THE EPISTEMOLOGY OF HEALTH
(How do we determine what is healthy and what is not?)

- Associations and Causes
  - Yellow fingers and lung cancer
  - Coffee and lung cancer
  - Smoking and lung cancer
  - Birth order and Downs syndrome
  - Hormone replacement therapy and coronary artery disease
  - Autologous bone marrow transplantation and breast cancer survival
  - Poor control of diabetes and microvascular and macrovascular events
  - HIV and AIDS

HOW DO WE ESTABLISH CAUSALITY?

- Experiments (strongest evidence)
- Observational data
  - Coherence with existing information (biological plausibility)
  - Consistency of association
  - Time sequence
  - Specificity of association
  - Reversibility of association
  - Strength of association
    * Quantitative strength
    * Dose-response relationship
    * Study design

- Are there any randomized trials that demonstrate the beneficial impact of diet and exercise on health outcomes such as death, disease, and disability?
GENERAL STRATEGY FOR IDENTIFYING THE DISEASE BURDEN/COSTS ASSOCIATED WITH ELEVATED BODY MASS INDEX

- Grab a bunch of people with elevated body mass indices (BMI) and a bunch of people with average/"ideal" BMIs
- Assess the difference in the disease burden / health care cost between the two groups
- Attribute the difference to elevated BMI

WHAT CAN GO WRONG?

- The two groups may not differ in BMI alone, but also may differ in other factors that affect disease burden/cost
  - Age
  - Gender
  - Socioeconomic status
  - Genetics
  - Medical conditions, obesity-related/unrelated
  - Other unmeasured/unmeasurable factors
- BMI might not be the cause of the disease/cost, but might be another expression of a common cause of both BMI and disease/cost (e.g., yellow fingers may not cause lung cancer, yellow fingers and lung cancer may both be caused by smoking)

HOW DO WE ADDRESS THESE ISSUES?

- To account for other differences between the groups:
  - Use statistical techniques that attempt to control for the differences
  - Often not possible to fully account for differences between groups in observational studies
- To sort out causal chain
  - Collect data that allow one to differentiate between the alternative, potential causes

HAVE WE SORTED OUT THE CAUSAL CHAIN?

- Do we know the independent effects of weight, physical activity, and fitness?
- Clinical judgment: What are health risks for an obese person who vigorously exercises an hour a day, 5 days a week, and -- where necessary -- maintains normal blood pressure, lipid, and blood sugar levels by taking niacin, statins, and metformin?
- Could our aesthetic judgments about overweight/obesity be affecting our scientific judgments?
BAD NEWS?

• The Swedish Obese Subjects (SOS) study invited participants to receive bariatric surgery (gastric banding, variable gastric banding, vertical banded gastroplasty, or gastric bypass).

• It constructed a comparison group by computerized matching, taking into account 18 variables related to morbidity and mortality.

  - Participants in this group were treated according to existing routines for obesity management at different primary health care centers.

• The study -- whose follow-up is ongoing -- periodically reports results:

  Sjostrom et al. NEJM. 2004; 351:2683-93

RESULTS, SOS 6-YEAR FOLLOW-UP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgery</th>
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<td></td>
<td></td>
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<tr>
<td>2 years (%)</td>
<td>-23.4</td>
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<td>10 years (%)</td>
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<td>0.18</td>
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<td>Cumulative inpatient costs ($), 6 years</td>
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<tr>
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<td>1905</td>
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<td>Years 2-6</td>
<td>1950</td>
<td>2048</td>
<td>?NS?</td>
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• What conclusions (if any) should we draw about whether or not weight loss reduces healthcare costs?
TYPES OF STUDIES FOR QUANTIFYING THE COSTS OF ELEVATED BMI / MODIFYING BMI

- Cost-of-illness
  - Prevalence-based cost-of-illness studies (PBCOI)
    * Cohort studies
    * Attributable risk/cost studies
  - Incidence-based cost-of illness studies

- Treatment of obesity studies
  - Randomized trials
  - Decision analyses/simulation models

