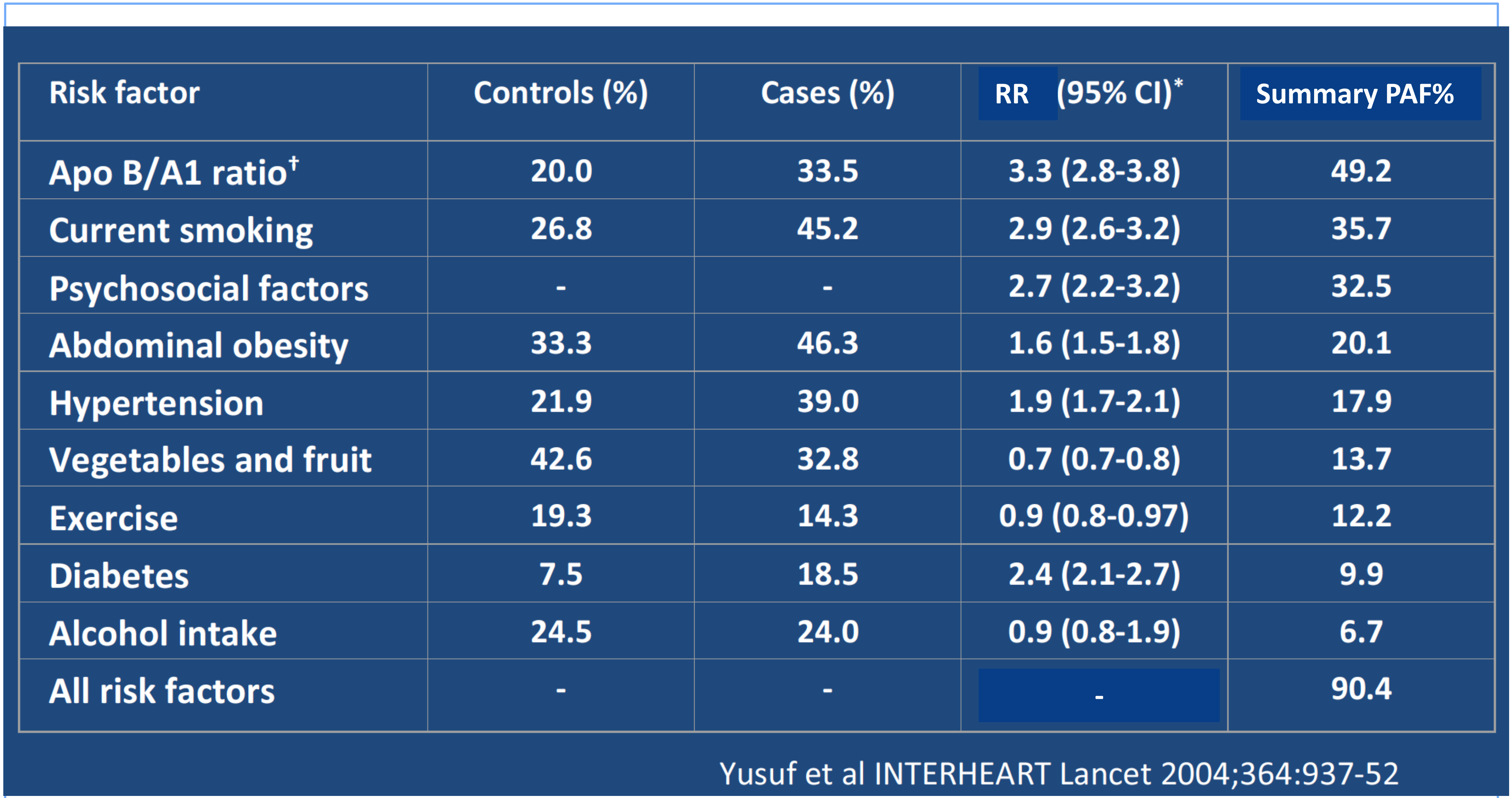
Example: INTERHEART study

Purpose: What are the most important risk factors for MI?

Study design: Case control studies in 52 Countries

Study population: 15,152 cases and 14,820 controls

Exposure variables/risk factors: smoking, diabetes, hypertension, abdominal obesity, psychosocial, fruit and vegetable intake, exercise, alcohol, ratio of ApoB/ApoA1



Risk factor	Controls (%)	Cases (%)	RR (95% CI)[*]	Summary PAF%
Apo B/A1 ratio[†]	20.0	33.5	3.3 (2.8-3.8)	49.2
Current smoking	26.8	45.2	2.9 (2.6-3.2)	35.7
Psychosocial factors	-	-	2.7 (2.2-3.2)	32.5
Abdominal obesity	33.3	46.3	1.6 (1.5-1.8)	20.1
Hypertension	21.9	39.0	1.9 (1.7-2.1)	17.9
Vegetables and fruit	42.6	32.8	0.7 (0.7-0.8)	13.7
Exercise	19.3	14.3	0.9 (0.8-0.97)	12.2
Diabetes	7.5	18.5	2.4 (2.1-2.7)	9.9
Alcohol intake	24.5	24.0	0.9 (0.8-1.9)	6.7
All risk factors	-	-	-	90.4

