Selection Bias in Epidemiological Studies

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Rising Impotency

A silent, embarrassing affliction sweeps Indian bedrooms, with men from all age groups and social classes desperately turning to doctors for cures.

By Madhu Jain, Subhadra Menon and Ramesh Vinayak

Lalit Bhasin is the kind of man most men envy. Just a year ago he would have thought so too. At 39, the suave, successful banker had a well-turned out wife and two precocious children, swung a mean club on the golf course. But a few months ago, things began to go wrong in the bedroom. The worst thing that could happen to a man happened to him: he became impotent. "It drove me nuts," confesses Bhasin. "I had money, but without my virility I was only half a man."

Leading Indian News Magazine:
One out of every 10 Indian males could be impotent!
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He didn't see a connection but whistle-stop work schedules and jetting round the globe chasing deals and dreams had sapped his sexual vitality. And so began a nightmarish odyssey: rounds of quacks and charlatans. It took Rs 25,000 and a great desperation before Bhasin finally summoned courage to seek medical help.

Bhasin's ordeal is not unique. In fact, it has become particularly common. The proverbial headache is getting to be the male preserve. One out of every 10 Indian males could be impotent, according to a survey of 1,500 men done in Delhi by the Alpha One Andrology Centre at Aashlok Hospital. "Impotence is a silent epidemic that is sweeping across the nation, the average victim being a middle-aged male otherwise healthy and successful," says the centre's director, urologist Vikram Sharma. Big city
Antidepressant medications: do they work?

Growing evidence of selective publication and publication bias in trials of antidepressant drugs

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Efthia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenkranz, Ph.D.

ABSTRACT

Evidence-based medicine is valuable to the extent that the evidence base is complete and unbiased. Selective publication of clinical trials — and the outcomes within those trials — can lead to unrealistic estimates of drug effectiveness and alter the apparent risk–benefit ratio.

METHODS

We obtained reviews from the Food and Drug Administration (FDA) for studies of 12 antidepressant agents involving 13,564 patients. We conducted a systematic literature search to identify matching publications. For trials that were reported in the literature, we compared the published outcomes with the FDA outcomes. We also compared the effect size derived from the published reports with the effect size derived from the entire FDA data set.

RESULTS

Among 74 FDA-registered studies, 32%, accounting for 2449 study participants, were not published. Whether and how the studies were published were associated with the study outcome. A total of 37 studies viewed by the FDA as having positive results were published; 1 study viewed as positive was not published. Studies viewed by the FDA as having negative or questionable results were, with 3 exceptions, either not published (22 studies) or published in a way that, in our opinion, conveyed a positive outcome (11 studies). According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive. Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and was 32% overall.

Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration

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ABSTRACT

Meta-analyses of antidepressant medications have reported only modest benefits over placebo treatment, and when unpublished trial data are included, the benefit falls below accepted criteria for clinical significance. Yet, the efficacy of the antidepressants may also depend on the severity of initial depression scores. The purpose of this analysis is to establish the relation of baseline severity and antidepressant efficacy using a relevant dataset of published and unpublished clinical trials.

Methods and Findings

We obtained data on all clinical trials submitted to the US Food and Drug Administration (FDA) for the licensing of the four new-generation antidepressants for which full datasets were available. We then used meta-analytic techniques to assess linear and quadratic effects of initial severity on improvement scores for drug and placebo groups and on drug-placebo difference scores. Drug-placebo differences increased as a function of initial severity, ranging from virtually no difference at moderate levels of initial severity to a relatively small difference for patients with very severe depression, reaching conventional criteria for clinical significance only for patients at the upper end of the very severely depressed category. Meta-regression analyses indicated that the relation of baseline severity and improvement was curvilinear in drug groups and showed a strong, negative linear component in placebo groups.

Conclusions

Drug-placebo differences in antidepressant efficacy increase as a function of baseline severity, but are relatively small even for severely depressed patients. The relationship between initial severity and antidepressant efficacy is attributable to decreased responsiveness to placebo among very severely depressed patients rather than to increased responsiveness to medication.
Antidepressant medications: do they work?

"I have countless examples of helping people with these medications. So I'm not ready to throw them out." - Psychiatrist

"Well, my personal experience has been that these pills have been extremely effective in the right patients," – Family Physician

So who is right - the authors of those two critical studies or the psychiatrists and GPs on the front lines?
Now lets define selection bias

- “Distortions that result from procedures used to select subjects and from factors that influence participation in the study.”

