

PHS 2000B Exam 1

Welcome to the first exam of the term! The exam is released at 3 pm on Wednesday, March 9th and will be open for submission until Friday at 11:59pm. Please complete it and upload to Canvas - under the **Assignments** tab – 48 hours after having opened it. We have opted to widen the window of time available to meet students' different needs.

As always, you may refer to your notes and any books you would like, but ****please do not discuss the exam with any other students from class or your tutor****. By typing your name below you affirm that the work you are submitting is yours alone and that you have not discussed the questions or responses with anyone other than the instructional team.

If you have clarifying questions for the instructional team, please email the whole team and we will get back to you as soon as possible. During our regular 11:30 am – 1:00 pm class period on Thursday, March 10th, you may also log on to the [Zoom meeting \(Links to an external site.\)](#) and get an immediate response from the instructional team.

There is a [Google Doc \(Links to an external site.\)](#) where we will be posting any clarifications that arise from questions we receive during the exam. If we post a clarification, we will also post an Announcement referring you to the Google Doc.

Please note that any math or drawings you want to include can be typeset into the document or can be pasted in as an image. You are not required to typeset the math.
Good luck!

Name:

Part I. Mediation (10 points)

The school district in city X is interested in understanding the indirect effect of education on wellbeing via middle-aged/adult income. To help answer this question, your job is to analyze the results from a study of 8000 people in city X. The study looked at education (measured at ages 25-35), income (measured age 35-45), and wellbeing (measured at ages 55-65). The EQ-5D generic descriptive system for health-related quality of life and a 3-item Satisfaction with Life Scale were used to assess wellbeing. Information on education and household income were obtained from a survey of study participants. *Some prior evidence suggests that the effect of income on wellbeing may vary by education level.* Assume that you have sufficient baseline demographic, social, and health information for vector C1 (confounders of the exposure-outcome relationship) and vector C2 (confounders of the mediator-outcome relationship) to control for confounding of the exposure-outcome and mediator-outcome relationships.

1. Please draw the DAG you would use to guide your analysis based on the information above, assuming that the data is sufficient for all necessary confounding control. Indicate the exposure (A), mediator (M), outcome (Y), and confounders (C1 and C2) used in your DAG below: (1 point)

- i) A = _____
- ii) M = _____
- iii) Y = _____

Draw DAG here:

2. Colleague 1 has proposed the following steps to determine the direct and indirect effect of education (here, continuous) on wellbeing via income.

Step 1. Estimate the following regression models:

$$E[Y|A = a, C = c] = \phi_0 + \phi_1 a + \phi_2' c1 + \phi_3' c2$$

$$E[Y|A = a, M = m, C = c] = \beta_0 + \beta_1 a + \beta_2 m + \beta_3' c1 + \beta_4' c2$$

Step 2. $\beta_1 = \text{direct effect}$

Step 3. $\phi_1 - \beta_1 = \text{indirect effect}$

Would you agree with this proposed approach? Why or why not? (1 point)

3. Colleague 2 notices that the survey has also captured information on subjective social status (age 35-45) and proposes considering both income and subjective social status as mediators (one at a time), and to use the counterfactual approach twice, with each mediator considered separately, to estimate the Natural Direct Effect (NDE) and Natural Indirect effect (NIE) of education on wellbeing via either income or subjective social status.

However, colleague 3 is skeptical because she believes that subjective social status may causally affect income. Why does colleague 3's hypothesis about the relationships between these factors affect the appropriateness of colleague 2's proposal? (Draw a DAG to support your answer) (2 points)

4. After scanning the literature, you decide that colleague 3's hypothesis is unlikely because in fact income affects subjective social status, rather than vice versa. Your team chooses to go ahead with a mediation analysis using only income as the mediator.

The investigators ultimately decided to dichotomize the outcome of well-being rather than use it as continuous (in contrast to question 2). Your mediation analysis uses the counterfactual approach to estimate the CDE(0), NDE, and NIE with (5 points):

- Exposure: high ($A=1$) vs. low levels of education ($A=0$).
- Mediator: income (continuous) (M)
- Outcome: high ($Y=1$) vs. low ($Y=0$) levels of wellbeing

- i) Because the outcome is relatively common, you fit a log-binomial model for the outcome. Please write out the models you would use to do this, assuming a linear regression for the mediator and a log-binomial regression for the outcome allowing for exposure-mediator interaction:

In your analysis, you mean-center the income variable so that $M=0$ denotes the mean income for the sample. Your analysis provides the following output on the risk ratio scale:

<i>Wellbeing**</i>			
	CDE(0)	NDE	NIE
<i>Education*</i>	1.01	1.06	1.23

*Education: low (reference)=primary and secondary school or similar (ie, 7–10 years of schooling) or vocational school or high school; high=college or university (less than 4 years) or college or university (4 years or more).