Yusuf et al INTERHEART Lancet 2004;364:937-52

If you could intervene on these 9 risk factors, you would prevent 90.4% of heart attacks

Even though these 9 risk factors account for 90% of the PAR for MI, it doesn't mean there is only 10% of the disease left to be explained by additional risk factors

Smulders et al., 2008

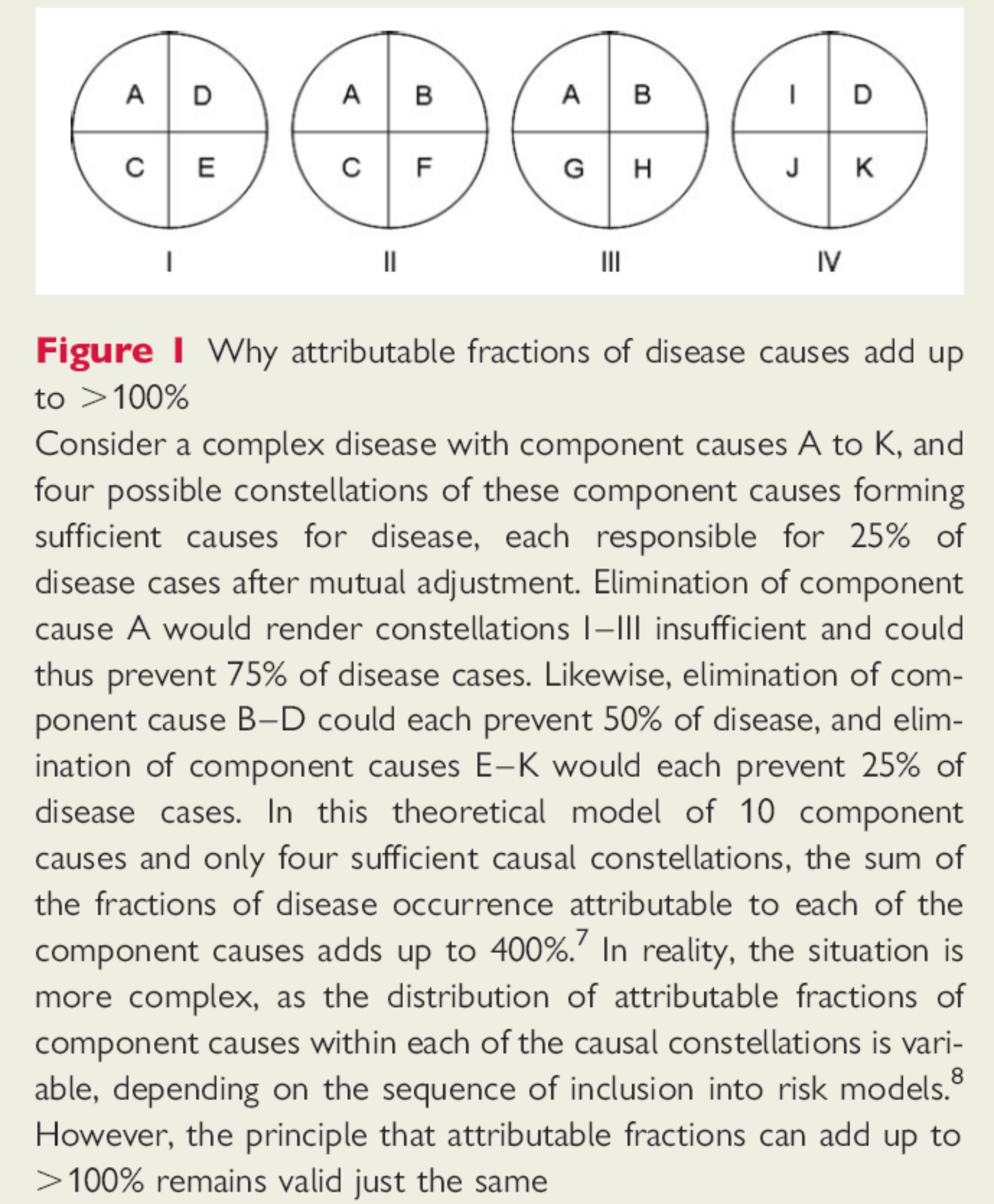


Figure 1 Why attributable fractions of disease causes add up to >100%

Consider a complex disease with component causes A to K, and four possible constellations of these component causes forming sufficient causes for disease, each responsible for 25% of disease cases after mutual adjustment. Elimination of component cause A would render constellations I–III insufficient and could thus prevent 75% of disease cases. Likewise, elimination of component cause B–D could each prevent 50% of disease, and elimination of component causes E–K would each prevent 25% of disease cases. In this theoretical model of 10 component causes and only four sufficient causal constellations, the sum of the fractions of disease occurrence attributable to each of the component causes adds up to 400%.[7] In reality, the situation is more complex, as the distribution of attributable fractions of component causes within each of the causal constellations is variable, depending on the sequence of inclusion into risk models.[8] However, the principle that attributable fractions can add up to >100% remains valid just the same

Important Considerations

When estimating attributable fractions, you need to consider:

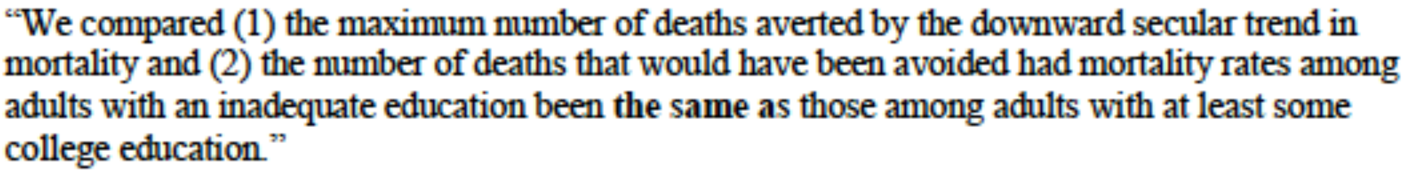
- Is there an intervention possible? Do we know it is causally related to the outcome?
  - How do you intervene on someone’s race or genes?
- Available interventions and their risks and benefits
  - Interventions may have side effects, costly
- Effect of interventions on other exposures
  - Interventions to reduce smoking may increase population prevalence of obesity

A bad example

Giving Everyone the Health of the Educated: An Examination of Whether Social Change Would Save More Lives Than Medical Advances

| Steven H. Woolf, MD, MPH, Robert E. Johnson, PhD, Robert L. Phillips, Jr, MD, MSPH, and Maike Philipsen, PhD

April 2007, Vol 97, No. 4 | American Journal of Public Health