- “Error introduced when the study population does not represent the target population”
  - Delgado-Rodriguez et al. J Epidemiol Comm Health 2004

Defining feature:
- Selection bias occurs at:
  - the stage of recruitment of participants
  - and/or during the process of retaining them in the study
- Difficult to correct in the analysis, although one can do sensitivity analyses
Hierarchy of populations

**FIGURE 1.6**
Summary of how research works.
**The source population may be defined directly, as a matter of defining its membership criteria; or the definition may be indirect, as the *catchment population* of a defined way of identifying cases of the illness. The catchment population is, at any given time, the totality of those in the ‘were-would’ state of: were the illness now to occur, it would be ‘caught’ by that case identification scheme [Source: Miettinen OS, 2007]**
Sampling of populations

Example: Nurses Health Study

Source population: registered nurses in the US?

Target (external) population: all women in the US? all women?

Study participants: eligible nurses were enrolled in the cohort if they responded to the baseline questionnaire (122,000 out of 170,000 nurses responded)

Eligible population: Married, registered nurses who were aged 30 to 55 in 1976, who lived in the 11 most populous states and whose nursing boards agreed to supply the study with their members' names and addresses.

Example: Nurses Health Study

Source population: registered nurses in the US?
Research question: What is the prevalence of HIV among IV drug users in the US?

Target population: IV drug users in the US

Source population: IV drug users seen at hospitals, clinics, and other healthcare facilities in the US

Eligible population: A random sample of adult IV drug users seen at 9 randomly selected hospitals and clinics during 12 consecutive months

Study participants: those who are eligible and agree to participate and get HIV testing

Selection bias can impact both internal and external validity
Warning: terminology is highly inconsistent! Focus on the concepts, not words!!
Selection probabilities (also known as ‘sampling fractions’)

\[ \alpha = \frac{\mathcal{A}^0}{\mathcal{A}} \quad \beta = \frac{\mathcal{B}^0}{\mathcal{B}} \]

\[ \gamma = \frac{\mathcal{C}^0}{\mathcal{C}} \quad \delta = \frac{\mathcal{D}^0}{\mathcal{D}} \]
Selection probabilities

Note: No selection bias if the cross product of $\alpha, \beta, \gamma, \delta = 1$
Selection bias occurs when selection probabilities are influenced by exposure or disease status.
Unbiased Sampling

Diseased

Exposed

REFERENCE POPULATION
(source pop)

STUDY SAMPLE

Sampling fractions appear similar for all 4 cells in the 2 x 2 table.
Biased sampling

Exposed and diseased group has a lower probability of being included in the study: this leads to imbalance and bias.
Selection bias in randomized controlled trials

**Sources:**

- **During randomization (at time $t_0$)**
  - Subversion of randomization due to inadequate concealment of allocation

- **After randomization (during follow up; after time $t_0$)**
  - Attrition***
    - Withdrawals
    - Loss to follow-up
    - Competing risks
    - Protocol violations and “contamination”

***Also seen in all cohort designs
Selection bias in randomized controlled trials

**Examples:**

- Bias due to lack of allocation concealment
  - RCT on thrombolysis with alternating day allocation
  - RCT comparing open versus laparoscopic appendectomy

- Bias due to attrition
  - RCT comparing medical versus surgical management of cerebrovascular disease

A prospective randomized trial comparing laparoscopic appendectomy with open appendectomy in patients with a diagnosis of acute appendicitis was conducted between October 1992 and April 1994. Of the 158 patients randomized, 7 patients were excluded because of protocol violations (conversion to laparotomy in 4, appendix not removed in 3). The 151 patients randomized to either a laparoscopic (n = 79) or an open appendectomy (n = 72) showed no difference in sex, age, American Society of Anesthesiology (ASA) rating, or previous abdominal surgery. The histologic classification of normal, catarrhal, inflamed, suppurative, and gangrenous appendicitis was not different between the two groups. Conversion from laparoscopic to open appendectomy was necessary in seven patients (9%) who had advanced forms of appendiceal inflammation. When compared to open appendectomy the laparoscopic group had a longer median operating time (63 minutes versus 40 minutes), fewer wound infections (2% versus 11%), less requirement for narcotic analgesia, and an earlier return to normal activity (median 7 days versus 14 days). There was no difference in morbidity, and both groups had a median time to discharge of 3 days. Laparoscopic appendectomy is as safe as open appendectomy; and despite the longer operating time, the advantages such as fewer wound infections and earlier return to normal activity make it a worthwhile alternative for patients with a clinical diagnosis of acute appendicitis.
The trial ran smoothly during the day. At night, however, the attending surgeon's presence was required for the laparoscopic procedure but not the open one; and the limited operating room availability made the longer laparoscopic procedure an annoyance.