**well-being was measured by the first three items from the Satisfaction with Life Scale (SWLS) measured on a seven-point scale. High well-being was defined as those who reported 6 or 7 for all three items

- ii) Interpret the CDE(0), NDE, and NIE in the context of the study.

iii) Calculate the total effect *on the risk ratio scale* and calculate the proportion mediated *on the risk difference scale* based on the numbers above. Interpret the proportion mediated.

5. Colleague 1 is surprised that the CDE(0) does not equal the NDE. How would you explain why this might be to them in one sentence? (1 point)

Part II. Interaction (3 points)

1. Assume there is a new study that collects data on the same variables as in part I, but the new study uses a different study design and randomizes participants to an interview training program at age 35. You are in particular interested in whether or not the association between the interview training program (A) and dichotomized wellbeing (Y) differs when stratified by high vs low level of education (Z) on the risk ratio scale. (3 points)
 - i) Do you need to control for the confounders of the education-wellbeing relationship to answer your question of interest?
 - ii) Please write out the expression of interest using counterfactual notation.
 - iii) Indicate if this is describing causal interaction or effect heterogeneity and how you can use this to make decisions around interview training programs.

Part III. Sensitivity Analysis and Measurement Error (12 points)

As part of your doctoral dissertation, you are interested in investigating the effect of housing on physical health conditions. You decide to begin by conducting a literature review. One recent study, which we will refer to as Study A, assessed the effect of livable space (measured in square feet of residential floor area) on incident hypertension among adults in Hong Kong.¹ The study reported 5% lower odds of incident hypertension for every 100 square foot increase in livable space after adjustment for several potential confounders (adjusted OR: 0.95, 95% confidence interval: 0.91 – 0.99).

1. You are concerned about potential unmeasured confounding in Study A. Calculate an E-value for (i) the point estimate and (ii) the 95% confidence interval. You do not have to provide interpretations. You may assume that incident hypertension is rare (prevalence <15%). (2 points)

¹ This scenario is based on the following paper: Sarkar et al. Liveable residential space, residential density, and hypertension in Hong Kong: A population-based cohort study. PLoS Med. 2021;18(11): e1003824. You do not have to read this paper to answer any of the exam questions.

2. A second study, Study B, reported the same E-value as Study A for their point estimate of the effect of livable space on incident hypertension. Your colleague argues that the potential for unmeasured confounding is therefore equal in these two studies. Do you agree? Provide two reasons why you either agree or disagree. Assume that you know nothing else about the study design of Study B apart from the information provided here. (2 points)

3. You are particularly worried about unmeasured confounding by residential green space in Study A. You decide to calculate a (multiplicative) bias factor using the 1978 formula by Schlesselman specifying the prevalence of this unmeasured confounder (Slide 29 of the sensitivity analysis lecture). You obtain an estimate of the risk ratio for low residential green space and incident hypertension based on a recent meta-analysis, which you will use in all calculations. You then obtain two sets of estimates for the prevalence of low residential green space: (i) estimates of $P(U = 1|a_1, c)$ and $P(U = 1|a_0, c)$ obtained from *a representative sample of all Hong Kong neighborhoods*, and (ii) estimates of $P(U = 1|a_1, c)$ and $P(U = 1|a_0, c)$ obtained from *a subset of Hong Kong neighborhoods that all have very similar levels of residential green space* due to uniform city planning. Which of these two sets of estimates would you expect to result in a bias factor closer to 1? Why? (2 points)

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4. Study A obtained information on incident hypertension (yes/no) using a combination of direct measurements and self-reported information on current anti-hypertensive use. Imagine that incident hypertension was mis-measured because anti-hypertensive use was sometimes inaccurately self-reported. Individuals with lower education level were more likely to misreport anti-hypertensive use. Education level is an important potential confounder in Study A. Assume no other study variables were mis-measured. What type of measurement error does this scenario describe? (1 point)
5. Draw a DAG to illustrate this measurement error. For simplicity, include only education level, the exposure, the outcome, and any mis-measured versions of these variables/measurement errors that are necessary to depict the scenario described above. (1 point)

