



**Master of Public Health, specialization: AI4PH
DESU: AI4PH**

TU PHS-PRIM: Principles and methods of public health sciences

This evaluation begins with some multiple choices questions and open questions about data analysis and bias. The second part focus on three articles that you can download on Ametice. You can answer the questions on this file and download it on Ametice. You will name it as follow:
Surname-first name-Homework-2-PHS-PRIM

Some multiple-choice questions to start:

1. What is a confidence interval (choose the right answer(s))?

- The confidence interval is an interval of values that contains 95% of the observed data
- **The 95% confidence interval is an interval of values that has a 95% chance of containing the true value of the estimated parameter**
- Neither
- Both

2. How can a confidence interval be reduced?

By collecting more data. The width of the CI is approximately proportional to the reciprocal of the square root of the sample size. So if you increase the sample size by a factor of four, you can expect the CI to be half as wide.

3. The relationship between exposure to cigarettes and lung cancer is studied and found to be $p < 0.05$. How can we conclude (choose the right answer(s))?

- **There is a statistical link between cigarette exposure and lung cancer**
- Exposure to cigarettes increases the risk of lung cancer
- Having lung cancer increases the risk of being exposed to cigarettes
- Having lung cancer and being exposed to cigarettes are both linked to another factor

4. What are alpha and beta risk? Which one is minimized in medicine? Why?

Type I error

When there really is no difference (or association or correlation) between the populations, random sampling can lead to a difference (or association or correlation) large enough to be a statistically significant. This is a Type I error. It occurs when you decide to reject the null hypothesis when in fact the null hypothesis is true. It is a false positive.

Type II error

When there really is a difference (or association or correlation) between the populations, random sampling (and small sample size) can lead to a difference (or association or correlation) small enough to be not statistically significant. This is a Type II error. It occurs when you decide not to reject the null hypothesis when in fact the null hypothesis is false. It is a false negative.

If you set α to a very low value, you will make few Type I errors. That means that if the null hypothesis is true, there will be only a small chance that you will mistakenly call a result statistically significant. However, there is also a larger chance that you will not find a significant difference, even if the null hypothesis is false. In other words, reducing the value of α will decrease your chance of making a Type I error but increase the chance of a Type II error.

If you set α to a very large value, you will make more Type I errors. If the null hypothesis is true, there is a large chance that you will mistakenly conclude that the effect is statistically significant. But there is



a small chance of missing a real difference. In other words, increasing the value of α will increase your chance of making a Type I error but decrease the chance of a Type II error. The only way to reduce the chances of both a Type I error and a Type II error is to collect bigger samples.

In medicine it is desirable to minimize alpha-risk as if you affirm “something” that turns out to be wrong, there could be consequences and you could be retained accountable for it whereas if you miss to identify “something”, nothing bad can happen. You “just” missed a chance for improvement, someone else will likely take it later.

It is better to miss the discovery of a new molecule compared to the release of a dangerous one on the market.

5. Link the different disciplines to their definition:

Descriptive epidemiology	•————→	To study the determinants of diseases (etiologies, risk factors) and health behaviors
Analytical epidemiology	•————→	Measuring the extent, evolution over time and geographical distribution of health-related phenomena in human populations
Clinical research	•————→	To understand and evaluate the management of sick people (diagnosis, prognosis, therapy, prevention)

6. Give an example of a possible action to minimize each of those four following difficulties that may arise when collecting survey data

- Reliability of data
 - Declarative data are conditioned by the respondent's knowledge of the subject and the way they understand the questions: correctly formalize the question in the most unambiguous way possible, rather exploit structured and objective data if available, make sure sampling is appropriated.
 - Measurement tools may give different results depending on the users: simplify/change the procedure, use a friendlier tool, reduce the number of operators involved, standardize the training of the operators, evaluate their understanding of the procedure, control conditions that may influence operators (time of the day, workload,
- Non-recruitment
 - Stigma associated with certain diseases: anonymity, non in-person contact.
 - Population difficult to reach: geographically? Technology. If any, involve other professionals in direct contact with such population. Identify key points in their care pathway.