Reluctant to call in a consultant, and particularly reluctant with specific senior colleagues, the residents sometimes adopted a practical solution. When an eligible patient appeared, the residents checked the attending staff and the lineup for the operating room and, depending on the personality of the attending surgeon and the length of the lineup, held the translucent envelopes containing orders up to the light. As soon as they found one that dictated an open procedure, they opened that envelope. The first eligible patient in the morning would then be allocated to a laparoscopic appendectomy group according to the passed-over envelope.

If patients who presented at night were sicker than those who presented during the day, the residents' behavior would bias the results against the open procedure.

This story demonstrates that if those making the decision about patient eligibility are aware of the arm of the study to which the patient will be allocated --if randomization is unconcealed (unblinded or unmasked)-- they may systematically enroll sicker-- or less sick-- patients to either treatment or control groups.

This behavior will defeat the purpose of randomization and the study will yield a biased result.

Careful investigators will ensure that randomization is concealed, for example, through (a) preparation of blinded medication in a pharmacy, (b) remote randomization, in which the individual recruiting the patient makes a call to a methods center to discover the arm of the study to which the patient is allocated, or (c) ensuring that the envelope containing the code is sealed (sealed, opaque envelope).
Selection bias after randomization (handled by intention-to-treat analysis)

Aspirin alone
- N=100
- 10 strokes

Aspirin plus surgery
- N=100
- 10 strokes

Surgery

1 mon
- 10 strokes
- 10 strokes

12 mon
- CI = 10/90
  - 11%
- CI = 20/100
  - 20%

Selection bias in cohort studies

- **Sources:**
  - Bias due to a non-representative “unexposed” group
    - Key question: aside from the exposure status, are the exposed and unexposed groups comparable?
      - Has the unexposed population done its job, i.e. generated disease rates that approximate those that would have been found in the exposed population had they lacked exposure (i.e. counterfactual)?
  - Bias due to non-response
    - More likely if non-response is linked to exposure status (e.g. smokers less likely to respond in a study on smoking and cancer)
  - Bias due to attrition (withdrawals and loss to follow up)
    - Bias will occur if loss to follow-up results in risk for disease in the exposed and/or unexposed groups that are different in the final sample than in the original cohort that was enrolled
    - Bias will occur if those who adhere have a different disease risk than those who drop out or do not adhere (‘compliance bias’)

Healthy User and Healthy Continuer Bias: HRT and CHD

- HRT was shown to reduce coronary heart disease (CHD) in women in several observational studies.
- Subsequently, RCTs showed that HRT might actually increase the risk of heart disease in women.
- What can possibly explain the discrepancy between observational and interventional studies?
  - Women on HRT in observational studies were more health conscious, thinner, and more physically active, and they had a higher socioeconomic status and better access to health care than women who are not on HRT.
  - Self-selection of women into the HRT user group could have generated uncontrollable confounding and lead to "healthy-user bias" in observational studies.
  - Also, individuals who adhere to medication have been found to be healthier than those who do not, which could produce a "compliance bias" [healthy user bias].

For a more in-depth analysis of this case study, see B-File #1
Selection bias in cohort studies

Other examples:
- Bias in using the general population as a comparison group for occupational cohorts
- Bias due to differential drop-out rates among exposed and unexposed
  - E.g. cohort study on progression to AIDS
- Bias when the analysis is restricted to individuals with complete follow-up
  - E.g. cohort studies on smoking and dementia
Example: Cohort study of progression to AIDS: IV drug users (IDU) vs homosexual men

- In general, getting sicker is a common reason for loss to follow-up.
- Therefore, persons who are lost to follow-up have different AIDS incidence than those who remain (i.e., informative censoring).
- In general, IDU more likely to be lost to follow-up - at any given level of feeling sick.
- Therefore, the degree of informative censoring differs across exposure groups (IDU vs homosexual men).
- Results in selection bias: underestimates the incidence of AIDS in IDU relative to homosexual men.
Selection Bias: Cohort Studies