COST-OF-ILLNESS STUDIES

- Prevalence- vs. Incidence-Based
  - Prevalence-Based (PBCOI)
    * Measure the value of resources used or lost due to a condition during a specified period of time (e.g., a year), regardless of the time of onset of the condition
    - If population/ disease is in steady state, correctly weights different durations of disease
    - If not in steady state -- for example if the prevalence is increasing -- can misweight some costs
  - Incidence-Based
    * Measure the value of resources used or lost due to a condition from its onset until cure or death
PBCOI: COHORT STUDIES

- Identify two groups of study participants, those who have been exposed to the risk factor under study (e.g., elevated BMI) and those who have not been exposed
  - Two main types of published cohort studies:
    * Nationally representative samples
    * Less representative samples
- Estimate health care costs of study participants
- Predict (with varying degrees of technical sophistication) cost as a function of BMI
  - The cost difference associated with BMI is taken to represent the cost difference due to the exposure

NATIONALLY REPRESENTATIVE COHORT STUDIES

- Use data from nationally representative samples of individual study participants, e.g.,
  - Medical Expenditure Panel Survey (MEPS): self-report confirmed through physician offices, hospitals, and insurance coverage
  - National Health Interview Survey (NHIS)
  - Healthcare for Communities household telephone survey (HCC)
  - National Health and Nutrition Examination Survey (NHANES)
  - CDC Behavioral Risk Factor Surveillance System (BRFSS)
- Obtain estimates of cost and BMI for each study participant
  - Cost: obtain direct measures or obtain measures of resource use and multiply by estimates of unit costs
- Predict cost as a function of BMI
LESS REPRESENTATIVE COHORT STUDIES

- Use less representative sample of individual study participants, e.g.,
  - HMO's
  - Employers
- Obtain estimates of cost and BMI
  - Administrative data on costs (e.g., HMO or employer insurance records)
  - Direct measurement of BMI and risk factors or self-report of BMI and risk factors
    - Health Risk Appraisals
    - Health Surveys
- Predict cost as a function of BMI

PBCOI: ATTRIBUTABLE RISK/COST STUDIES

- Obtain national estimates of the one-year cost of diseases associated with BMI (from various sources)
- Obtain estimates of the population-attributable risk% (PAR%) or obesity-attributable etiologic fractions (i.e., proportion of disease/cost that is due to obesity)
  - e.g. suppose 40% of the population is nonoverweight/obese and 5% have coronary heart disease (CHD); suppose 60% of the population is overweight/obese and 20% have CHD, then the PAR% equals:
    \[
    \frac{(0.6 \times (0.20-0.05))}{(0.6 \times 0.2) + (0.4 \times 0.05)} \times \frac{\text{Fract OW} \times (\text{Risk diff})}{\text{Expected risk}}
    \]
    \[
    = 0.09 / (0.12 + 0.02) = 0.64
    \]
    i.e., 9% of the 14% total is “due” to obesity
  - More formally:
    \[
    \frac{P(RR - 1)}{(1 + P(RR - 1))}
    \]
    where P equals prevalence of obesity and RR equals the relative risk for disease (e.g., 0.2/0.05)
- Multiply cost x PAR% to obtain the cost-of-illness
Issues with PAR%

- Cause vs. association
- Can PAR% be transferred between studies, or are they specific to the prevalence of the risk factor, the prevalence of disease, other factors?
  * Prevalence of overweight differs widely
  * Prevalence of disease differs within ethnic groups at the same BMI

<table>
<thead>
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<th>Nonrep Cohort</th>
<th>Attrib Risk/Cost</th>
<th>Other</th>
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<td>2. Sturm</td>
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<td>3. Heitoff</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>4. Detournay</td>
<td>x +</td>
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<td>5. Andreyeva</td>
<td>x</td>
<td></td>
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</tr>
<tr>
<td>6. Kuriyama</td>
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<td>7. Thorpe</td>
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<td>9. Goetzel</td>
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<td></td>
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<tr>
<td>20. Colditz</td>
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<td>21. Wolf (1996)</td>
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</tr>
<tr>
<td>22. Birmingham</td>
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<td>23. Swinburn</td>
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<td>26. Thompson (1999)</td>
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</table>
COST-EFFECTIVENESS STUDIES