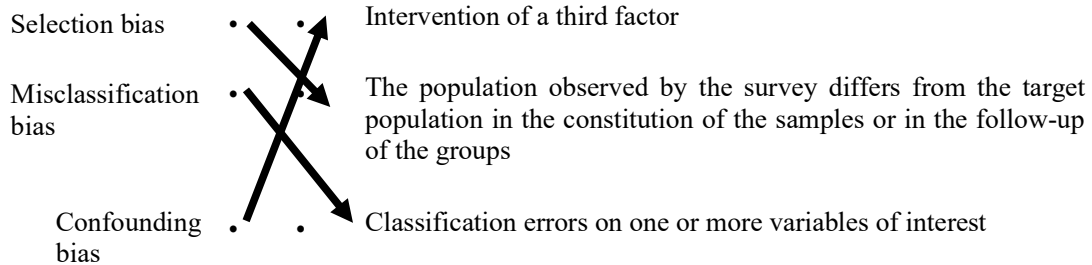
7. Fill-up that table with the following information for each data sources: example of collectable data, the data scale (individual or collective scale), the name of a structure that collects this type of data, the initial purpose for their collection (research, policy making, funding...) and an advantage and a disadvantage of this type of database:

Data source	Example	Scale	Structure	Initial collection purpose	advantage	disadvantage
cohorts/registers	E4N	Individual or collective scale (i.e. the target could be <i>individuals</i> or <i>families</i>)	Inserm (research institutes)	Research	<ul style="list-style-type: none"> • Clarity of temporale sequence of exposure.s-event.s • Allow calculation of incidence, RR, risk difference, attributable proportion • Measure of dose-effect relationship • Facilitate study of rare exposure • Allow examination of multiple effects of a single exposure • Avoid Selection Bias at Enrollment: Cohort studies, especially prospective cohort studies, reduce the possibility that the results will be biased by selecting subjects for the comparison group who may be more or less likely to have the outcome of interest, because in a cohort study the outcome is not known at baseline when exposure status is established. <p>Nevertheless, selection bias can occur in retrospective cohort studies (since the outcomes have already occurred at the time of selection), and it can occur in prospective cohort studies as a</p>	<ul style="list-style-type: none"> • Not adapted for rare diseases • Study duration+++ if latency+++ • Cost and complexity • Lost to follow-up • Change of exposure status during follow-up • Ethical questions • Sample size • Huge database size requiring data management skills

					result of differential loss to follow up.	
dedicated studies	Case control studies	Individual	Clinical research units	Research	<ul style="list-style-type: none"> • Possible (mainly) if disease is rare • Possible and short even if long latency • Lower costs • Lack of lost of follow-up (but selection of surviving cases) • Lack of ethical problems Possible to study several exposures	<ul style="list-style-type: none"> • Results will be quantified via poorly intuitive concepts, OR in particular • Estimation of incidence not possible • Memory and other bias can heavily influence data quality
patient records	Clinical narratives	Individual	Any hospital	Clinical cares	Usually readily available as it is already collected for administrative purposes	Non necessarily structured or digitalized
administrative records	PMSI	Individual	Hospitals/C NAM	Funding	<ul style="list-style-type: none"> • Structured and readily available. • Codes <u>can</u> be very reliable depending on the pathology. 	<ul style="list-style-type: none"> • Biased in a research context as it is not collected for this purpose. • Different coding habitudes among different services • Not every code is reliable
public data	Base de données publique des médicaments	Collective	HAS (Haute autorité de santé)	Research/pol icy making	<ul style="list-style-type: none"> • Allows transparent research • Assessing a community' need • Can lead to a flow of useful insights coming from 3rd parties 	<ul style="list-style-type: none"> • Can be misused or misunderstood • Privacy can be violated unintentionally • Can be subject to an embargo period not allowing the publication of recent data • Database itself is transparent but what's "behind" it may not hence data quality is not a guarantee



