Polytechnic University of Catalunya

To reduce the dozens of catalog biases to a few units

Nan

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横看成岭侧成峰
(It's a range viewed in face and peaks viewed from the side)
远近高低各不同
(Assuming different shapes viewed from far and wide)
不识庐山真面目
(Of Mountain Lu we cannot make out the true face)
只缘身在此山中
(For we are lost in the heart of the very place)

苏东坡Su Dongpo(1037–1101)

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1 Abstract

There is no official list of medical research biases to refer to. As a consequence, a number of these terms are used differently by different people. I have included competing definitions wherever I found them. In view of so many arguments, I put these bias into three broad categories. Some of the classifications may be far-fetched, but in practical applications, these classifications are convenient for understanding and solving subsequent problem. Some biases are actually not statistical biases, and some are fundamentally of human nature. Classifications can reduce confusion in this area.

2 Introduction

2.1 Definitions of Bias

According to Wikipedia, those conceptions of bias are quite different in social sciences and Mathematics. In social science, it may be an inclination towards something, or a predisposition, partiality, prejudice, preference, or predilection. But in science and engineering, a bias(statistical) is a systematic error. Statistical bias results from an unfair sampling of a population, or from an estimation process that does not give accurate results on average.Statistical bias is a systematic tendency in the process of data collection, which results in lopsided, misleading results. This can occur in any of a number of ways, in the way the sample is selected, or in the way data are collected.

It is a property of a statistical technique or of its results whereby the expected value of the results differs from the true underlying quantitative parameter being estimated.

2.2 Bias in Statistics and Clinical Trials

The first time I came into contact with the concept of bias was "bias of estimator" in statistical inference. In statistics, the bias of an estimator is the difference between this estimator's expected value and the true value of the parameter being estimated. An estimator or decision rule with zero bias is called unbiased. In statistics, "bias" is an objective property of an estimator. Bias can also be measured with respect to the median, rather than the mean (expected value). Statistical bias is a feature of a statistical technique or of its results whereby the expected value of the results differs from the true underlying quantitative parameter being estimated. The bias of an estimator of a parameter should not be confused with its degree of precision as the degree of precision is a measure of the sampling error. Mathematically bias can be defined as:

Let $\mathbf{T}$ be a statistic used to estimate a parameter θ. If

$$E(T) = \theta + bias(\theta)$$

then $bias(\theta)$ is called "the bias of the statistic $\mathbf{T}$", where $E(\mathbf{T})$ represents the expected value of the statistics $\mathbf{T}$. If $bias(\theta) = 0$, then $E(\mathbf{T}) = \theta$. So, $\mathbf{T}$ is an unbiased estimator of the true parameter, say θ .

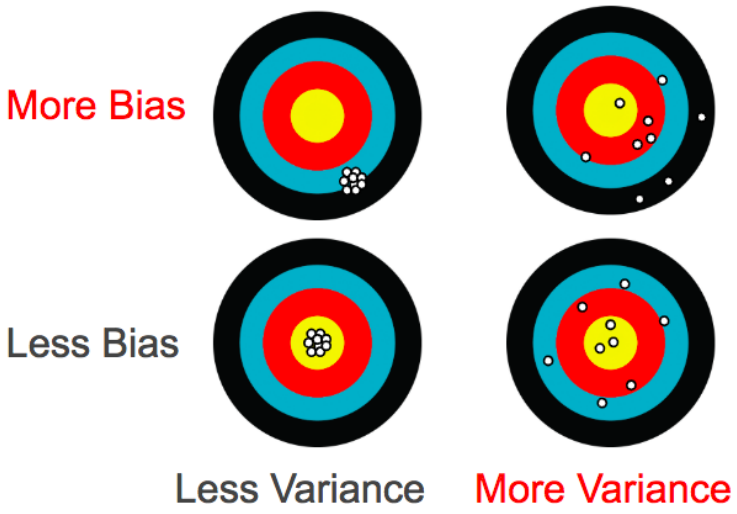

Figure 1: Statistical Bias

All else being equal, an unbiased estimator is preferable to a biased estimator, although in practice, biased estimators (with generally small bias) are frequently used. When a biased estimator is used, bounds of the bias are calculated. A biased estimator may be used for various reasons.

A bias in clinical is any factor that leads to conclusions that are systematically different from the truth. Bias is universal. Some study designs are better than others, but there is no perfect study. Although in general parlance "bias" has moral or ethical implications, research bias does not refer to the researcher's character, just the validity of the study.

Bias is not something that can be accounted for with statistics. Larger sample sizes will can create more precision, but that doesn't help if the numbers aren't accurate. Ideally, we want to see research that is both precise and accurate, but I would take accurate over precise any day. I really believe that most types of research bias are actually quite easy to understand.

2.3 Bias in some other Humanistic and Social Science

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For many humanities, bias is an inclination toward something, or a predisposition, partiality, prejudice, preference or predilection. It is difficult to define whether it is perceptual or rational. It is often associated with the word "prejudice" or "stereotype". Bias is mainly due to the fact that people build subjective social reality based on subjective feelings rather than objective information.

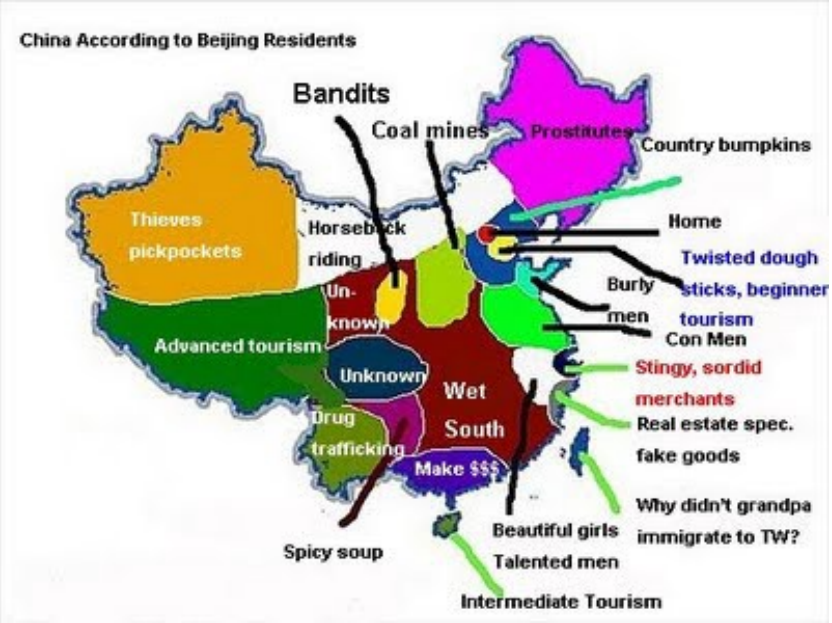

Figure 2: Prejudice to China According to Residents of Pekin

Bias can lead to distortion of perception, inaccurate judgment, illogical interpretation, or various results collectively referred to as "irrational". Some cognitive biases are widely accepted. Biases can often save thinking time and make actions more efficient, so they are sometimes referred to as Genius, but other biases are built-in limitations of people's thinking systems. , It is easy to cause inappropriate psychological reactions and thoughts.

I am not going to make a deep analysis of bias in humanities subjects, but here is an important thing that may happen during clinical research–the bias caused by the subjective assumptions of researchers. As a clinical trial researcher, this conscious or unconscious error has a great impact on the correctness of the research results. To some extent, it may be a moral or ethical problem. I categorize related types of bias as "doing silly thing" (see below). How to avoid these types of prejudice is not only an experimental scientific problem, but more related to the category of human nature or psychology.

3 Summary and conclusions of previous studies — an essential website

To better understand the persistent presence, diversity, and impact of biases, the CEBM are compiling a Catalogue of Bias(https://catalogofbias.org/),

stemming from original work by David Sackett. The entries are a work in progress and describe a wide range of biases – outlining their potential impact in research studies.

Sackett recognized the importance of bias in research. His 1979 paper "Bias in Analytic Research", published in the Journal of Chronic Diseases, reported the first draft of a catalog of biases which may distort the design, execution, analysis, and interpretation of research.' Sackett cataloged 35 biases that arise in sampling and measurement, in the context of clinical trials, and listed 56 biases potentially affecting case-control and cohort studies.

The Collaboration meets regularly to develop and refine the contents of the Catalog and in between work on updating content. If readers are interested in learning more about various bias, you can go to this website. During the collection and sorting period, I have also visited the personal websites or academic achievements (papers, etc.) of the editors, associate editors and other authors of this website, which was very helpful for in-depth understanding of bias and subsequent classification work.

In addition, I also found another similar website(https://first10em.com/bias/) in the process of accessing information and obtaining data. The editor of this website is also based on Sackett's research, supplementing and improving the bias in clinical trials. Its website is clearly organized and has several more sub-categories than catalogofbias.org. Also if readers are interested, you can go for browsing.

4 Summary of classification

In my opinion I classified those into 3 groups as:

- Confusion of Effects
- Generalized Selection bias
- Silliness

In the selection of study subjects, the establishment (inclusion criteria) of the experimental group and the control group was incorrect, which caused the two groups to have significant differences other than the processing factors at the beginning, resulting in selection bias. Here are some classical selection biases such as attrition bias, non-response bias, survival bias and so on.

Besides, we found that There are differences in frequency and/or intensity when observing or measuring the observation group and the control group, which makes the final judgment result biased. In the unblinded observation, because the observer knows who are in the observation group and who are in

the control group, this kind of bias is more likely to occur. When confounding (confusion) factors exist, a certain factor may be mistakenly regarded as the cause of a certain result when analyzing the results. That is, there is confounding. Confounding makes the research conclusions unable to reflect the true causal link. These kind of bias are often caused by the researcher's professional knowledge limitation, ignorance of the existence of confounding, or even though he knows it, but ignoring its existence. Confounding is often revealed during the data analysis stage.

The rest of biases seem to be comical because the results didn't depend on methods or experiments, but humanity. As we could not eliminate them all completely, we need to try to optimize the professionalism of scientific researchers and try to dilute the impact of human nature on scientific research.

5 Confusion of Effects

Confusion of Effects is one of several threats to the internal validity of a research study because when we establish relationships of causes and effects, internal validity represents the truthfulness of conclusions about causal relationships. Internal validity means that a true cause-and-effect relationship exists between an exposure (the cause) and outcome (the effect) variable. Confusion of Effects is defined as a possible source of bias in studies in which an unmeasured third variable is related to the exposure of interest (although not causally) and causally related to the outcome of interest. Understanding confounding is critical in determining what inferences can be drawn from study findings. In statistics, a confounding variable is a variable that influences both the dependent variable and independent variable, causing a spurious association. The importance of confounding is that it suggests an association where none exists or masks a true association.