- Even if we can prove that elevated BMI is associated with excess costs, does not necessarily mean that we can save money by having people reduce their BMI.
- Should therefore evaluate the value for the cost of weight loss programs.
- Cost-effectiveness studies compare the difference in costs and difference in outcomes between patients who "lose weight" with those who do not. Observed differences in costs and outcomes (assumed to be) caused by observed weight loss: \( \Delta C / \Delta E \)

COST-EFFECTIVENESS STUDIES (II)

- Two main types of studies: trial-based evaluations vs decision analyses/simulation models.
  - Strength: Direct observation
  - Weakness: Usually short term in duration.
- Decision analyses/simulation models: Usually directly observe weight loss only; use epidemiologic models for relationships between weight loss and outcome and weight loss and cost.
  - Strength: Can model life-time costs
  - Weakness: Assumption- rather than data-driven
COST-EFFECTIVENESS STUDIES (III)

- Studied Interventions include:
  - Lifestyle intervention (multidisciplinary)
    * University-based
    * Commercial weight loss programs
    * Managed care programs
  - Weight loss medications
  - Bariatric surgery

- Outcomes used for these studies vary
  - lb/kg/BMI units lost
  - Case of diabetes mellitus prevented
  - Quality-adjusted life years saved

- How should we compare studies with these different outcomes?

<table>
<thead>
<tr>
<th>Study</th>
<th>Nationally Rep Trial</th>
<th>Nonrepres Trial</th>
<th>Decision Analysis</th>
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</tr>
<tr>
<td>Martin</td>
<td>x †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christou</td>
<td>x † K</td>
<td></td>
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</tr>
<tr>
<td>Agren</td>
<td>x † K</td>
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<td></td>
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<tr>
<td>Craig, Fang</td>
<td>x</td>
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<tr>
<td>Lamotte</td>
<td>x</td>
<td></td>
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<tr>
<td>DPP (Eddy)</td>
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* Partial results of Medline search
† Nonrandomized
K Non-US
### STUDY RESULTS. PREVALENCE OF OVERWEIGHT/OBESITY *

<table>
<thead>
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<th>Study</th>
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<td>HMO</td>
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</table>

* Overweight commonly defined as BMI >25 and <30; obesity commonly defined as BMI >30
† NHANES 2001-2002
‡ Overweight defined as BMI >25 and <29; obesity defined as BMI >29

### ONE-YEAR PER-PERSON COST/EXPENDITURE/CHARGE ESTIMATES

<table>
<thead>
<tr>
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* Generally pooled by assuming that the prevalence of overweight is 34.7% and the prevalence of obesity is 30.5% (Hedley), except for Kuriyama et al (Japan), where prevalences are 26% and 2.8%, respectively

K Non-US
### ONE-YEAR NATIONAL COST ESTIMATES *

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<thead>
<tr>
<th>Study</th>
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<th>Obese</th>
<th>Total</th>
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<td>Nationally representative cohort</td>
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<td>13.5</td>
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<td>62.5</td>
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<td>Average (N)</td>
<td>11.6 (8)</td>
<td>38.5 (11)</td>
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* Overweight = Cost per overweight person * 70,500,000; obesity = cost per obese person * 61,610,000

### COST-EFFECTIVENESS OF TREATMENT OF OBESITY

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Outcome measure</th>
<th>Result</th>
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<tbody>
<tr>
<td>Randomized controlled trials, nationally representative</td>
<td>DPP Lifestyle vs placebo</td>
<td>DM Prevented</td>
<td>$24,400</td>
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<td>DPP Metformin weakly dominated by lifestyle</td>
<td>Wylie-Rosett Computerized lifestyle</td>
<td>Lb lost</td>
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<td>Martin Medical vs surgical</td>
<td>Foxcroft Orlistat QALY</td>
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<tr>
<td>Cohort Studies</td>
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<td>&gt;$250 both arms, NS</td>
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COST-EFFECTIVENESS OF TREATMENT OF OBESITY

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<td>Dominates</td>
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SUMMARY OF FINDINGS (I)

- Prevalence
  - Overweight: 34% - 37%
  - Obesity: 19% - 34%

- Conclusion: Self-reported weight and height seems to be consistent across a number of studies

- Might there be a consistent reporting bias?