8. Which specific selection bias can artificially improve the result of a meta-analysis because of the way results are disseminated?
9. Biases are systematic errors that will limit the validity of a study. Which definition best fits each of the following categories:



10. Give the name of a method used to control an identified confounding bias:

Adjustment

11. Give the name of a method used to control unidentified confounding bias:

Randomization

12. About representativeness and selection bias, choose the right answer(s):

- Extrapolation of the results of a study to the targeted population can't be done when there is a selection bias
- Drawing the study sample from a database representative of the target population contribute to avoid selection bias
- A way to reduce selection bias is to standardize data collection conditions
- Representativeness is needed to analyze the effect of an exposure on an outcome
- Representativeness is needed to extrapolate the results of a study to the targeted population in real life

13. Give an example of selection bias in a case-control study

In case-control studies, selection bias can occur in the selection of cases if they are not representative of all cases within the population, or in the selection of controls if they are not representative of the population that produced the cases

Example: in a hospital-based case-control study looking at the relationship between alcohol consumption and development of liver cirrhosis, in the first instance we select our controls from patients hospitalised due to trauma (Controls A). We classify our exposure (alcohol consumption) into 'heavy alcohol use' and 'light / no alcohol use'.

Exposure	Cases (liver cirrhosis)	Controls A (trauma ward)	OR
Heavy OH use	80	40	6.0
Light/No OH use	20	60	reference
Total	100	100	

But, how representative are hospitalised trauma patients of the population which gave rise to the cases? In the trauma ward, where we have selected our controls, there may be a higher proportion of patients who report heavy alcohol use compared to those who report heavy drinking in the population which produced the cases (the general population), leading to an underestimation of

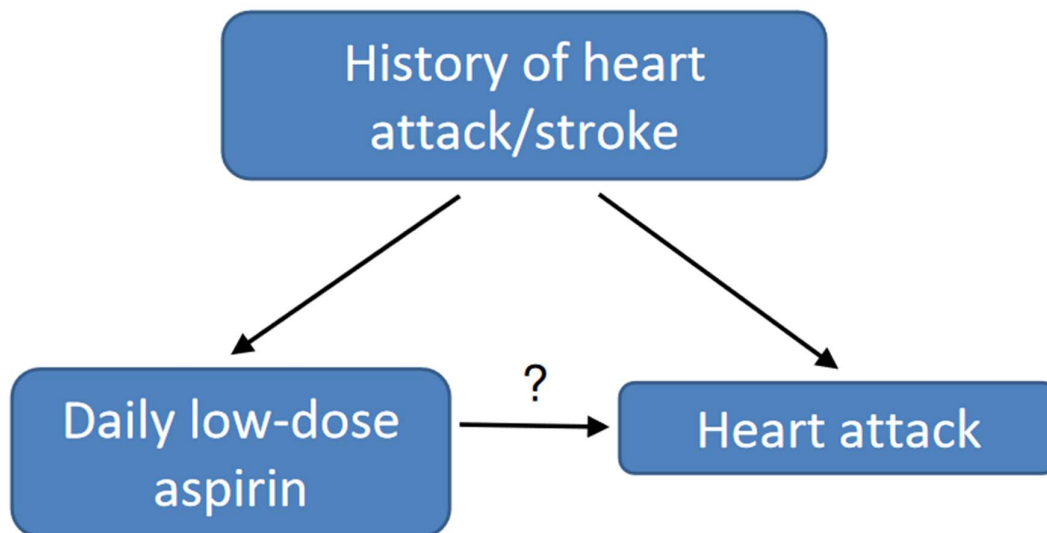
the odds ratio (OR). Compare this to the situation if we select our controls from hospitalised patients in a non-trauma ward (Controls B).