Effect of informative censoring in IDU group

Effect of informative censoring in homosexual male group

Survival assuming no informative censoring and no difference between IDU and homosexual men

IDU who are sick are likely to be lost during follow-up. Those who remain are likely to have a better prognosis.
Selection Bias: Cohort Studies

Example: Cohort studies of smoking and dementia:

Cigarette Smoking and Dementia

Potential Selection Bias in the Elderly

Miguel A. Hernán, Alvaro Alonso, and Giancarlo Logroscino

Abstract: We conducted a systematic review of published prospective studies that estimated the association between smoking and the incidence of Alzheimer disease and dementia. The relative rate for smokers versus nonsmokers ranged from 0.27 to 2.72 for Alzheimer disease (12 studies) and from 0.38 to 1.42 for dementia (6 studies). The minimum age at entry (range: 55–75 years) explained much of the between-study heterogeneity in relative rates. We conjecture that selection bias due to censoring by death may be the main explanation for the reversal of the relative rate with increasing age.

(Epidemiology 2008;19: 448–450)
Selection Bias: Cohort Studies

- Smoking harmful in studies that enrolled younger subjects, and appeared protective in studies that enrolled the oldest subjects.

Two possible explanations:

- First, the effect of cigarette smoking on the risk of dementia is modified by age: smoking harmful at younger ages, beneficial at older ages.

- Second, the effect of cigarette smoking is harmful overall but appears beneficial at older ages because of selection bias, eg, most smokers who are susceptible to developing dementia due to their smoking do so by age 75, and thus the group of 75-year-olds without dementia at baseline is depleted of susceptible smokers.

FIGURE 2. Log RR of dementia by the minimum age at baseline in the study. The area of the circle is proportional to the precision (1/variance) of the log RR estimate.
Selection bias in case-control studies

- Sources:
  - Bias in selection of cases
    - Cases are not derived from a well defined study base (or source population)
  - Bias in selection of controls
    - Controls should provide an unbiased sample of the exposure distribution in the study base
    - Control selection is a more important issue than case selection!
Selection bias in case-control studies

Examples:

- Bias due to control selection:
  - Case-control study tampons and toxic shock syndrome (Reingold AL et al. Rev Infect Dis. 1989 Jan-Feb;11 Suppl 1:S35-41)
  - Bias due to selection of hospital controls
Selection bias in case-control studies

- Risk factors for menstrual toxic shock syndrome: results of a multistate case-control study.

For assessment of current risk factors for developing toxic shock syndrome (TSS) during menstruation, a case-control study was performed.

- Cases with onset between 1 January 1986 and 30 June 1987 were ascertained in six study areas with active surveillance for TSS.

- Age-matched controls were selected from among each patient's friends and women with the same telephone exchange.

- Of 118 eligible patients, 108 were enrolled, as were 185 "friend controls" and 187 telephone exchange-matched controls.

Reingold AL et al. Rev Infect Dis. 1989 Jan-Feb;11 Suppl 1:S35-41
Selection bias in case-control studies

- Risk factors for menstrual toxic shock syndrome: results of a multistate case-control study

- Results for tampon use as a risk factor:
  - OR when both control groups were combined = 29
  - OR when friend controls were used = 19
  - OR when neighborhood controls were used = 48

- Why did use of friend controls produce a lower OR?
  - Friend controls were more likely to have used tampons than were neighborhood controls (71% vs. 60%)

Reingold AL et al. Rev Infect Dis. 1989 Jan-Feb;11 Suppl 1:S35-41
### Direction of bias

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>No</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

If cases and controls share similar exposures (e.g. friend controls), then $a$ and $b$ will tend to be nearly the same -- this will bias the OR towards 1 (towards null).

$$\text{OR} = \frac{ad}{bc}$$
In general, use of partners/spouses or friends as controls can result in bias.
Controls in this study were selected from a group of patients hospitalized by the same physicians who had diagnosed and hospitalized the cases' disease. The idea was to make the selection process of cases and controls similar. It was also logistically easier to get controls using this method. However, as the exposure factor was coffee drinking, it turned out that patients seen by the physicians who diagnosed pancreatic cancer often had gastrointestinal disorders and were thus advised not to drink coffee (or had chosen to reduce coffee drinking by themselves). So, this led to the selection of controls with higher prevalence of gastrointestinal disorders, and these controls had an unusually low odds of exposure (coffee intake). These in turn may have led to a spurious positive association between coffee intake and pancreatic cancer that could not be subsequently confirmed.
Case-control Study of Coffee and Pancreatic Cancer: Selection Bias