- What would be the impact of such a bias on the results of cohort studies?
  - Under-reporting of the prevalence of obesity would underweight the impact of obesity costs
    * If mis-reporting generally leads to the classification of higher cost overweight/obese people as being normal weight, the average cost among normal weight people would be increased (thus attributing some of the costs of overweight/obesity to normal weight)
  - Impact on mean cost among overweight/obese people would depend on whether the misreporting was uniformly distributed among overweight/obese people
SUMMARY OF FINDINGS (II)

- Annual Cost Per Person

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Attrib Risk/Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td>-$104 - $273</td>
</tr>
<tr>
<td>Obesity</td>
<td>$262 - $767</td>
</tr>
</tbody>
</table>

- Conclusions
  - Overweight/obesity associated with substantial costs
  - Cohort studies appear to yield lower estimates of the cost of disease than do attributable risk/cost studies

SOURCES OF DIFFERENCE BETWEEN COHORT STUDIES AND PBCOI (I)

- Data used in cohort studies usually come from one or a small number of studies, often with consistent data, whereas data used in attributable risk/cost studies often come from many studies, often with inconsistent data
  - e.g., the population attributable fraction may be specific to a particular population with a particular prevalence of overweight/obesity and of disease. It may not be transferable to other populations with other prevalences

  * In the short-term, what do you think would happen to the PAR% if there was a sudden increase in the number of overweight/obese people?

SOURCES OF DIFFERENCE BETWEEN COHORT STUDIES AND PBCOI (II)

- Data used in attributable risk/cost studies potentially prone to double counting
  - e.g., Most of these studies included national cost estimates for some or all of the following diseases:
    * Coronary heart disease (CHD)
    * Hypertension
    * Hypercholesterolemia
    * Gall bladder
    * Stroke
    * DVT/Pulmonary embolism
    * Type II diabetes
    * Osteoarthritis
    * Breast cancer
    * Colon cancer
    * Endometrial cancer
    * Obstructive sleep apnea
    * Congestive heart failure
    * Gastroesophageal reflux disease
  - However, the cost of diabetes can include CHD, hypertension, and hypercholesterolemia; the costs of hypertension can include CHD and stroke, and the cost of hypercholesterolemia can include CHD. Thus the cost of CHD might be counted four times in these studies
SUMMARY OF FINDINGS (III)

- Some studies suggest that costs of overweight/obesity are greater for overweight/obese women than for overweight/obese men (data not shown)

  - Occurs even though men are more likely to be overweight, and there is at most a tendency for more women than men to be obese

SUMMARY OF FINDINGS (IV)

- J-Shaped Curve for the association between BMI and costs (i.e., higher costs for underweight and obese)

  ![Graph showing J-shaped curve for health care expenditures relative to BMI for males and females.](image)

  **Source:** Heithoff, 1997

- Strong or weak evidence reported in 7 of the cohort studies (Heithoff, Goetzel, Quesenberry, Thompson, Burton, Wang '02, Kuriyama)

- "Ideal" BMIs vary between 21 and 27.5

- What conclusions (if any) about weight loss should we draw from the J-shaped curve?
SUMMARY OF FINDINGS (V)

- Overweight/obesity, Chronic Disease, and Cost
  - Most of the studies that controlled for chronic medical conditions associated with obesity found that there was still an "independent" effect of weight after accounting for these.
  - Some studies controlled for variables that may be in the causal pathway of overweight/obesity (e.g., poor nutritional habits, hyperlipidemia, blood glucose, depression, etc.).
  - What conclusions (if any) should we draw about whether or not overweight/obesity alone increases health care costs?

- Overweight/obesity, Other Risk Factors, and Cost
  - Some studies accounted for confounding, while others did not.