5.1 Channeling Bias

When an exposure appears to be associated with an outcome, the outcome may, in fact, be caused by the indication for which the exposure was used, or some factor associated with the indication. The apparent association between the exposure and the outcome is then said to be Channeling Bias, which is the true cause of the outcome. In some cases, the indication may mask the outcome. Channeling Bias is very common in observational studies (e.g. case-control and cohort studies). It can occur in relation to either beneficial outcomes or harmful outcomes and can result in either an increase or a reduction in the apparent risk of the outcome.

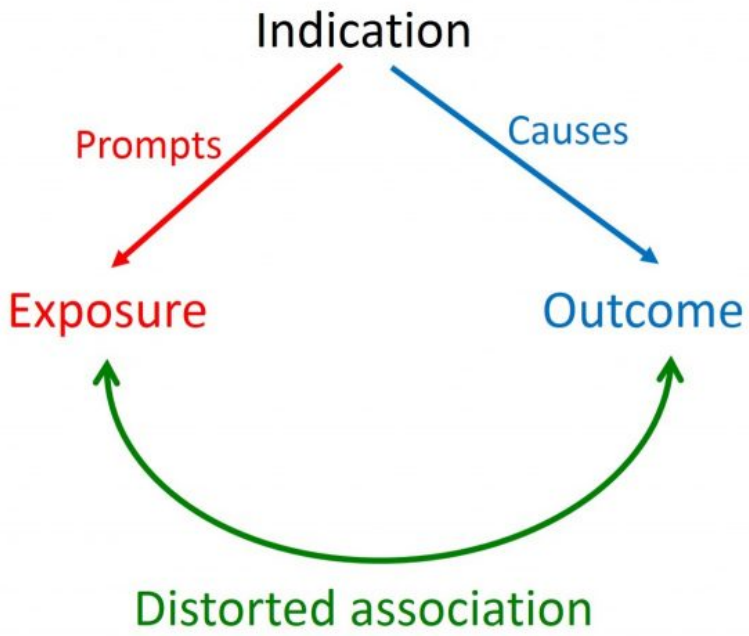

Figure 3: Confounding by Indication

An observational study suggested that children who had been given paracetamol were more likely to develop asthma, rhinoconjunctivitis, and eczema in later life; however, this result may have been confounded by an association between fever or infection and a later risk of asthma etc.

5.2 Information Bias

Information bias is a distortion in the measure of association caused by a lack of accurate measurements of key study variables. Information bias, also called measurement bias, arises when key study variables (exposure, health outcome, or confounders) are inaccurately measured or classified. Here are some types of bias that I classified them into information bias(broad term).

5.2.1 Apprehension Bias

The fact or process of investigation can result in measurements being different from the usual for a study participant. This can partly be due to behavioural change, as described in the Hawthorne effect, which can be to some extent a conscious response to being studied. In addition, this reaction

to being studied can result in altered physiological measurements, presumably largely unconsciously, and this can be termed apprehension bias.

A well-documented example of apprehension bias could be found in the measurement of hypertension. According to Cobos 2015, this was first described by Riva-Rocci in 1896. Patients could become anxious as a result of visiting their health professional. They may also become anxious at the thought of having their blood pressure taken before it has actually been taken. As a result, this could raise their blood pressure, giving a biased record of what their physiological blood pressure actually is.

5.2.2 Detection Bias

Detection bias refers to any systematic or non-random error that occurs in the collection of data in a study. Another broad term for this type of bias is "measurement bias".A test or treatment for a disease may perform differently according to some characteristic of the study participant, which itself may influence the likelihood of disease detection or the effectiveness of the treatment. Detection bias can occur in trials when groups differ in the way outcome information is collected or the way outcomes are verified.

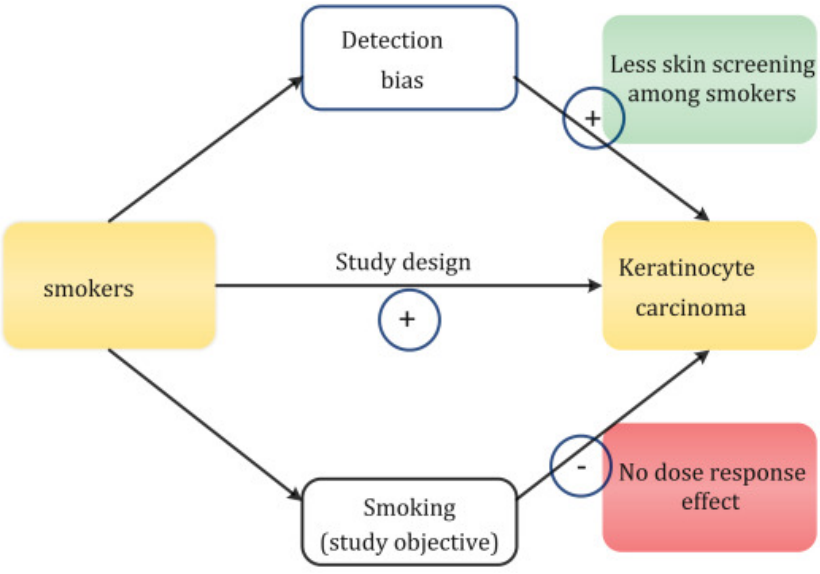

Figure 4: Detection Bias

An example is that larger men have bigger prostates, which makes diagnosing prostate cancer via biopsy more difficult (it is harder to hit the target). Therefore, men with larger prostates are less likely to be accurately

diagnosed with prostate cancer. Thus, a real association between obesity and prostate cancer risk may be underestimated. This was shown by researchers who found that obesity increased prostate cancer risk. Without accounting for the size of the prostate, however, the relationship between obesity and prostate cancer was under-estimated.(see below)

TABLE 3 Associations between body size and prostate cancer incidence before and after adjustment for prostate volume

	Baseline model[a] odds ratio (95%CI)	Baseline model with further adjustment for prostate volume[b] odds ratio (95%CI)
Body size		
Normal	1	1
Overweight	1.41 (1.01, 1.97)	1.52 (1.08, 2.14)
Obese	1.59 (1.09, 2.33)	1.77 (1.20, 2.62)
Prostate size (per 10 CC)	NA	0.92 (0.88, 0.97)

[a]Baseline model accounts for matching and adjusts for family history, PSA level, and number of PSA tests and DRE during follow-up.
[b]Model accounts for matching and adjusts for family history, PSA level, and number of PSA tests and DRE during follow-up and prostate volume.

Figure 5: Detection Bias 2

5.2.3 Hawthorne Effect(also called Attention Bias)

The Hawthorne effect occurs when people behave differently because they know they are being watched. It can affect all sorts of behaviours such as dietary habits, or hygiene practices because these have considerable opportunity for instantaneous modification. It can also affect study results, e.g. a survey of smoking by watching people during work breaks might lead to observing much lower smoking rates than is genuinely representative of the population under study. It can also contaminate an intervention study if one of the control groups changes its behaviour because it is being observed more frequently than the other.

The original Hawthorne study looked at changing the amount of light at the Hawthorne Works and its impact on working practices. However, the effect was also found in the field of clinical trials. A study of hand-washing among medical staff found that when the staff knew they were being watched,

compliance with hand-washing was 55% greater than when they were not being watched.

5.2.4 Insensitive-Measure Bias

Insensitive-measure bias occurs when the method or tool or test used to detect the outcome of interest lacks accuracy. In compiling his 1979 list of biases in research, David Sackett defined insensitive-measure bias as: "When outcome measures are incapable of detecting clinically significant changes or differences, Type II errors occur." A Type II error is one in which a true association is not detected and genuine differences between groups are missed. Porta's definition of Type II error: "The error of failing to reject a false test hypothesis; e.g., in null testing, declaring that a difference does not exist when in fact it does." Insensitive-measure bias can be considered a subtype of information bias or a measurement bias.

An example focusing on two common gynaecological cancers (ovarian and womb cancers): "Insensitive-measure bias would exist if non-gynaecologic oncologists inaccurately staged gynecologic cancers compared with gynecologic oncologists." To determine if insensitive-measure bias was affecting results obtained by using SEER data, they examined the rate of "staging violations" (errors in the assessment of the staging of tumours) in their data records, as recorded by oncologists specialising in gynaecological cancers and by oncologists not specialising in gynaecological cancers:

TABLE 2
Staging Accuracy (103 Cases)

	Major staging violations	95% Confidence interval	*P*
Gynecologic oncologists	0		
Nongynecologic oncologists	16 (22%)	15–29%	0.002
	Minor staging violations	**95% Confidence interval**	***P***
Gynecologic oncologists	4 (14%)	5–23%	
Nongynecologic oncologists	32 (42%)	32–52%	0.005

Figure 6: Insensitive-Measure Bias

The researchers concluded that the level of misclassification of tumour

stage was too high for the data to be used reliably to examine hypotheses about causes of cancer or prognosis, due to insensitive-measure bias.

5.2.5 Misclassification Bias

Misclassification bias occurs when a study participant is categorised into an incorrect category altering the observed association or research outcome of interest. Correct classification of individuals, and of exposures and participant characteristics, is an essential element of any study. Misclassification occurs when individuals are assigned to a different category than the one they should be in. This can lead to incorrect associations being observed between the assigned categories and the outcomes of interest.

For example, among healthy male never-smokers, misclassifications affecting the overweight category and the reference categories changed significantly the hazard ratio for overweight from 0.85 with measured data to 1.24 with self-reported data. Both the magnitude and direction of bias varied according to the hazard ratios with the measured data. Because of misclassification effects, self-reported weight and height could not reliably indicate the lowest-risk BMI category. Where an association between a category of body size and a health outcome is found, misclassification bias may have influenced that observation, sometimes increasing a risk estimate, sometimes decreasing it. This is important because understanding the relationship between obesity and underweight and health is a key factor in public health. The study also highlights that the underlying hazards influence the way that misclassification affects risk estimates in each study, and the necessity to understand misclassification bias within the specific group or population under study and its effect on outcomes.

5.2.6 Observer Bias

Parta's Dictionary of Epidemiology gives the following definition of Observer bias : "Systematic difference between a true value and the value actually observed due to observer variation" and continues to describe observer variation.