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6. You decide to conduct an external validation study among those with low education level. In this validation study, 8.7% of those who were classified as not having incident hypertension using the mis-reported measure truly had hypertension based on the gold standard. In addition, 12.4% of those who were classified as having incident hypertension using the mis-reported measure did not have hypertension based on the gold standard. Using this information, calculate (i) the positive predictive value for hypertension among those with low education and (ii) the negative predictive value for hypertension among those with low education. (2 points)

Part IV and Part V: Propensity Score and Marginal Structural Model

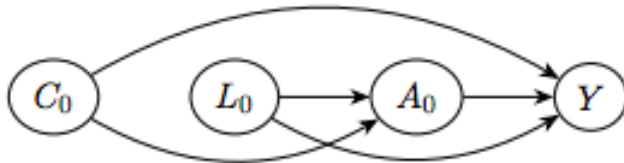
Part IV and Part V are inspired by an ongoing study.

Overview: A research team is interested in understanding the comparative effectiveness of two treatment regimens in treating patients with pulmonary arterial hypertension (PAH), a rare disease where blood pressure in the lungs can become dangerously high due to narrowing and thickening of the tiny arteries in the lung. Specifically, using observational data, the team wants to know whether a medication regimen containing two different classes of medication (hence called “dual therapy”) is more effective in protecting against all-cause hospitalization among patients with PAH, compared with the conventional regimen containing a single medication (hence called “mono therapy”).

Throughout PART IV and PART V, unless otherwise specified, we assume that the study design is valid (e.g., a new-user design that avoids time-related bias including immortal time bias) and that there is no measurement error or selection bias. You do not need to look up any new medical information.

PART IV. Propensity Score [6 pts]

For part IV, we assume that all patients adhere to their medication throughout the study. The research team assumes the following DAG:



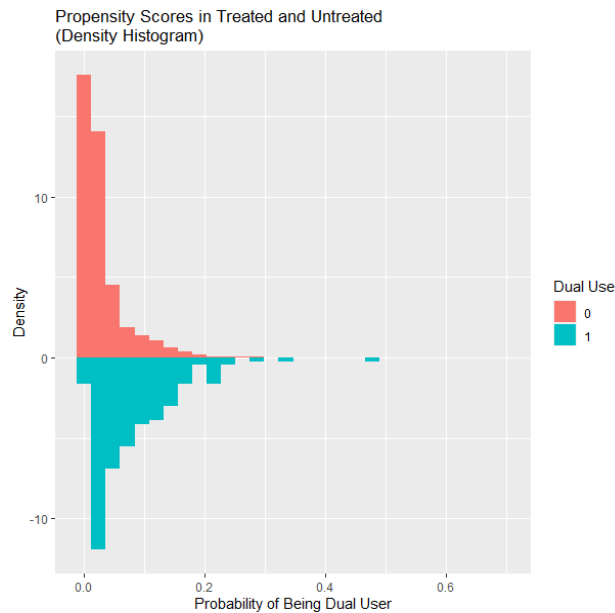
where A_0 is being treated with dual therapy versus mono therapy, C_0 includes patient baseline age, birth sex, baseline Syncope symptom, and baseline utilization of echocardiography. L_0 is the comorbidity index (i.e. Charlson-Quan Comorbidity Index) at baseline; the greater the index value, the more comorbidities a patient has. Outcome $Y = 1$ when there is a PAH event during follow-up and $Y = 0$ otherwise. Assume that we have no unmeasured confounding (conditional exchangeability) *at baseline*, conditional on all listed baseline confounding variables C_0 and L_0 .

In the protocol, the investigator did not specify a causal estimand of interest but proposed several methods to adjust for baseline confounding. Before conducting propensity score-based analysis, the investigator looked at the distribution of baseline confounding variables stratified by treatment groups in the original eligible population (SMD: standardized mean difference):

Table 1. Stratified Distribution of Baseline Confounding Variables

Variable Type	Confounding Variable	Mono	Dual	SMD
	N	5527	182	
C_0 , Continuous	Age at baseline (mean(SD))	58.14 (11.60)	55.58 (11.51)	0.221
L_0 , Continuous	Comorbidity Index (mean (SD))	2.66 (2.40)	3.84 (3.17)	0.417
C_0 , Binary: 1= Male, 0= Female	Sex assigned at birth: Male (%)	3658 (66.2)	58 (31.9)	0.731
C_0 , Binary, 1=Yes, 0=No	PAH symptoms: Syncope (%)	353 (6.4)	22 (12.1)	0.198
C_0 , Binary, 1=Yes, 0=No	PAH-related procedure, Echocardiography (%)	3273 (59.2)	141 (77.5)	0.4

The team fits a propensity score model and obtains the following propensity score distribution for those who actually used dual therapy (Dual Use =1) and monotherapy (Dual Use = 0):



The team also calculated stabilized propensity score weights which have the following distribution:

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
0.06789	0.97633	0.98176	0.99571	1.00333	8.37986

1. The team is thinking about using propensity score matching or weighting. Give at least one potential concern we would generally have for each approach (matching and weighting). Then explain in one or two sentences why you think there is or is not any issue for each method with this particular dataset (hint: there is more than one right answer) [2pt].