"We compared (1) the maximum number of deaths averted by the downward secular trend in mortality and (2) the number of deaths that would have been avoided had mortality rates among adults with an inadequate education been the same as those among adults with at least some college education."

Misinterpretation of PAF%

Example:

Seidman et al. estimated population attributable fractions of 0.21 in the 30 to 54-year age group and 0.29 in the 55 to 84-year age group for 10 breast cancer risk factors.

Results: “Given our current understanding about breast cancer risk factors, we are unable to identify the ‘causes’ of more than one quarter of all cases”

Correct & incorrect interpretation

PAF% = 25%

✓ 25% of the population risk of breast cancer would be eliminated if all 10 risk factors were to be eliminated from the population

✓ 25% of cases of breast cancer would be prevented if all 10 risk factors were removed

X **Does not mean that 25% of women with breast cancer will have one or more of the risk factors**

X **Does not mean we can identify the causes of breast cancer for 25% of women**

Measures of Impact: Protective Exposures

- Absolute Risk Reduction (ARR)
- Relative Risk Reduction (RRR)
- Number Needed to Treat (NNT)

Risk Reduction

Absolute Risk Reduction= I_o-I_e

Difference (reduction) in rates of bad outcomes between experimental and control participants in a trial

Relative Risk Reduction= (I_o-I_e) / I_o

Proportional reduction in rates of bad outcomes between experimental and control participants in a trial

(Barratt et al., 2004)

Example

- **Diabetes Control and Complications Trial (DCCT):** Effect of intensive diabetes therapy on the development and progression of neuropathy.
- Neuropathy occurred in 9.6% of patients randomized to usual care and 2.8% of patients randomized to intensive therapy.

Occurrence of endpoint		**ARR**	**RRR**
Io (control)	Ie (intervention)	Io - Ie	(Io – Ie) / Io
9.6%	2.8%	9.6% - 2.8% = 6.8%	$\frac{9.6\% - 2.8\%}{9.6\%} = 71\%$

Number Needed to Treat

Number of patients who would have to receive the treatment for **ONE** of them to benefit

Number of patients to whom a clinician would need to administer a treatment to prevent 1 patient from having an adverse outcome

- E.g., NNT=10
- Doctors would have to treat 10 patients with a drug therapy to prevent 1 patient from having an adverse outcome.

Calculating NNT

NNT= 1/ARR

If the absolute risk reduction is large, you need to treat only a small number of patients to observe a benefit in at least some of them.