Many healthcare observations are open to systematic variation. For example, in the assessment of medical images, one observer might record an abnormality but another might not. Different observers might tend to round up or round down a measurement scale. Colour change tests can be interpreted differently by different observers. Where subjective judgement is part of the observation, there is great potential for variability between observers, and some of these differences might be systematic and lead to bias. Obser-

vation of objective data, such as death, is at much lower risk of observer bias. Biases in recording objective data may result from inadequate training in the use of measurement devices or data sources or unchecked bad habits. By recording subjective data, predispositions of the observer are likely to underpin observer biases. Observers might be somewhat conscious of their own biases about a study or may be unaware of factors influencing their decisions when recording study information.

5.2.7 Recall Bias

Recall bias is a systematic error that occurs when participants do not remember previous events or experiences accurately or omit details: the accuracy and volume of memories may be influenced by subsequent events and experiences. Recall bias is a problem in studies that use self-reporting, such as case-control studies and retrospective cohort studies.

Recall bias can increase or decrease the strength of the observed associations. For instance, when individuals recall lower than actual rates of unhealthy food intake, associations will suggest that lower levels of intake increase risk. When people recall higher than actual levels of fruit and vegetable intake (a desirable habit) a protective association will suggest eating more fruit and veg is necessary to reduce disease risk.

In the early 2000s, there was considerable publicity arising from a claim that the measles, mumps and rubella (MMR) vaccine was related to and possibly caused autism in children (the originating claim was subsequently found to be based on fraudulent data and the publication was withdrawn) (Andrews 2002). Researchers found that parents of autistic children diagnosed after the publicity tended to recall the start of autism as being soon after the MMR jab more often than parents of similar children who were diagnosed prior to the publicity.

5.3 Immortal Time Bias

"Immortal time" is when participants of a cohort study cannot experience the outcome during some period of follow-up time. When immortal time is misclassified or excluded during analysis, immortal time bias leads to a biased association. This usually happens when researchers assign participants to treated or exposed groups by using information that is observed after the participant enters the study (after time-zero). This is common in pharmacoepidemiological studies where there is a delay in classifying participants as 'treated' until they fill their first prescription some time after entering

the study. Because these participants must have survived (be alive or event-free) the time between entering the cohort and filling their first prescription, they are considered 'immortal' and contribute 'immortal time' to the treated group by design. Bias is introduced when this period of 'immortality' is misclassified or excluded during analysis, resulting in a distortion of observed effects in favour of the treatment (or exposure) under study by conferring a spurious survival advantage to the treated (or exposed) group (see picture below).

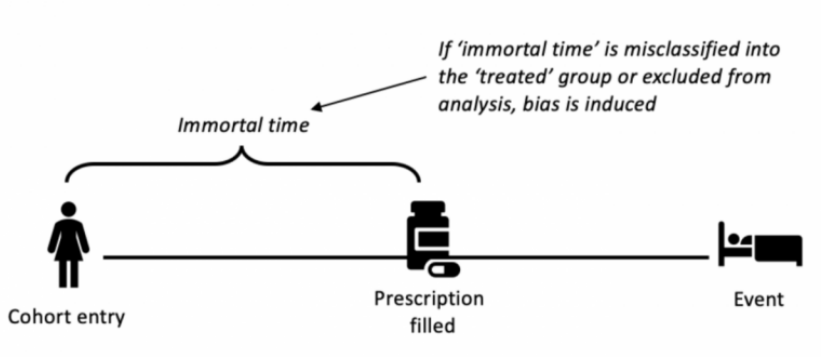

Figure 7: Immortal Time Bias

To highlight one example, several observational studies reported that inhaled corticosteroids could effectively prevent readmission and mortality in patients previously hospitalised with COPD. In the original studies, immortal time bias was introduced because participants entered the cohort on the day they were discharged and were then assigned to the treated group if they filled a prescription for a corticosteroid within the first 90 days from discharge. By design, participants allocated to the treated group could not have died or been readmitted between the time of entering the cohort and the time of filling their first prescription. In effect, they contributed 'immortal time' to the treated group. The original studies misclassified this immortal person-time to the treated group (rather than the untreated group) and immortal time bias was induced (see below).

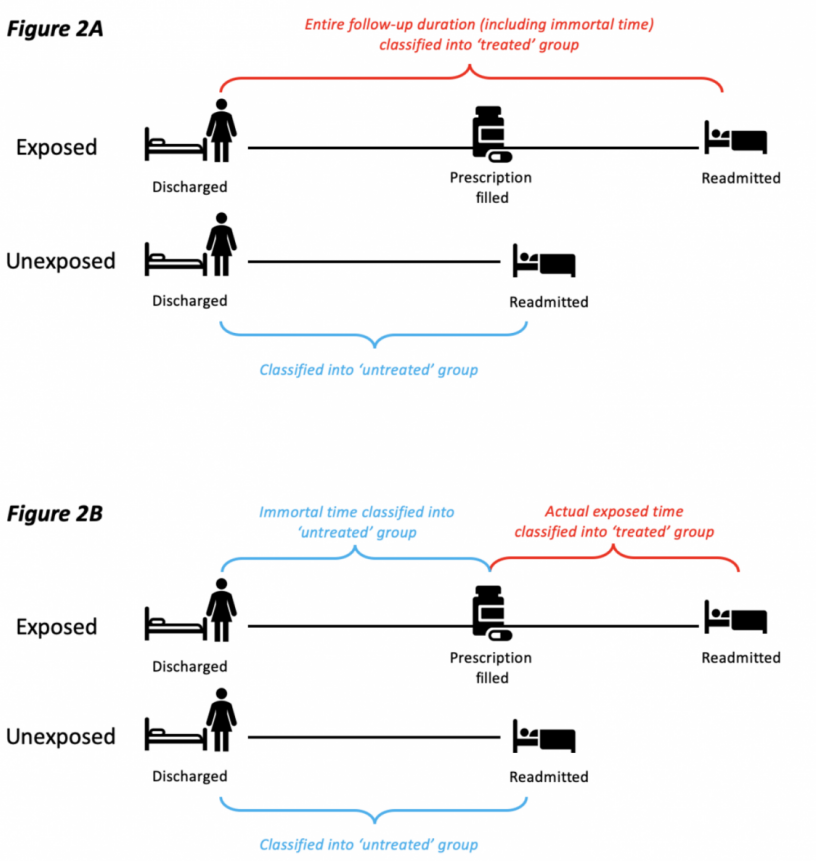

Figure 8: Immortal Time Bias 2

Figure	Classification of immortal time	Treated group definition	Untreated group definition
2A	*Immortal time is misclassified (the biased method)*	Prescription of corticosteroids filled within 90 days from discharge	No corticosteroid prescriptions filled during follow-up
2B	*Immortal time is correctly classified using person-time definitions (the unbiased method)*	Person-time between first corticosteroid prescription to end of follow-up	No corticosteroid prescriptions filled during follow-up AND Person-time from cohort entry to first corticosteroid prescription

Figure 9: Immortal Time Bias 3

5.4 Performance Bias

Performance bias happens when one group of subjects in an experiment (for example, a control group or an treatment group) gets more attention

from investigators than another group. The difference in care levels result in systematic differences between groups, making it difficult or impossible to conclude that a drug or other intervention caused an effect, as opposed to level of care. A similar bias is verification bias, where outcomes are more likely to be found in treatment groups due to investigators knowing which person is in which group.

For example, if the investigators know that an experimental group have been given an active drug, they may focus their attention on this group. The participants might receive more frequent exams and more diagnostic tests. This could result in the experimental group having a greater chance of a positive outcome — not because they have been given an active drug, but because they received very focused attention.

5.5 Previous-opinion Bias

Previous opinion bias describes how the diagnostic process may be influenced by an investigator who is aware of previous test, results and diagnoses in a patient. Having previous opinions has a knock-on effect on the prior probability of a symptom or sign being recorded as present or of a diagnosis being included or excluded.

An example is: a doctor is asked to examine an unwell patient by his colleague. How the first doctor makes this request is vital if bias is not to be introduced. If the doctor asks, 'Could you examine this patients heart, I think he has a murmur' this introduces a previous opinion bias, as it is difficult to consider that the patient has anything else than a heart murmur. Previous opinion bias occurs if a colleague passes on the diagnosis: 'could you examine this patient, I think they have a DVT,' or if an opinion about treatment is passed on: 'I don't think this patient will benefit from this treatment, do you?'

The impact of previous opinion bias is hard to determine. It will impact on the decision to undertake subsequent testing, the accuracy of diagnosis, or the outcome or treatment decisions made. In areas such as emergency departments, where there is a need to work at speed and with numerous colleagues previous opinion bias may introduce cognitive errors. Previous opinion bias has many similarities with confirmation bias, where initial or preconceived ideas about something lead to the collection of information that confirms a given view.

5.6 Verification Bias

When only a proportion of the study group receives confirmation of the

diagnosis by the reference standard, or if some patients receive a different reference standard at the time of diagnosis, the verification bias will occur.

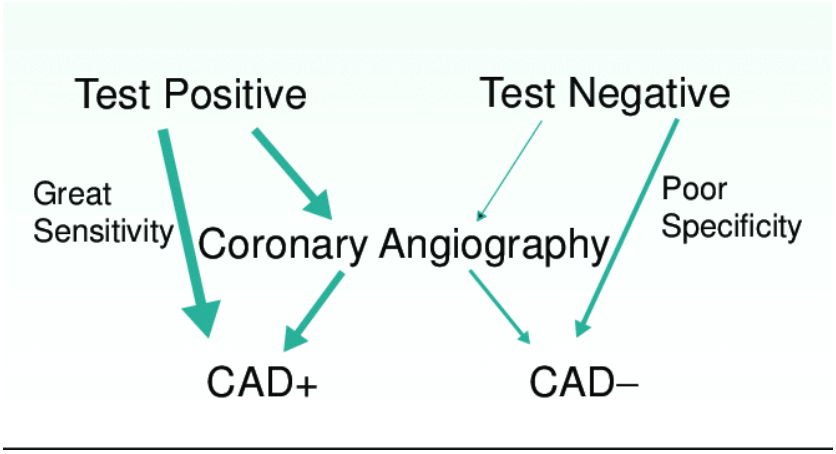

Figure 10: Verification Bias

Here is an example of verification bias(See picture above). Among patients referred for noninvasive testing, some will have a "positive" result, while others will have a "negative result"(top line). Because physicians strongly believe that a positive result means that coronary angiography will show disease, patients with positive tests are much more likely to be referred for angiography (thick arrow) than patients with negative tests (thin arrow).