Potential bias due to inclusion of controls with over-representation of GI disorders (which, in turn, under-estimated coffee drinking in controls)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>No cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>coffee</td>
<td></td>
</tr>
<tr>
<td>no coffee</td>
<td></td>
</tr>
</tbody>
</table>

SOURCE POPULATION

STUDY SAMPLE
### Direction of bias

<table>
<thead>
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<th>Case</th>
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</tr>
</thead>
<tbody>
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</tr>
<tr>
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<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

If controls have an unusually low prevalence of exposure, then b will tend to be small -- this will bias the OR away from 1 (over-estimate the OR)

\[
\text{OR} = \frac{ad}{bc}
\]
Coffee and cancer of the pancreas: Use of population-based controls

• Gold et al. *Cancer* 1985

<table>
<thead>
<tr>
<th>Coffee:</th>
<th>Case Control</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 1$ cup/day</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>No coffee</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

OR = (84/10) / (82/14) = 1.4 (95% CI, 0.55 - 3.8)

So, when population-based controls were used, there was no strong association between coffee and pancreatic cancer.
For a more in-depth analysis of this case study, see B-File #2
Bias due to selection of hospital controls

- Example:
  - In a case-control study of smoking and chronic obstructive pulmonary disease (COPD), controls were selected from the same hospital with other lung diseases (e.g. tuberculosis, lung cancer, occupational lung diseases).
  - The authors found a weak association between smoking and COPD
  - What is the problem with this study??

  - Smoking causes many diseases resulting in higher hospitalization rate of smokers
  - Hospital controls do not represent the prevalence of exposure (smoking) in the source population from which cases of COPD arose
  - Also, hospitalized people tend to have multiple diseases, and this can result in the distortion of the exposure frequencies in hospitalized controls (Berkson’s bias)
### Direction of bias due to hospitalized controls

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>No</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

If controls have an unusually high prevalence of exposure, then b will tend to be large -- this will bias the OR towards 1 (under-estimate the OR)
Selection bias in cross-sectional studies

- Sources:
  - Bias due to sampling
    - Selection of “survivors” or “prevalent” cases
    - Non-random sampling schemes
    - Volunteer bias
    - Membership bias
  - Bias due to non-participation
    - Non-response bias
Descriptive Study: Unbiased Sampling

Sampling fraction is equal for all, or at least known

REFERENCE/
TARGET/
SOURCE
POPULATION

STUDY SAMPLE
Descriptive Study: Biased sampling

Some subjects have a higher probability of being included in the study sample.
Selection bias in sample surveys

1. Sampling frame bias

3. Non-coverage bias

2. Non-random sampling bias
Selection bias in telephone surveys

Table 1  Continuing and emerging challenges for telephone survey research

<table>
<thead>
<tr>
<th>Ongoing challenges</th>
<th>New and emerging challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selecting participants</td>
<td></td>
</tr>
<tr>
<td>Sampling</td>
<td>Cell phone sampling</td>
</tr>
<tr>
<td>Telephone coverage</td>
<td>Number portability</td>
</tr>
<tr>
<td>Response rates</td>
<td>Answering machines</td>
</tr>
<tr>
<td>Participation rates</td>
<td>Caller ID</td>
</tr>
<tr>
<td>Call scheduling</td>
<td>Privacy managers and call blocking</td>
</tr>
<tr>
<td>Collecting information</td>
<td></td>
</tr>
<tr>
<td>Reliable and valid responses</td>
<td>Privacy and confidentiality</td>
</tr>
<tr>
<td>Mode effects</td>
<td>Respondent burden</td>
</tr>
</tbody>
</table>

Figure 1
Steps in the selection of participants in telephone surveys.
Selection bias in cross-sectional studies

- Examples:
  - Bias due to sampling:
    - Healthy worker effect (or bias): survey on occupational lung disease (silicosis among stone quarry workers)
    - Volunteer bias: bias in screening programs (e.g. leukemia among nuclear test observers)
  - Non-response bias
    - Survey on prevalence of self-reported diabetes (Pai et al. 1999)
  - Survivor bias
    - Study to determine neurological status of patients who had survived after CPR in a hospital in India (Rajagopalan et al, 1999)
Example: Study on mental health disorders among marines deployed to combat