See Table, end of handouts

SUMMARY OF FINDINGS (VI)

- Cost of treating obesity
  - Few studies
  - Heterogeneous outcomes
  - The three studies that directly compared lifestyle intervention with medications found lifestyle to be more cost-effective (what does insurance cover?)
  - Only three published studies estimated lifetime benefits (vs. within-trial benefits)
  - The two long-term decision analyses of the DPP (Herman et al, Eddy et al) arrived at very different conclusions about the cost-effectiveness of treating obesity (why?)
TECHNICAL FINDINGS

- Cost data (in cohort studies) highly skewed
  - Where reported, the median much smaller than the mean or mean much smaller than the S.D. (given costs can’t be negative, can infer observations with very high costs)
  - Makes appropriate statistical analysis difficult, and many of the cost estimates used in the papers may be flawed

- "Cost" data inconsistent
  - Different studies use different measures:
    * Costs
    * Expenditures
    * Charges
  - Known to differ consistently in health care (most likely increase in the listed order)
  - From a social perspective, costs are more important than expenditures or charges

SO WHAT?

- You perform a cost-of-illness study, and report that overweight/obesity is responsible for between $60 and $375 in health care costs per person per year in the U.S. (i.e., between $30 and $70+ billion per year)

- What are these numbers supposed to be?
  - Actual measures of cost?
  - Warning signs?
  - Projections of what they will be?

- What incentives do investigators have to report higher or lower results?

- How do these numbers help us make decisions?
  - About treatment?
  - About Prevention?

- What numbers would be better?
CONCLUSIONS (I)

"Overweight/obesity is a major public health problem that costs society billions of dollars, and we should be doing everything we can to combat it."

- Reasons to agree with this statement
  - Consistent association between BMI, health, and cost
  - Biological plausibility
  - Quantitatively strong association
  - Dose response
  - Correct time sequence

CONCLUSIONS (II)

- Reasons to question this statement
  - The bulk of the evidence we have for this statement come from studies like the ones that supported our public health decisions about smoking and lung cancer and about hormone replacement therapy and CAD
  - We haven’t performed a single trial that demonstrates the impact of weight loss on final health outcomes such as death, disease, and disability
    * When we had the chance (randomizing 5,000 patients and following them for 7 years), why did we decide to study weight loss in diabetics rather than weight loss in the general public?
  - We haven’t disaggregated the independent effects of weight, physical activity, and fitness
  - Even if overweight/obesity is a health/economic problem, it is not clear we have cost-effective interventions for its treatment / prevention

CONCLUSIONS (III)

- At the moment, there are better and worse opinions about statements of this kind, but definitive evidence is lacking
REFERENCES

NATIONALLY REPRESENTATIVE COHORT STUDIES

US


Non-US


LESS REPRESENTATIVE COHORT STUDIES


15. Bungum T, Satterwhite M, Jackson AW, Morrow JR. The relationship of body mass index, medical costs, and job absenteeism. American


SPECIAL INTEREST


Demonstration that
\[
P_H \frac{(R_H - R_L)}{\{(P_H R_H) + (P_L R_L)\}} = P(RR - 1) / \{1 + P(RR - 1)\}
\]

1. Begin with:
\[
P_H \frac{(R_H - R_L)}{\{(P_H R_H) + (P_L R_L)\}} = P(RR - 1) / \{1 + P(RR - 1)\}
\]

2. Substitute 1-P_H for P_L on left-hand side:
\[
P_H \frac{(R_H - R_L)}{\{(P_H R_H) + (P_L R_L)\}} =
\[
P_H \frac{(R_H - R_L)}{\{(P_H R_H) + ((1-P_H) R_L)\}}
\]

3. Multiply out:
\[
P_H \frac{(R_H - R_L)}{\{(P_H R_H) + ((1-P_H) R_L)\}} =
\[
\frac{((P_H R_H) - (P_H R_L))}{((P_H R_H) + R_L - (P_H R_L))}
\]

4. Divide numerator and denominator by R_L; if the result equals R_H / R_L, substitute RR:
\[
= \frac{(P_H RR - P_H H)}{(1 + P_H RR - P_H H)}
\]

5. Simplify elements containing P_H:
\[
= \frac{P_H (RR - 1))}{\{1 + P_H (RR - 1)\}}
\]

QED
## RESULTS GIVEN CONTROL FOR COMORBIDITIES

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<tr>
<th>Study</th>
<th>Unadj BP</th>
<th>Lipids</th>
<th>Depres</th>
<th>CHD</th>
<th>Other</th>
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Average cost, unadjusted: 1070
Average cost, adjusted: 361