Exposure	Cases (liver cirrhosis)	Controls A (trauma ward)	OR	Controls B (non-trauma ward)	OR
Heavy OH use	80	40	6.0	10	36.0
Light/No OH use	20	60	reference	90	reference
Total	100	100		100	

14. Give an example of confusion bias in a cohort study

The quantitative association between exposure and outcome is distorted by a third factor with the following characteristics:

- associated with the exposure
- associated with the outcome
- not an intermediate on the causal pathway between exposure and outcome



15. Give an example of misclassification bias in a randomized trial

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.

Included studies in a systematic review could use different classification systems, potentially causing misclassification bias when the studies are pooled in a meta-analysis.

A meta-analysis of body size and development of prostate cancer found that the criteria used to define nonaggressive and aggressive prostate cancer varied between cohorts which may have lead to misclassification bias. (PMID: 29228634)

In measuring relationships between exposures and disease risk, misclassification bias can have unpredictable effects, i.e. it could increase or decrease an observed association.

In this article (PMID: 29309516) the authors investigated misclassification bias in hazard ratios (estimates of risk) in studies looking at the relationship between body mass index (BMI) and mortality.

Misreporting at higher BMI categories tended to bias hazard ratios upwards for some categories, but that effect was counterbalanced or even reversed by misreporting in other BMI categories, in particular, those that affected the reference category.

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.

Articles (to download on AMetice)

Article 1: *The Safety and Short-Term Efficacy of Aliskiren in the Treatment of Immunoglobulin A Nephropathy – A Randomized Cross-Over Study*

16. What is the rationale for this study?

Immunoglobulin A (IgA) nephropathy is the most common type of primary glomerulonephritis worldwide yet the optimal therapy remains unknown. ACE inhibitors or angiotensin receptor blockers (ARB) don't seem to be enough to treat severe patients. Preliminary data suggest a more complete suppression of the intra-renal RAAS with direct renin inhibition as compared with ARBs and ACE inhibitors. Laboratory research and previous study suggest that aliskiren, a direct renin inhibitor, has also an anti-proteinuric effects. That's the effect the authors are looking to quantify.

17. What is the experimental design chosen for this study? Explain it.

It's a randomized crossover study.

In a crossover trial, all participants receive all the interventions but the order in which they receive the interventions (the sequence) is randomised.

For example, if you have 3 interventions, participants will be randomised to one of the 3 sequences (ABC or ACB or BCA). Each stage of the assessment in a crossover trial is called a period. Period 1 is when the first intervention is introduced, period 2 is when participants move to the next intervention in the sequence, and so on.



It's important to consider that some interventions have a carryover effect. Interventions that can produce longer-lasting effects are not appropriate for crossover trials because the sequence of interventions may impact the results. For example, crossover trials are good for interventions that treat symptoms, but do not work for interventions that cure a condition.

Between the periods, you can introduce a washout period, where participants receive no intervention to let the effects of the previous intervention diminish.

In a crossover trial, participants act as their own control. Their data is analysed by comparing participants to themselves – before the intervention was introduced and after each intervention period – to find out if there was a change in the outcome you are measuring. Thil