And some types of bias actually are the sub-types of verification bias: differential reference bias, incorporation bias and partial reference bias.

5.6.1 Differential Reference Bias

In diagnostic studies, a differential reference bias occurs when study participants receive different reference tests. The presence of a differential reference bias can mean that the mixing of data ignores potential differences in the accuracy of the reference tests. As a result, combining outcome data can misrepresent the "true" pattern of disease presence or absence.Many reference tests are invasive, expensive, or carry a procedural risk (e.g. angiography, biopsy, surgery), and therefore, patients and clinicians may be less likely to pursue the gold standard test in all cases.

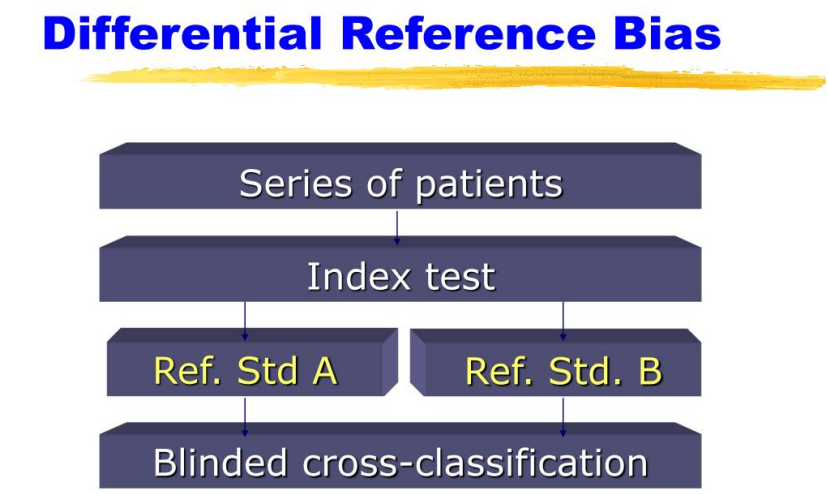

Figure 11: Differential Reference Bias

In one study of an elbow extension test to rule out elbow fracture, participants with a positive index test received the reference test of radiography. Those who did not undergo radiography (for example because the index test was negative) received a structured follow-up assessment by telephone. There is consistent evidence of an association with accuracy when differential reference bias is present, but the direction of the effect varies. Some reviews have reported an overestimation of test accuracy, while others have noted an effect on specificity but not sensitivity. In general, it is difficult to predict the magnitude and direction of the effect of differential reference bias on the results as its presence can lead to a test perceived as being more or less accurate.

Studies, where the reference standard was an expensive and/or invasive test, are particularly prone to differential reference bias. Although these designs may have been used for ethical, funding or practical/clinical reasons, they introduce the potential for this kind of verification bias.

5.6.2 Incorporation Bias

In a diagnostic accuracy study, ideally the index test and the reference test should be independent of each other. But incorporation bias occurs when results of the index test form part of the reference test. This occurs most

frequently when the reference test is a composite of the results of several tests.

For example, when studying high sensitivity troponins, the final diagnosis of MI frequently depends on a measurement of a troponin. The researchers are testing troponin to determine if it predicts MI, but they are also using troponin to define MI. That circularity artificially increases both the sensitivity and the specificity. (Most of the time they will use different troponin assays, but there is still incorporation bias there).

5.6.3 Partial Reference Bias

A partial reference bias results in missing data and a potential misrepresentation of the accuracy for a new test against a reference standard test. So only a proportion of the study group receive both the index and reference standard test when investigating for diagnostic accuracy. Various mechanisms or reasons can be offered as to why a study group would not receive both tests. For example, many reference tests are invasive, expensive, or carry a procedural risk (e.g. angiography, biopsy, surgery), and therefore, patients and clinicians may be less likely to pursue further tests, especially if a preliminary test is negative.

In a study, designed to evaluate the accuracy of positron emission tomography (PET) to determine the presence of malignancy in patients with lung nodules, their standard reference test was histological examination, commonly known as a biopsy. As only positive PET exams could receive the biopsy test, in effect, only the patients who were positive on the PET exam were tested using the reference standard.

6 Generalized Selection bias

Selection bias is the bias introduced by the selection of individuals, groups or data for analysis in such a way that proper randomization is not achieved, thereby ensuring that the sample obtained is not representative of the population intended to be analyzed. It is sometimes referred to as the selection effect.

Let $\mathbf{\Omega}$ be the population(amount $m+n$) of all patients(like universal set $\mathbf{U}$), $\mathbf{X}_i (i = 1, 2, 3, ..., n)$ are samples we collect(amount n), $\mathbf{A}$ is the set of all $\mathbf{X}_i$ so $\mathbf{X}_i \in \mathbf{A}$, $\mathbf{Y}_j (j = 1, 2, 3, ..., m)$ are the elements of complementary set of $\mathbf{A}$. Obviously we know that $\mathbf{A} \subset \mathbf{\Omega}$ and $\mathbf{Y}_j \in \complement_U A$. If we choose samples absolutely randomly, then all statistics we need ($\mathbf{T}_1(\mathbf{X})$, $\mathbf{T}_2(\mathbf{X})$, ...) should

be at least unbiased and sufficient and thus $\mathbf{A}$ could represents $\mathbf{\Omega}$. That is:

$$\mathbf{P}(\mathbf{X}_i) = \mathbf{P}(\mathbf{Y}_j) = \frac{1}{m+n}$$

Apparently we have:

$$\mathbf{T}_1(\mathbf{X}) = \mathbf{T}_1(\mathbf{Y})$$
$$\mathbf{T}_2(\mathbf{X}) = \mathbf{T}_2(\mathbf{Y})$$
$$...$$

But due to some reasons we may choose the estimates not representative. We may face the risk of:

$$\mathbf{P}(\mathbf{X}_i) > \mathbf{P}(\mathbf{Y}_j)$$

or even more extreme situations:

$$\mathbf{P}(\mathbf{X}_1) = \mathbf{P}(\mathbf{X}_2) = ... = \mathbf{P}(\mathbf{X}_n) = \frac{1}{n}$$

$$\mathbf{P}(\mathbf{Y}_1) = \mathbf{P}(\mathbf{Y}_2) = ... = \mathbf{P}(\mathbf{Y}_m) = 0$$

There are many reasons for this situation, but once the sample are no longer chosen with equal probability, The estimates calculated from these samples are no longer unbiased

The phrase "selection bias" most often refers to the distortion of a statistical analysis, resulting from the method of collecting samples. If the selection bias is not taken into account, then some conclusions of the study may be false. Actually selection bias is a huge group. In my opinion, most of the bias in clinical trials can be broadly classified as this type.

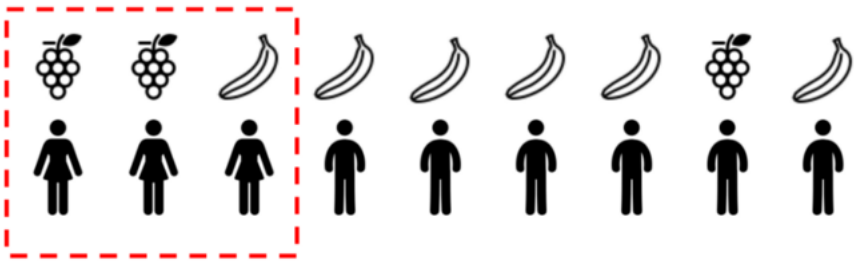

Figure 12: Selection Bias

6.1 Admission Rate Bias(also called Berkson's Bias)

It arises when the variables under study are affected by the selection of hospitalized subjects leading to a bias between the exposure and the disease under study.The combination of exposure to a risk and occurrence of the disease makes it more likely that an individual will be admitted to hospital. In a case-control study, this means the hospital cases could have higher risk exposures or disease than cases from the population at large. This can affect the estimates of the association between the exposure and the disease.This happens frequently when cases are selected in a hospital whose activity is linked to the studied exposure. The admission rate bias may be due to a number of factors e.g. access to care, popularity of certain hospitals/ doctors etc.

Exposure	Cases of lung cancer	Controls from surgical wards	OR
Contact with asbestos	a↑	b	OR↑
No contact with asbestos	c	d	reference
Total			

Figure 13: Asbestosis and Lung Cancer

For example(see above): in a study of risk factors for lung cancer, cases were compared to controls with regard to history of exposure to asbestos. Cases were recruited in the respiratory department of a hospital which is the National Reference center for asbestosis. Controls were selected in the surgical wards of the same hospital. In that situation, it is likely that lung cancer cases of this respiratory department do not represent other cases with regard to history of asbestos exposure. Here, the selection of cases is linked to exposure. Selected cases are more likely to have been exposed to asbestos (than other lung cancer cases in the population), with an overestimation of 'a', resulting in an overestimation of the odds ratio.

6.2 Allocation Bias

Allocation bias may result if investigators know or predict which intervention the next eligible participant is supposed to receive. This knowledge may influence the way investigators approach potentially eligible participants and how they are assigned to the different groups, thereby selecting participants with good prognoses (i.e. anticipated good outcomes and treatment responses) into one group more than another.

In a trial of different blood pressure medications the use of sealed envelopes to conceal the allocation schedule resulted in imbalances in baseline blood pressure between the treatment and control groups. In turned out that participants in the control group already had lower blood pressures compared to participants in the treatment group at the outset. The observed imbalance could have arisen if the investigator opened the envelopes before allocating participants to groups.