Conversely, if the absolute risk reduction is small, you must treat many people to observe a benefit in just a few.

A small NNT value is better than a large NNT value

Number Needed to Harm

- Calculated in the same way as the NNT
- Used to describe adverse outcomes
- Want to see a large value for NNH, because it means that adverse events are rare
- Small NNH value means adverse events happen frequently

Proportions versus percentages

- You need to take care to notice whether the event rates and risk difference are presented in proportions (e.g., $I_o = 0.025$) or percentages (=2.5%)

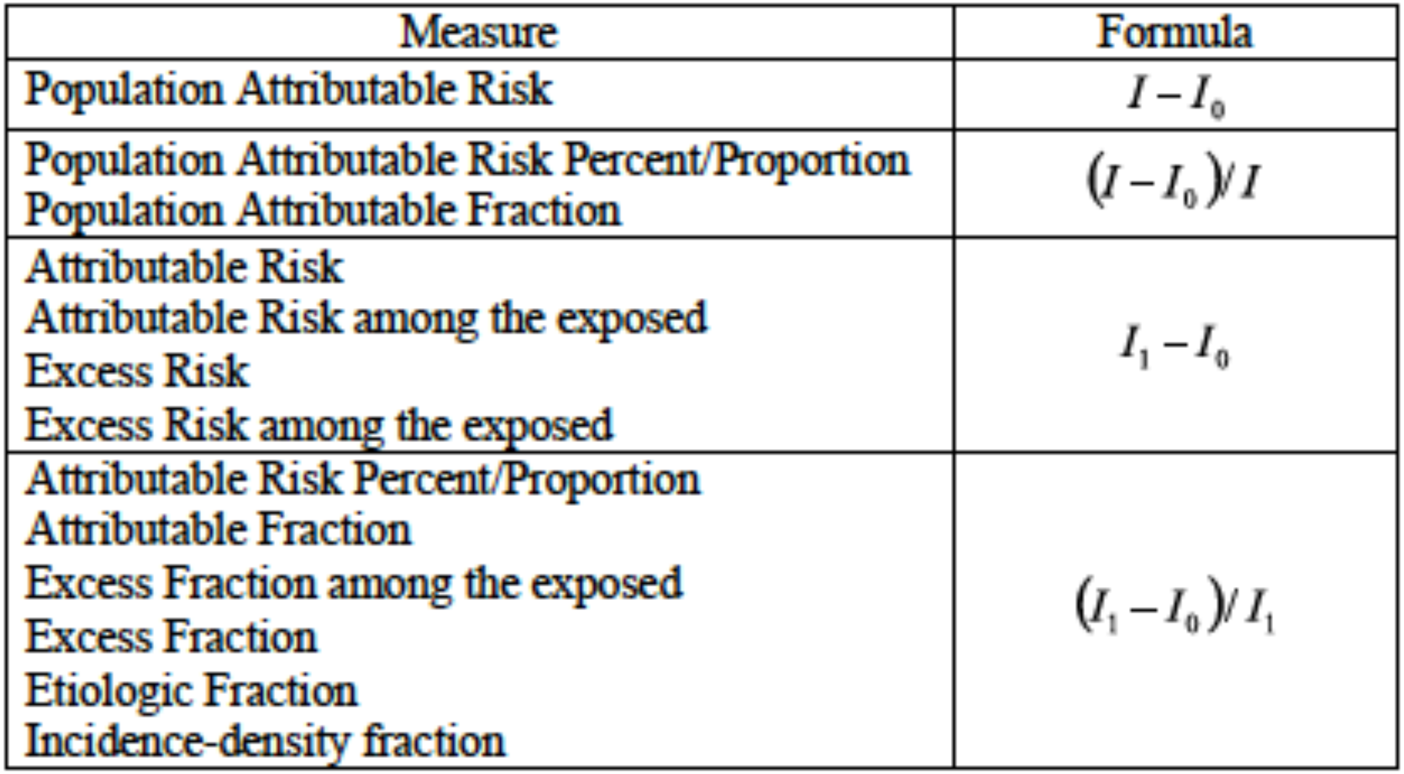
- If ARR is expressed as a proportion:

$$NNT = 1/ARR$$

- If ARR is expressed as a percent:

$$NNT = 100/ARR$$

Summary



Measure	Formula
Population Attributable Risk	$I - I_0$
Population Attributable Risk Percent/Proportion Population Attributable Fraction	$(I - I_0)/I$
Attributable Risk Attributable Risk among the exposed Excess Risk Excess Risk among the exposed	$I_1 - I_0$
Attributable Risk Percent/Proportion Attributable Fraction Excess Fraction among the exposed Excess Fraction Etiologic Fraction Incidence-density fraction	$(I_1 - I_0)/I_1$