18. What is the primary end point?

The change in proteinuria

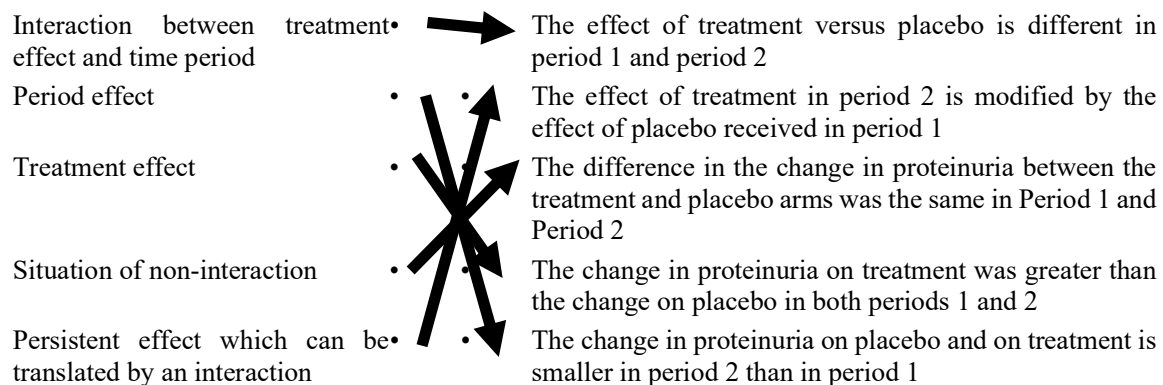
19. What are the advantages and constraints of this type of design compared to a parallel group trial?

- Advantages:
 - a crossover RCT potentially more efficient than other RCTs of a similar size.
 - better for long-term or chronic conditions with stable symptoms
 - the crossover design removes the variation between participants which exists in a parallel trial where each participant only receives one intervention.
- Constraints:
 - not well suited for acute conditions
 - carry-over effects
 - potentially more LoS since it takes longer to participate in multiple treatment arms

20. The intermediate phase of 4 weeks between the two treatment periods is intended to:

reduce carryover effects from the previous treatments and help researchers determine whether the outcome of the study is due to the effects of the study drug.

21. Link the effect to its definition



22. The role of randomization in this type of design is (choose the right answer(s)):

- To control the treatment effect
- To control the period effect
- To control for the possible effect of an interaction between the treatment and the period



- To allow a causal judgement to be made in the absence of an interaction between the treatment effect and the period
23. A placebo is administered in the control arm. In the absence of additional information, it can be assumed that (choose the right answer(s)):
- The study is mandatorily double-blinded
 - The study is not blinded at all because of the need for immediate intervention in case of renal failure
 - The study is not blinded at all, because blinding is not useful if the study is randomized
 - **Blinding, which ensures comparability between groups, is not useful if the study is randomized**
 - The study is certainly blinded, but we cannot say if it is single or double-blinded
24. Among the following proposals, give the criterion that can be used to judge a causal relationship between a risk factor and a disease (choose the right answer(s)):
- **Temporality: the effect occurs after the cause**
 - **Reproducibility**
 - **Dose-response relationship**
 - **The existence of a known mechanism that can explain the relationship**
 - No suitable proposal

Article 2: Deep learning for prediction of colorectal cancer outcome: a discovery and validation study

25. What was the aim of that study?

The aim of the present study was to develop a biomarker of patient outcome after primary colorectal cancer resection by directly analysing scanned conventional haematoxylin and eosin stained sections using deep learning.

26. What kind of methodology could be used in a future study to increase the level of proof of the result? Why is that methodology increasing the level of proof?
27. The authors found that the DOMore-v1-CRC classifier has a sensitivity of 52%, a specificity of 78%, a positive predictive value of 19% and a negative predictive value of 94% when comparing 3-year CSS to DOMore-v1-CRC good prognosis vs uncertain and poor prognosis. Define those parameters and rephrase those results.
- Sensitivity: $\frac{TP}{TP+FN}$
 - Specificity: $\frac{TN}{TN+FP}$
 - Positive predictive value: $\frac{TP}{TP+}$
 - Negative predictive value: $\frac{TN}{TN+FN}$



- The DOMore-v1-CRC classifier has a sensitivity of 52% when comparing 3-year CSS to DOMore-v1-CRC good prognosis vs uncertain and poor prognosis:

52% of positives are true positives = 52% of people placed in the uncertain and poor prognosis group correctly belong to it

- The DOMore-v1-CRC classifier has a specificity of 78% when comparing 3-year CSS to DOMore-v1-CRC good prognosis vs uncertain and poor prognosis:

78% of negatives are true negatives = 78% of people place in the good prognosis group correctly belongs to it.