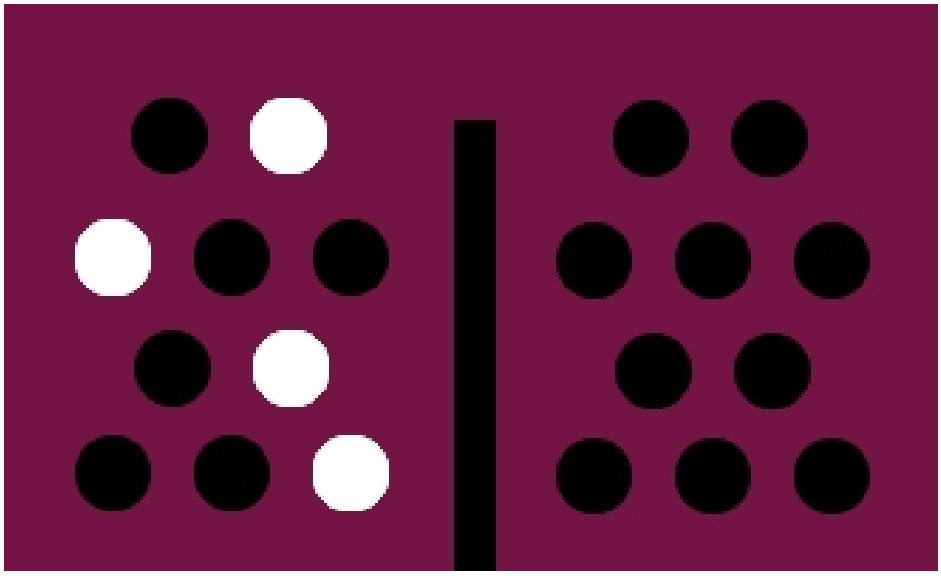

Figure 14: Allocation Bias

6.3 Ascertainment Bias

Ascertainment bias arises when data for a study or an analysis are collected (or surveyed, screened, or recorded) such that some members of the target population are less likely to be included in the final results than others. The resulting study sample becomes biased, as it is systematically different from the target population. Ascertainment bias is related to sampling bias, selection bias, detection bias, and observer bias. Ascertainment bias can happen when there is more intense surveillance or screening for outcomes among exposed individuals than among unexposed individuals, or differential recording of outcomes.

Ascertainment bias can occur in screening, where take-up can be influenced by factors such as cultural differences. It can occur in case-control studies in the initial identification of cases and controls, which can be skewed by relevant exposures, leading to biased estimates of associations.

6.4 Attrition Bias

Attrition bias is a typical selection bias, it occurs when participants leave during a study. It almost always happens to some extent. Different rates of loss to follow-up in the exposure groups, or losses of different types of participants, whether at similar or different frequencies, may change the characteristics of the groups, irrespective of the exposure or intervention. Losses may be influenced by such factors as unsatisfactory treatment efficacy or intolerable adverse events. When participants leave, it may not be known whether they continue or discontinue an intervention; there may be no data on outcomes for these participants after that time. Systematic differences between people who leave the study and those who continue can introduce bias into a study's results – this is attrition bias.

In some cases, those who leave a study are likely to be different from those who continue. For instance, in an intervention study of diet in people with depression, those with more severe depression might find it harder to adhere to the diet regimen and therefore more likely to leave the study. This means that the two groups of people do not have the same length of possible follow-up time. This often occurs when the new treatment is compared with the old treatment. For example, the new treatment only started in 2020 and the old treatment started in 2015. The tracking time is relatively short, so there are relatively few incidents.

6.5 Centripetal Bias

Centripetal bias as defined by Sackett in his 1979 indicates that the number of cases recorded at different institutions may be biased because patients might seek out clinicians or institutions with a good reputation in that clinical area, thus artificially inflating the numbers recorded. This may impact estimates of prevalence and the population under investigation may not reflect the characteristics of the wider population.

The responsibility for this bias cannot be attributed to the institution. On the contrary, Surveys should be aware that patients will make their own choices for different hospitals or institutions according to their personal circumstances, so that different institutions can count different results. The key to reducing this deviation is to count as many patients(different institutions) as possible.

6.6 Collider Bias

In statistics and causal graphs, a variable is a collider when it is causally

influenced by two or more variables. The name "collider" reflects the fact that in graphical models, the arrow heads from variables that lead into the collider appear to "collide" on the node that is the collider.

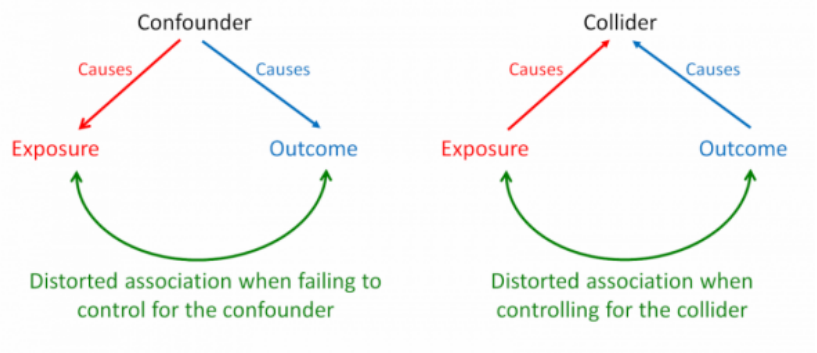

Figure 15: Confounding and Collider Bias

A clear example of collider bias was provided by Sackett in his 1979 paper. He analysed data from 257 hospitalized individuals and detected an association between locomotor disease and respiratory disease (odds ratio 4.06). The association seemed plausible at the time – locomotor disease could lead to inactivity, which could cause respiratory disease. But Sackett repeated the analysis in a sample of 2783 individuals from the general population and found no association (odds ratio 1.06). The original analysis of hospitalized individuals was biased because both diseases caused individuals to be hospitalized. By looking only within the stratum of hospitalized individuals, Sackett had observed a distorted association. In contrast, in the general population (including a mix of hospitalized and non-hospitalized individuals) locomotor disease and respiratory disease are not associated.

6.7 Diagnostic Access Bias

Individuals may have different access to diagnostic tests, due to cultural, geographic, economic or other reasons, and these factors affect the detection of disease. Certain populations of patients have more access to or higher use of diagnostic tests. This leads to diagnostic access bias, which may cause a study's results to be biased, or unrepresentative of the broader population of interest and under or overestimate the true incidence of disease in the population depending on the level of access.

Often sarcoidosis (an inflammatory disease usually affecting the lungs) does not cause symptoms and so whether an individual has a diagnosis of sarcoidosis depends in part on access to medical methods of detection. In an

observational study, 46% of health professional were diagnosed via routine exam compared to 19% of the general population. Health professionals were therefore 2.4 times more likely to be diagnosed with sarcoidosis (95% CI: 1.34 to 4.33) due to the presence of diagnostic access bias.

6.8 Diagnostic Suspicion Bias(also called Provider Bias)

Diagnostic suspicion bias is a type of selection bias.Knowledge about a patient can impact the diagnostic process that a physician goes through, and therefore can impact the outcome of that diagnostic process.Information about a group or individual coupled with suspicions or prejudices of medical staff could influence how diagnoses are made, by affecting what examinations are performed and how quickly people are investigated, which can affect rates of diagnosis. This can be termed diagnostic suspicion bias. This is a very common prejudice, because people of different occupations naturally have a high incidence of different special diseases.

For example, a patient presenting to the emergency department without any classic coronary risk factors might get a truncated cardiac workup (no repeat troponins, or no follow-up testing) and therefore ACS might be under-diagnosed in these patients. On the other hand, a patient with multiple coronary risk factors might get a very extensive workup, even with atypical chest pain. Resulting research could therefore be biased toward the traditional risk factors, and alternative risk factors could be hidden.

Another example is, if a group of workers in the industry find out that one of the chemicals they have been exposed to is a carcinogen, then these workers might present to a medical facility sooner, or be more likely to attend screening, than a non-exposed population. Also, medical staff might more readily suspect these individuals than others to have cancer, because of the knowledge of their exposure to the carcinogen, and this might influence what tests are done and how quickly they are ordered.

6.9 Informed Presence Bias

The presence of a person's information in an electronic health record is affected by the person's health status. Because the presence of a person's record in an electronic health record database is not random but is usually a result of presenting to medical services for some condition or illness. People in electronic health records are therefore systematically different from those not in electronic health records. Health records contain people with more medical encounters than the general population. When examining the electronic health records for associations between different conditions, this bias

can lead to spurious associations.

In electronic health records, the prevalence of depression among pregnant women might be seen to be greater than that of non-pregnant women. However, pregnant women attend medical services throughout and after their pregnancy, giving them more opportunities than women not attending medical services to be assessed and diagnosed with mental health conditions. This might distort a relationship between pregnancy and depression. There might be a relationship between the number of times each woman was seen by a healthcare worker, and the likelihood of receiving a diagnosis of depression. Caution must thus be taken when extrapolating results to women in the general population (rather than the electronic health record group).

6.10 Lead-time Bias

Lead time bias refers to the phenomenon where early diagnosis of a disease falsely makes it look like people are surviving longer. This occurs most frequently in the context of screening.

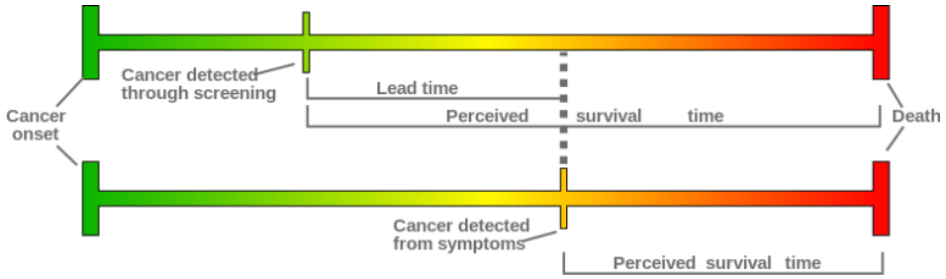

Figure 16: Lead-time Bias

For example, a man with metastatic lung cancer dies at age 70. His cancer was discovered 1 year ago, when he was 69. Therefore, it appears as if he lived for 1 year with the cancer. However, imagine that instead his cancer was discovered on a screening CT scan when he was 65 years old. If he still dies at the age of 70, it now looks like he survived for 5 years with the diagnosis of cancer (the 5 year survival rate is much better), but in fact there was no real change in his survival.

6.11 Membership Bias

Membership bias is when a group of people tend have a specific characteristic that can affect a study's outcome. Assignment to the group is

based on this particular characteristic. In order for a characteristic to create membership bias, group membership can't be random in any way.

In order for a characteristic to create membership bias, group membership can't be random in any way. For example, membership to the group "people with lupus" requires the person to have a lupus diagnosis (the "characteristic"), and assignment to the group "people with lupus" is based on that diagnosis. However, if you take that group and randomly assign them to a treatment group or a control group, those individual groups no longer have membership bias.

6.12 Mimicry Bias

When looking at how exposures relate to disease, it is important to be sure that the outcome being investigated is the true disease, and not a condition mimicking the disease, which could lead to false conclusions about the causes of the disease of interest.