- Research studies have identified heightened psychiatric problems among veterans of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF).
- Study done to determine incidence rates of diagnosed mental disorders in a cohort of Marines deployed to combat during OIF or OEF in 2001–2005 and to compare these with mental disorder rates in two historical and two contemporary military control groups.
- All psychiatric conditions except post-traumatic stress disorder occurred at a lower rate in combat-deployed personnel than in personnel who were not deployed to a combat zone.
Research studies have identified heightened psychiatric problems among veterans of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF). However, these studies have not compared incidence rates of psychiatric disorders across robust cohorts, nor have they documented psychiatric problems prior to combat exposure. The authors’ objectives in this study were to determine incidence rates of diagnosed mental disorders in a cohort of Marines deployed to combat during OIF or OEF in 2001–2005 and to compare these with mental disorder rates in two historical and two contemporary military control groups. After exclusion of persons who had been deployed to a combat zone with a preexisting psychiatric diagnosis, the cumulative rate of post-OIF/OEF mental disorders was 6.4%. All psychiatric conditions except post-traumatic stress disorder occurred at a lower rate in combat-deployed personnel than in personnel who were not deployed to a combat zone. The findings suggest that psychiatric disorders in Marines are diagnosed most frequently during the initial months of recruit training rather than after combat deployment. The disproportionate loss of psychologically unfit personnel early in training creates a “healthy warrior effect,” because only those persons who have proven their resilience during training remain eligible for combat.
Bias due to non-response

- Survey to estimate prevalence of self-reported chronic diseases in a city in India (Pai et al, 1999)
  - 705 adults were interviewed (of an eligible population of 808)
    - 29.1% had been told (by a doctor or health professional) that they had hypertension
- Proxy data was obtained for 32 of the non-responders [who could never be contacted, despite repeated attempts]
  - 45.8% of non-responders had self reported hypertension
  - If these people had been included, the overall prevalence would have been higher

<table>
<thead>
<tr>
<th>Prevalence of self-reported hypertension</th>
<th>Responders n=705</th>
<th>Non-responders n=32</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29.1%</td>
<td>45.8%</td>
</tr>
</tbody>
</table>
Leukemia Incidence Among Observers of a Nuclear Bomb Test (Volunteer bias)

Caldwell GG et al. *JAMA* 1980

- Smokey Atomic Test in Nevada
- 76% of troops at site was later found; occurrence of leukemia determined

82% contacted by the investigators

18% contacted the investigators on their own

4.4 greater risk of leukemia than those contacted by the investigators
More on selection probabilities

Suppose in a study of asbestos exposure and lung cancer the exposure is distributed among the cases and controls in the target population as follows:

<table>
<thead>
<tr>
<th></th>
<th>Diseased</th>
<th>Nondiseased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>Unexposed</td>
<td>100</td>
<td>400</td>
</tr>
</tbody>
</table>

The true OR in the target population is $(100 \times 400) / (100 \times 200) = 2.0$. 
More on selection probabilities

If the selection probabilities for all the cells in the table are equal at 90%, the 2x2 table of selection probabilities would look like the following.

<table>
<thead>
<tr>
<th></th>
<th>Diseased</th>
<th>Nondiseased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>=90%</td>
<td>=90%</td>
</tr>
<tr>
<td>Unexposed</td>
<td>=90%</td>
<td>=90%</td>
</tr>
</tbody>
</table>

This cross-product is called Selection bias factor

And the 2x2 table of individuals in the case-control study will look like the following.

<table>
<thead>
<tr>
<th></th>
<th>Diseased</th>
<th>Nondiseased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>100 x .90=90</td>
<td>200 x .90=180</td>
</tr>
<tr>
<td>Unexposed</td>
<td>100 x .90=90</td>
<td>400 x .90=360</td>
</tr>
</tbody>
</table>

OR = (90 x 360) / (90 x 180) = 2.0

Is there selection bias?
More on selection probabilities

If the selection probabilities are unequal, but still proportional (that is, alpha / beta = gamma / delta), we still do not observe any selection bias in our study. If the selection probability is 90% among the diseased individuals and the selection probability is 70% among the nondiseased individuals the resulting 2x2 table would look like the following.

\[
\begin{array}{|c|c|}
\hline
 & \text{Diseased} & \text{Nondiseased} \\
\hline
\text{Exposed} & 100 \times 0.90=90 & 200 \times 0.70=140 \\
\text{Unexposed} & 100 \times 0.90=90 & 400 \times 0.70=280 \\
\hline
\end{array}
\]

\[
\text{OR} = \frac{(90 \times 280)}{(90 \times 140)} = 2.0
\]

Within cases and controls, the exposure odds is maintained

Is there selection bias?
More on selection probabilities

If however the selection probabilities are unequal, and also nonproportional, then selection bias will occur. The following table shows how selection bias occurs when the selection probability for the unexposed controls is different than that of the other three groups of study members.