- The DOMore-v1-CRC classifier has a positive predictive value of 19% when comparing 3-year CSS to DOMore-v1-CRC good prognosis vs uncertain and poor prognosis:

If you have been labeled “uncertain/poor prognosis”, there is a 19% chance that you are effectively a true positive.

- The DOMore-v1-CRC classifier has a negative predictive value of 94% when comparing 3-year CSS to DOMore-v1-CRC good prognosis vs uncertain and poor prognosis:

If you have been labeled “good prognosis”, there is a 94% chance that you are effectively a true negative.

28. In general, if you develop a new test, what parameter will you favor if the disease is very severe but easily curable with a non-invasive treatment (sensitivity or specificity)? Why?

Sensitivity. As the disease is very severe I want to make sure I treat ALL those who are in need. Given that the treatment isn't invasive, it's not a big deal: I'd rather treat (with no consequences) a few healthy people but make sure I don't miss any true positive.

29. In general, if you develop a new test, what parameter will you look first if the disease is severe with a difficult treatment and a high risk of side effects (sensitivity or specificity)? Why?

Specificity. As the treatment is no joke, I really need to rule out healthy people as I cannot afford to treat false positives.

Article 3: Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population-based screening programme in Australia

30. The introduction refers to “Phase III studies”. What those terms refers to? What are the other phases for drug development (purpose, population involve)?

Let's take the example of a clinical trial for vaccine development.

Phase I - Preclinical stage

This research-intensive stage takes place in the laboratory and it aims to find natural or synthetic antigens—foreign substances that induce an immune reaction in your body—that trigger the same reaction an actual virus or bacteria would. We are still looking for something to be tested.



Phase II - Is it safe, what's the right dose?

Phase 1 testing marks the first time the vaccine is tested in a small group of adults, usually between 20 to 80 people, to evaluate its safety and measure the immune response it generates. Phase 2a studies aim to determine the most effective dose, and expand the safety experience with the vaccine. Phase 2b involves more patients.

Phase III - How effective is the drug?

As in previous phases, adverse events can potentially occur and are not uncommon, particularly in large studies like this. If an unexpected serious adverse event occurs, recruitment or medication dosing may be paused so all pertinent medical information can be reviewed before deciding whether to restart the clinical trial. Phase 3 trials can sometimes take years.

Phase IV - Regulatory approval and licensing

Phase III trials are large, pivotal trials to determine safety and efficacy in sufficiently large numbers of patients with the targeted disease. If safety and efficacy are adequately proved, the new molecule advances to the new drug application stage.

Phase V - Post market surveillance

Even after the new drug is approved and licensed, regulatory agencies stay involved, continuing to monitor production; inspecting manufacturing facilities; and testing vaccines for potency, safety and purity. Adverse effects are monitored.

31. Why the authors made the choice to focus on women who presented for their first smear test?

Primary objective was to estimate the effectiveness of the quadrivalent vaccine in the population of sexually naïve young women with no previous infection but information on sexual history was not available from study participants → Women new to screening may be closer to sexual debut than women who have been regularly screened and for longer, despite having a history of only negative cytology results.

32. Some abnormalities may have gone unnoticed and undiagnosed. What kind of bias can this cause? Justify

Exposure opportunity bias, whereby control participants may have had systematically greater opportunity for vaccination owing to longer duration in the cohort overall.

33. A high level of education in the family is associated with a higher frequency of vaccination and less risky sexual behavior. What kind of bias is this?

Selection bias

34. Which ethical procedures have been implemented for this study?

This study underwent approval by the University of Queensland medical research ethics committee and Queensland Health human research ethics committee

35. What procedure has been implemented to avoid that the researchers have access to the name of the women involve in the study during the linkage of the databases?

Anonymisation