For instance, can mimic a wide variety of diseases, in each of its phases. Primary syphilis presents atypically meaning only 30 to 40% of patients are diagnosed in this early phase. At this time Mimicry bias would happen. Another example is intussusception, which is a common abdominal emergency in early childhood, but other diseases mimicking intussusception should be kept in mind when making the differential diagnosis. The BMJ has a series easily missed dedicated to heightening awareness of conditions that are easily missed at first presentation in primary care, where undifferentiated symptoms and signs, mean an immediate diagnosis is often difficult to make.

6.13 Non-contemporaneous Control Bias

Differences in the timing of selection of case and controls within in a study influence exposures and outcomes resulting in biased estimates. If in a case-control study, cases are selected during one period and controls are selected during another period, then the relationships observed between exposures and outcomes of interest may be affected. Changes in disease or diagnostic definitions, exposures over time, and treatments, could all contribute to non-contemporaneous bias.

An intervention study using historical controls assessed the effect of a psycho-social intervention program for parents of premature infants. The intervention aimed to improve the coping capacity of parents, reduce the length of hospital stay and readmission rates. The intervention had already been implemented. The researchers, therefore, used a pragmatic evaluation by selecting a historical comparison group (they obtained data on outcomes

for infants before the introduction of the intervention). However, Other factors could have changed between the two-time points, such as the degree of ill health of the infants, improvements in medical care and new treatments.

6.14 Non-response Bias

Non-response bias is a bias that occurs due to systematic differences between responders and non-responders. It occurs when non-responders from a sample differ in a meaningful way to responders (or early responders). This bias is common in descriptive, analytic and experimental research and it has been demonstrated to be a serious concern in survey studies. Participants who do not respond may differ from those who do in their exposures or outcomes. This can then result in mistakes in estimating population characteristics based on the under-representation of these phenomena due to non-response.

A study which aimed to investigate the potential effects of non-respondent bias on prevalence estimates of self-reported health behaviours and well-being demonstrated a strong and consistent effect of non-response on all health estimates, as well as considerable effects on the distribution of demographic characteristics. Non-response was determined to contribute to underestimated health risks.

In a community cardiovascular follow-up study, females, older individuals, and those with higher levels of education are more likely to participate in postal surveys. However, non-response may also occur as a result of the actual outcome variables of interest. Those with poorer health tend to avoid taking part in health surveys and those who do take part report better health status and behaviours.

6.15 Popularity Bias

Popularity bias could result from an increased awareness of the condition within the general population, making a condition "fashionable" and more likely to be cited as the cause of perhaps somewhat unspecific symptoms. For example, in the last decade, population awareness of coeliac disease (an autoimmune condition due to gluten intolerance) has led to large numbers of media articles on coeliac disease and related putative gluten intolerance syndromes. Sufferers of abdominal discomfort might be therefore more likely to suspect coeliac disease as the cause, and present to healthcare settings and seek investigations.

Also, a provider of health services might be the instigator of increased interest/popularity in a certain disease or condition. Advertisements by health

providers for testing for conditions that otherwise might go undiagnosed, or otherwise might cause no overt health problems, could lead to an increase in "popularity" of presenting with certain symptoms or concern about a condition.

Both instances lead to selection bias. If a study is affected by popularity bias it could influence the results if certain groups of people were admitted to certain interventions or observations and other groups, which could happen over time, and these differences between groups might affect the study's outcomes.

6.16 Prevalence-incidence Bias(also called Neyman Bias)

Prevalence-incidence bias or Neyman's bias occurs due to the timing of when cases are included in a research study. David Sackett wrote in 1979: "A late look at those exposed (or affected) early will miss fatal and other short episodes, plus mild or 'silent' cases and cases in which evidence of exposure disappears with disease onset." Excluding patients who have died will make the disease appear less severe. Excluding patients who have recovered will make the disease seem more severe. The Greater the time between exposure and investigation means more likelihood of individuals dying or recovering from the disease and therefore being excluded from the analysis, and this bias is more likely to impact long-lasting diseases than short-acting conditions.

A case-control study investigating pneumonia that only enrols cases and controls admitted to a hospital. Those with pneumonia who died prior to admission will not be included the sample. The selected sample will, therefore, include moderately severe cases, but not fatal cases.

6.17 Referral Filter Bias

Referral filter bias was listed by David Sackett in 1979 and indicates that participants in a study may not properly represent the population being looked at. This is a typical selection bias. Due to this the results in a study may not be applicable and may have low external validity.

An example is: People with high blood pressure studied in the community may have different characteristics compared to those studies in the hospital. These patients are more likely to have unusual features, to have more severe high blood pressure and have secondary causes. They may not, therefore, represent the population with high blood pressure as a whole.

6.18 Spectrum Bias

Spectrum bias occurs when a diagnostic test is studied in a different range of individuals to the intended population for the test. The ideal diagnostic test would have both high sensitivity (the proportion of people testing positive who actually have the disease) and high specificity (the proportion of people testing negative who do not have the disease). However, the sensitivity and specificity of diagnostic tests vary in different settings. One of the contributing factors is spectrum bias, where the sensitivity and specificity of a test can be affected by the differences in the patient characteristics in different settings because each setting has a different mix of patients.

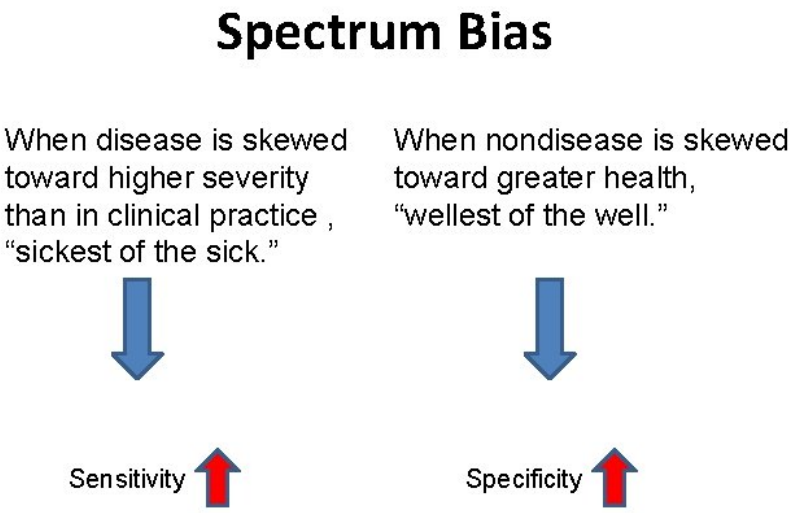

Figure 17: Spectrum Bias

A review of meta-analyses of diagnostic accuracy studies found that the largest overestimation of accuracy occurred in studies that included severe cases and healthy controls (relative diagnostic odds ratio, 4.9, 95% confidence interval 0.6–37). Severe cases would be easier to detect, therefore increasing the estimated sensitivity, while healthy controls would mean there are less false positive results, therefore overestimating the specificity. Studies that used other case-control designs produced similar estimates of accuracy to diagnostic cohort studies. Studies that do not include patients consecutively

are associated with an overestimation of the diagnostic odds ratio by 50% compared with those that used a consecutive series of patients.

6.19 Survival Bias

Survival bias is a type of sampling error or selection bias that occurs when the selection process of a trial favours certain individuals who made it past a certain obstacle or point in time and ignores the individuals who did not (and are generally less visible).

A classic example comes from a study of bombers during world war two. Planes were studied after returning from bombing runs, and it was recommended that the areas of the planes with the most damage should be reinforced. The problem with this solution was that they were only looking at the planes that survived battle. In fact, the areas of the planes that looked like they sustained the least damage were the most important to reinforce, because those were the areas that, if hit, would cause the plane to be lost (and therefore not included in the sample).

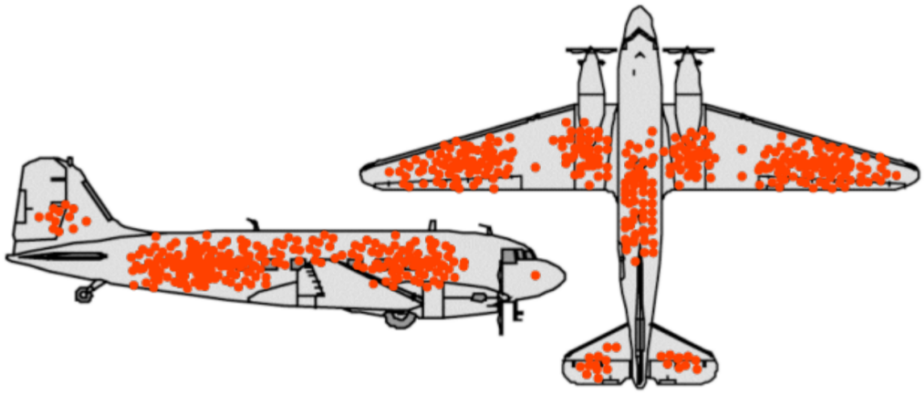

Figure 18: Survival Bias

Another classic (and somewhat tragic) example comes in the study of cats falling from high rise buildings. Observational data indicated that cats falling from higher than 6 stories actually had fewer injuries than cats falling from less than 6 stories. A number of different theories have been suggested to explain this observation, but the most likely explanation is that cats that are obviously dead are not brought to veterinarians and therefore are not captured in the data. Cats falling from higher are more likely to die, and also more likely to have a greater number of injuries, but are excluded from the data, resulting in a biased sample.

In emergency medicine, trials often only start when the patient is stable enough to be consented for research. Unfortunately, this might result in a biased sample of patients, because it excludes everyone who dies very early in their resuscitation, or who is too sick to consent.

6.20 Unacceptability Bias

David Sackett listed unacceptability bias in his 1979 paper documenting sources of bias in research studies, and provided the following explanation: "Measurements which hurt, embarrass or invade privacy may be systematically refused or evaded."

Here is an example: the collection of information about street drug use could be affected by unacceptability bias, with higher users of street drugs potentially less likely to report their use accurately than lower users, due to the perception that the questions about use are too invasive. We have not found reports of unacceptability bias per se in the literature. Alcohol under-reporting is one example, E.g. ? Drinking pattern is more strongly associated with under-reporting of alcohol consumption than socio-demographic factors: evidence from a mixed-methods study and Underreporting in alcohol surveys: whose drinking is underestimated. And also sexual behaviours presents methodological challenges in survey research due to unacceptability bias.

6.21 Unmasking Bias

Some exposures cause some groups of people to be given a diagnosis earlier, or at an overall higher rate than other groups of people, and these might not be causes of the disease; if this happens, unmasking, or detection signal, bias has occurred.