<table>
<thead>
<tr>
<th></th>
<th>Diseased</th>
<th>Nondiseased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>100 x .90=90</td>
<td>200 x .90=180</td>
</tr>
<tr>
<td>Unexposed</td>
<td>100 x .90=90</td>
<td>400 x .70=280</td>
</tr>
</tbody>
</table>

\[ \text{OR} = \frac{(90 \times 280)}{(90 \times 180)} = 1.6 \]

Within cases, the exposure odds is maintained.
Within controls, the exposure odds is distorted.

Is there selection bias?
Can selection bias be “fixed”?  

- Not easy  
  - Best avoided at the design stage; can try hard to retain participants in the study  
- Can collect data to ‘estimate’ magnitude/direction of selection bias and do sensitivity analysis  
  - e.g., collect data from a sample of non-respondents, and use this to do sensitivity analysis  
- Effect estimates can be ‘adjusted’ if selection probabilities are known  
  - Good sources: Kleinbaum’s ActivEpi book/CD & new book on bias analysis by Lash et al.

To adjust, we need selection probabilities. But how do we get them??
A tool for deterministic and probabilistic sensitivity analysis of epidemiologic studies

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Stockholm, Sweden

Sander Greenland  
Departments of Epidemiology and Statistics  
University of California, Los Angeles  
Los Angeles, CA
Book on bias analysis (sensitivity analysis)

Applying Quantitative Bias Analysis to Epidemiologic Data
Springer, 2009
Lash, Timothy L., Fox, Matthew P., Fink, Aliza K.

Includes SAS codes for programs
Readings this week

- Rothman: Chapter 5: Biases in Study Design
- Gordis:
  - Chapter 14: From Association to Causation
  - Chapter 15: More on Causal Inferences: Bias, Confounding, and Interaction
- Article:
  - ERIC Notebook handout on Selection Bias, UNC
An Introduction to QUANTUM Gradnamics

Although Quantum Gradnamics explains many of the phenomena in pursuing a Ph.D., most aspiring scientists still object to such an uncertain and probabilistic description of academic reality.

The Austrian scientist Erwin Schrödinger was particularly uncomfortable not knowing whether he would ever graduate or not, and illustrated this with his now famous thought experiment known as “Schrödinger’s Cubicle.”

According to the experiment, grad students exist in a state of both productivity and unproductivity (many students do report feeling like...)

Schrödinger’s Cubicle

...they’re in limbo the whole time). Only direct intervention reveals whether or not an enormous amount of time has been wasted, a phenomenon known as “expectation collapse”.

Einstein was also uncomfortable with this indeterminate view of academia and openly disagreed with the Copenhagen Interpretation, which states that graduation is an entirely random process. In deciding whether or not to graduate a student, Einstein famously said, “Professors don’t throw dice (do they)?”

More recent theories describe grad students as soggy strings of ramen noodles, which is just as useful.

(Thanks to Wikipedia for all the background info)

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An Introduction to QUANTUM Gradnamics

Another principal concept in Quantum Gradnamics is the observation that graduate students do not move toward graduation in a steady and continuous manner. Rather, they make progress through discrete bursts of random productivity called “wants” (short for “want data”) whose energy is proportional to the frequency of meetings with their advisor.

Grad students, or “p-ons” as Einstein called them, can only occupy a discrete number of energy states:

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A direct consequence of this is the “Heisenberg Uncertainty Principle”, perhaps the most well-known theorem of Quantum Gradnamics. Developed by Heisenberg during a particularly unproductive period in his graduate career, the principle states that it is not possible to know where a grad student is and where it is going at the same time:

Heisenberg attributed this to the fact that meetings with professors are non-commu-nicative (that is, the order in which orders are given doesn’t tell you whether they are worth doing).