If a medication can cause vaginal bleeding, and people with this symptom go sooner to the doctor and receive earlier or more intensive examination and investigations to diagnose cancer, it may appear that the medication caused the cancer. However, all that may have happened is that the medication has prompted an earlier or more intensive search for the disease, leading to an apparently increased rate among those using the medication. This is unmasking bias.

Another example is: a large number of patients might develop severe GERD after eating spicy burritos. Because of their GERD, they are more likely to undergo endoscopy than the general pubic. During endoscopy, a number of patients are found to have gastric cancer, and statistical correlation

is identified, despite there being no real association between burrito intake and gastric cancer.

6.22 Volunteer Bias

Participants volunteering to take part in a study intrinsically have different characteristics from the general population of interest, and that will occur volunteer bias.

Studies of human health use samples to obtain information on the whole population, the aims being for the sample to represent the population of interest accurately. Selection should be done in such a manner that the population remains representative of the whole population. When the sample consists of volunteers, the risk is that they are not representative of the general population. Volunteer bias can occur at all stages of the trial from recruitment, retention through to follow-up. Differences between volunteers and the target population are not restricted to socio-demographic factors but can include attitudes towards the trial and institutions involved.

Figure 19: Volunteer Bias

A study exploring volunteer bias using data from a trial of probiotic supplementation for childhood atopy found that as the trial progressed, representation of the most deprived decreased. These participants were more likely to be lost to follow-up at six months, and two years, and consent to

infant blood sample donation. They also found that mothers interested in probiotics were more likely to attend research clinics and consent to skin-prick testing. Mothers participating to help their children were also more likely to consent to blood sample donation.

It is difficult to estimate the impact of volunteer bias and the direction of its effect. Volunteers tend to be more educated, come from high social class and more approval motivated. One report found that females are more likely to volunteer than males and are healthier and adhere to treatment more often.

6.23 Wrong-sample-size Bias

Studies of human health use samples to obtain information on the whole relevant population and to represent the population of interest accurately. When small sample size is used, wrong sample size bias would occur. However, while larger studies can detect tiny or small associations, they might not be important or relevant to improving human health.

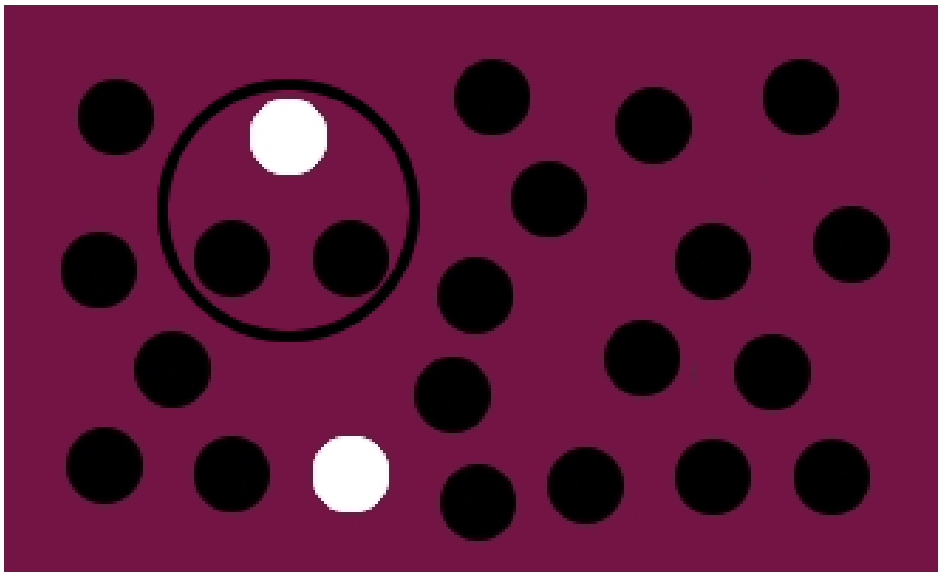

Figure 20: Wrong-sample-size Bias

Statistical indicators, including p-values and confidence intervals, are used to help determine how certain we are that the results observed did not arise by chance. So, huge sample sizes can often show a large number of statistically significant results, but these may not be important, if the effect size is small, or if the relationship is not clinically relevant to health. A comparison of the

estimated benefits of treatment between large trials (at least 100 patients per arm) and small trials found that on average, treatment effects were greater in small than in large trials. In neuroscience study sizes tend to be typically small, giving low power to detect associations and therefore the likelihood that a finding is true is small.

7 Silliness

It is important to be aware that the medical literature is full of examples of both major and minor research fraud. Some of these are conscious and some are unconscious. These biases should not appear in rigorous, objective and fair medical research, because the treatment of natural science should reduce our own subjective ideas. Some bias show the ugliness of human nature: greed, hypocrisy, or being controlled by capital. Unfortunately, because medical research is always done by people, these bias are unavoidable. In addition to supervising as much as possible, we try to optimize the professionalism of scientific researchers and try to dilute the impact of human nature on scientific research.

7.1 Biases of Rhetoric

Rhetoric refers to speaking or writing that is designed to have a persuasive or impressive effect but is lacking in meaningful content. The bias may be for or against certain types of medical intervention or health practices, and can often be identified when arguments are based on opinions or beliefs rather than verifiable facts, or when there is a lack of evidence-based content. Rhetoric may be particularly relevant in online sources of healthcare information, new and emerging technologies and policies not underpinned by high-quality evidence. Rhetoric can often be found in press releases and newspaper articles as a means to entice the reader.

The idea that childhood vaccinations caused autism was widely publicized in 1998. The interpretation of these publications at the time is an example of rhetoric as it provides an unsupported link between autism and vaccination. Since then, the original paper suggesting this link has been shown to be fraudulent and has been retracted, but the idea that there is a link still has an influence. It can be seen that rumors are easy to generate and spread. Although it is possible to prove the incorrectness of rumors in the end, its influence is not easy to eliminate.

7.2 Confirmation Bias

Confirmation bias is the tendency to search for, interpret, favor, and recall information in a way that confirms or supports one's prior beliefs or values. People display this bias when they select information that supports their views, ignoring contrary information, or when they interpret ambiguous evidence as supporting their existing attitudes.

Figure 21: Confirmation Bias

The effect is strongest for desired outcomes, for emotionally charged issues, and for deeply entrenched beliefs. Confirmation bias cannot be eliminated entirely, but it can be managed, for example, by education and training in critical thinking skills.

Table 1. Examples of confirmation bias and conflict of interest

Source	Publication type	Conflict of interest	Confirmation bias
ACC/AHA	2013 Cholesterol guidelines	Yes	Failure to incorporate contradictory evidence
ACC/AHA	2014 NSTE-ACS guidelines	Yes	Misrepresentation of evidence Failure to incorporate contradictory evidence
NLA	2015 Statin diabetes safety task force report	Yes	Failure to incorporate contradictory evidence
JACC	2015 Editorial—*Treatment of dyslipidemia in elderly patients with CHD*	Yes	Failure to incorporate contradictory evidence
NEJM	2015 Editorial—*Proof that lower is better–LDL cholesterol and IMPROVE-IT*	No	Failure to incorporate contradictory evidence
ADA	2016 Standards of medical care in diabetes	Yes	Misrepresentation of evidence Failure to incorporate contradictory evidence

ACC/AHA, American College of Cardiology/American Heart Association; NSTE-ACS, non-ST elevation acute coronary syndrome; NLA, National Lipid Association; JACC, Journal of the American College of Cardiology; NEJM, New England Journal of Medicine; ADA, American Diabetes Association.

Figure 22: Confirmation Bias 2

The impact of confirmation bias can be at the level of the individual all the way up to institution level. DuBroff showed that confirmation bias influenced expert guidelines on cholesterol and was highly prevalent when conflicts of interests were present. He found that confirmation bias occurred due to a failure to incorporate evidence, or through misrepresentation of the evidence, which had the potential to skew guideline recommendation(see above).

7.3 Hot Stuff Bias

Fashionable scientific areas induce a bandwagon effect, making it more likely that investigators will be keen to take part and more likely that their approach will be less critical than it should be, and investigators and editors may not be able to resist the temptation to publish the results. Therefore, concentrate on trying to confirm the findings of others rather than trying to falsify them. Negative findings may be less likely to be published (see Publication bias). In such cases, the positive predictive value becomes progressively smaller as more studies accumulate, making it less likely that the published findings are true; this may also be partly due to regression to the mean. Furthermore, the current popularity of a topic can affect how much publicity is given to it. Current excitement about a particular topic can lead to the inappropriate publication of research findings (or opinions) earlier, or in greater volume, or with greater prominence, or with less scrutiny than would otherwise be the case in the normal course of events. Similarly, topics that are regarded as controversial may be given more publicity by editors who are keen to draw attention to their journals, even though they may not be aware of it or may subsequently deny that it was so, and by journalists looking for an interesting copy.

Controversial topics may lead to a heated debate about the relative merits of a hypothesis or intervention. Examples include the current debate about the use of statins, the long-standing debate about the efficacy of antidepressants, such as the SSRIs, and previous debates about the use of hormone replacement therapy

7.4 Hypothetical Bias

Hypothetical bias occurs when individuals report unrealistic behaviours or values to researchers in surveys or in experimental studies. In other words, what individuals say they would do hypothetically is not necessarily what they would do in reality. This bias occurs in stated preference studies (individuals' stated choices/valuations of goods/services), e.g. discrete choice

experiments, which are widely used across health sciences. Hypothetical bias impacts the validity of a study's results. It is considered particularly prevalent in healthcare because there are many treatments and services that individuals may experience in the future or may not experience at all.

Buckell and Hess used an online Discrete Choice Experiments in the US tobacco market, and US tobacco market data, to show the presence of (and correct for) hypothetical bias. Their findings suggest that hypothetical bias can affect the predicted market shares of tobacco products; that is, the predicted proportion of smokers that purchase cigarettes or e-cigarettes appears to be distorted by hypothetical bias. Moreover, both the direction and magnitude of predictions of tobacco policy changes appear to be distorted by hypothetical bias.

7.5 Industry Sponsorship Bias

Industry sponsorship bias is shorthand for a host of ways in which studies get skewed—in the design, conduct and/or publication of research–in order to promote commercial interests. Mechanisms include, but are not limited to: posing a research question such that the answer is true but misleading; choosing unrepresentative study populations; administering a competitors drug at a non-optimal dose (in comparator trials); questionable choices made while analysing the data; non-publication of statistically nonsignificant results; selective reporting of outcomes; and multiple publication of positive results.

Table 4. Association between Characteristics of Industry-Funded Articles ($n = 95$) and Statistically Significant Results and Conclusions that Favor the Test Drug: Univariate Logistic Regression

Characteristic	Category	Results Favor Test Drug			Conclusions Favor Test Drug		
		Favorable *n*/Total *n* (%)	OR (95% CI)	*p*-Value	Favorable *n*/Total *n* (%)	OR (95% CI)	*p*-Value
Blinding	Not adequate	27/42 (64)	1.00		28/42 (67)	1.00	
	Adequate	19/53 (36)	0.31 (0.13–0.72)	0.007	27/53 (51)	0.52 (0.22–1.20)	0.13
Sample size	Quartile 1 (7–35)	5/15 (33)	1.00		3/15 (20)	1.00	
	Quartile 2 (36–92)	8/17 (47)	1.78 (0.42–7.5)	0.43	9/17 (53)	4.5 (0.92–21.9)	0.06
	Quartile 3 (93–272)	7/24 (29)	0.82 (0.21–3.3)	0.78	11/24 (46)	3.4 (0.76–15.1)	0.78
	Quartile 4 (287-4162)	26/39 (67)	4.0 (1.13–14.2)	0.03	32/39 (82)	18.3 (4.05–82.5)	<0.001
Funding source	Comparator drug	3/30 (10)	1.00		4/30 (13)	1.00	
	Test drug	43/65 (66)	17.6 (4.8–64.5)	<0.001	51/65 (79)	23.7 (7.08–79.2)	<0.001
Author financial ties	Tie with sponsor	25/47 (53)	1.00		29/47 (62)	1.00	
	No tie with sponsor	21/48 (44)	0.68 (0.30–1.54)	0.36	26/48 (54)	0.73 (0.32–1.66)	0.46

Figure 23: Industry Sponsorship Bias

Statins are prescribed to reduce cholesterol which in turn is intended to reduce mortality from coronary events. Researchers identified 95 RCTs in which multiple statins were compared or a statin was compared to an older treatment. Statistical comparisons between drugs were classified as

"favorable" to statins if the newer drug outperformed the competitor, "inconclusive" if the results were not statistically significant, and "unfavorable" if the older competitor drug was superior and the result was statistically significant. Of the 65 trials where the trial was sponsored by the maker of the newer drug, favorable results were reported in 66% of the studies and favorable conclusions drawn in 79% of the cases. Of the 30 studies in which the trial sponsor was the maker of the older drug, only 3 (10%) reported favorable results for the non-sponsored drug (i.e. the newer statins), and only 4 (13%) endorsed the non-sponsored drug in the conclusion. The researchers concluded that 'the main factor associated with the results and conclusions of industry-sponsored research is research sponsorship"(See above).

7.6 One-sided Reference Bias

One-sided reference bias occurs when authors restrict their references to only those works that support their position. This bias may arise when researchers cite publications that support their preconceptions or hypotheses, ignoring evidence that does not support their view. This can happen in any study report, but a particular problem arises when this occurs in literature reviews, which are supposed to represent a comprehensive collection of all relevant information, along with description and appraisal of quality and content. The result can be a misrepresentation of the current totality of evidence and can lead to spurious claims or needless additional research.

An analysis of one-sided reference bias examined reference lists of articles reporting on clinical trials in rheumatoid arthritis. From 111 articles reviewed, 22 showed a negative selection of references and 44 a positive selection (while 35 were not amenable to analysis because all the references gave the same outcome).

7.7 Perception Bias

Perception bias is the tendency to be somewhat subjective about the gathering and interpretation of healthcare research and information.There is evidence that although people believe they are making impartial judgements, in fact, they are influenced by perception biases unconsciously.There are some situations which include this bias: individuals hold attitudes towards people, or associate stereotypes with them, without being aware of this; individuals tend to blame their failings on circumstances around them, but consider that others are responsible for their shortcomings; expectations about people or situations affect perception.

An example is, in a study of students reporting fruit and vegetable consumption , the investigators measured intake by self-report before and after receiving different information messages. Students in the low normative group (receiving the message they were in the lowest 20th percentile of intake) reported a half-cupful increase in fruit and vegetable intake and a one-cup increase in perception of peers' consumption, while there were no significant differences in the other groups (highest 20th percentile or no message).

7.8 Reporting Bias

Reporting biases is an umbrella term that covers a range of different types of biases. It is described as the most significant form of scientific misconduct. Reporting bias occurs when only some trial outcomes are reported. This can occur within a trial, so that researchers looked at many outcomes, but only report the results of some. It can also occur with entire trials, so that some research that is done never gets published. In general, positive results are much more likely to be reported than negative results.Our definition of reporting biases is a distortion of presented information from research due to the selective disclosure or withholding of information by parties involved with regards to the topic selected for study and the design, conduct, analysis, or dissemination of study methods, findings or both.

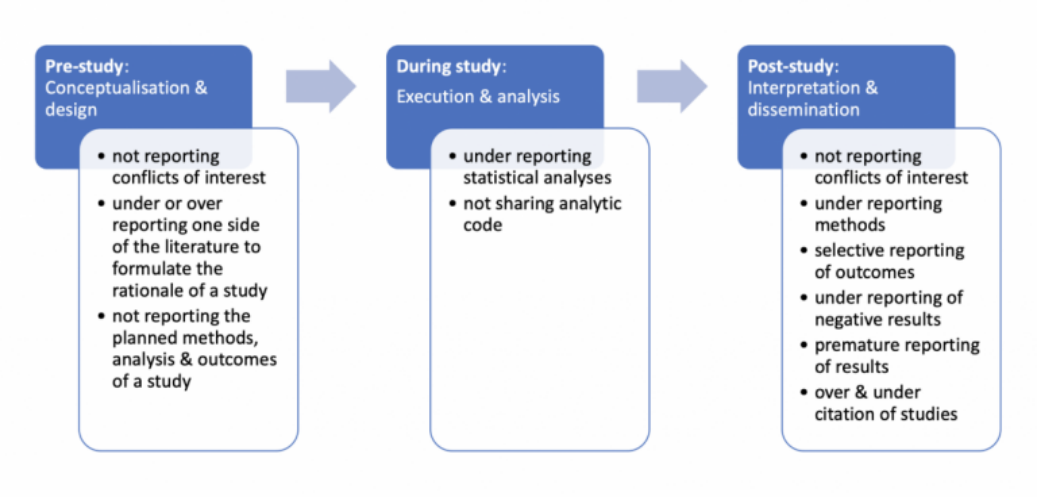

Figure 24: Reporting Bias

7.8.1 Language Bias

The English language has been the predominant language in medical re-

search. Publication in other languages can sometimes be regarded as of secondary importance. Studies publishing positive results might also be more likely to publish in English. Reading and using only English language research could provide a biased assessment of a topic, and can lead to biased results in systematic reviews.

7.8.2 Outcome-reporting Bias

Selective reporting of pre-specified outcomes – depending on the nature and direction of the analysed results – occurs among a large proportion of published clinical trials, resulting in outcome reporting bias. Selective reporting of outcomes can potentially compromise the validity of a trial and any subsequent meta-analyses.

Selective reporting can occur through different ways:

1. omitting outcomes which are deemed to be unfavourable or statistically insignificant
2. adding new outcomes based on collected data to favour statistical significance
3. including only a subset of the analysed data in the published study
4. failing to report data that was analysed in the trial (such as adverse effects)
5. changing outcomes of interest (from primary outcomes to secondary outcomes if they do not yield significant results)

Outcome reporting bias can be difficult to detect. One way is to obtain the protocol of a clinical trial or trial registry and compare the intended outcomes of interest to the analysed outcomes published in the final paper. If these differ then outcome reporting bias is present.

7.8.3 Positive-results Bias

Positive results bias means that the researchers tend to submit, accept and publish positive results rather than non-significant or negative results. Positive results bias occurs because a considerable amount of research evidence goes unpublished, which contains more negative or null results than positive ones. This leads to spurious claims and overestimation of the results of systematic reviews and can also be considered unethical. Non-publication of results can also lead to research wastage as researchers may unnecessarily repeat studies because the results are unpublished.

A review of empirical studies and assessment of 300 systematic review found that trials with positive outcomes are twice as likely to be published, and published faster, compared with trials with negative outcomes (Song et

al.). This review also found that there was 'convincing evidence that outcome reporting bias exists and has an impact on the pooled summary in systematic reviews.

7.8.4 Publication Bias

Publication bias occurs when some studies are published and others are not. Studies that remain unpublished tend to be systematically different from those that are published, meaning that conclusions drawn from the published literature will be systematically different from the truth (or biased). Positive trials and "exciting trials" are more likely to be published. Sometimes publication bias is nefarious: companies selling medications have a vested interest in hiding negative trials about their products. However, publication bias can also occur because researchers don't think their results are interesting, or because journals are less interested in publishing negative or "boring" research results.

An example is: a drug company researcher analyzed 53 papers in top journals and found that he couldn't replicate 47 of them. This proves that there are too many omissions in publications. Since the public isn't privy to information they cant access, this problem is not represented to them, thus unearthing the crux of the problem in publication bias.

7.9 Spin Bias

Spin bias occurs when researchers intentionally or unintentionally distorted interpretation of research results, unjustifiably suggesting favorable or unfavorable findings that can result in misleading conclusions. Researchers may be tempted to distort the interpretation of their (or others') results, misleading readers so that results are viewed in a more favorable (or unfavorable) light than is justified, and thus misleading readers, by adding "spin". Such actions can be tempting. For example, it may be a way of suggesting that a hypothesis was correct when it was not, or that it was not correct when it was, or demonstrating "impact" attracting media attention, or act as a marketing tool to influence research users.

Spin may influence the interpretation of information by evidence users; however, few studies have explored this. A randomised control trial allocated 150 clinicians to assess a sample of cancer-related report abstracts with spin and another 150 clinicians to evaluate the same abstract with the spin removed. Although the absolute size of the difference observed was small, the study found that the presence of spin was more likely to induce clinicians to report that the treatment was beneficial. Paradoxically, the study also

showed that spin caused clinicians to rate the study as being 'less' rigorous and they were more likely to want to review the full-text of the article.

8 Gratitude

Thanks my parents, who funded me study abroad and supported me to communicate with international friends. I spent over 40,000 euros in Spain these 2 years and without their support I could not finish it. I love them.

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