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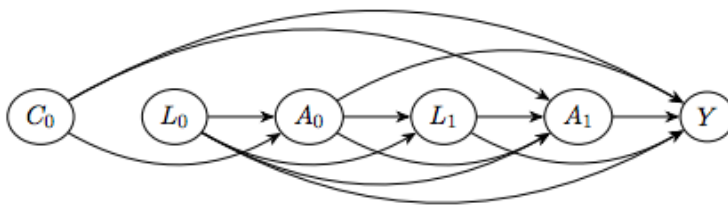
Now, regardless of your answer to previous questions, let's suppose the research team proceeded with the propensity score analyses as part of the primary analysis. The investigators proposed the following methods in the protocol:

- Method 1: using logistic model, regress all-cause hospitalization indicator on treatment group and the baseline confounding variables.
 - Method 2: using logistic model, regress all-cause hospitalization indicator on treatment group (dual therapy versus monotherapy), weighted by the following propensity score weights:
 $\frac{1}{\hat{P}\{A_0=1|c_0,l_0\}}$ for the dual therapy users and $\frac{1}{\hat{P}\{A_0=0|c_0,l_0\}}$ for the mono therapy users.
 - Method 3: conduct a 1:1 nearest-neighbor matching to the dual therapy user group (without discarding dual therapy users), then run a logistic regression, regressing all-cause hospitalization indicator on treatment groups (dual therapy versus mono therapy) within the matched data.
2. Suppose a patient advocacy group is interested in knowing what would happen to the dual therapy users' all-cause hospitalization outcome had they been treated with mono therapy instead, the result from which method(s) would be the most relevant to answer the above research question? What effect is this method estimating? [2 pt]
3. Among the three methods:
- a. Which propensity score-based method(s) can be used with bootstrap to obtain the valid standard error? No explanation needed. [1 pt]
 - b. Which method imposes the most modeling assumptions on the relationship between covariate and outcome? No explanation needed. [1 pt]

Part V. Marginal Structural Model [7 pts]

In Part IV, the researchers assumed that all patients fully adhere to their medications but this assumption is clearly not realistic in a non-clinical trial setting. For example, patients experiencing changes in comorbidities level may switch from dual therapy to monotherapy.

So now for part V we will allow patients to switch between dual therapy and mono therapy during study follow-up. **We are now interested in the joint effect of staying on dual therapy for both time points compared with staying on mono therapy for both time points in preventing all-cause hospitalization.** One question of interest, among others, concerns the joint effect among those patients whose baseline comorbidity index is equal to 0. In this setting, let's assume the following new DAG:



where A_0, A_1 is being treated with dual therapy (=1) or monotherapy (=0) at baseline and at follow-up time point 1 respectively; L_0, L_1 is the comorbidity index value at baseline and at follow-up time point 1. C_0, Y has the same representation as in the DAG in part IV.

1. Write out our causal estimand on the odds ratio scale using counterfactual notation for the joint effect of staying on dual therapy for both time points compared with staying on mono therapy for both time points among the subgroup with baseline comorbidity index equal to 0 [1 pt].
2. Your friend, who is a Biostatistics PhD student at another university, suggests using all of the longitudinal data you have to simply run a logistic regression, regressing Y on A_0, A_1 and C_0, L_0 and L_1 , potentially including polynomial terms and product terms to allow non-linearity and effect modification. Which single arrow from the DAG in part V would you need to remove such that this analysis approach would give us the valid joint treatment effect conditional on C_0, L_0 and L_1 values [2 pt]? No explanation is needed.

Fortunately, you do not listen to him because you know that arrow cannot be removed based on your subject matter knowledge. Instead, to estimate the causal estimand, you use a marginal structural model for the joint effect of dual vs. mono therapy at the two timepoints, *conditional on baseline comorbidity*.

3. Write a formula for the stabilized weight for a patient who uses dual therapy at baseline but switches to mono therapy at time point 1, in terms of the probability of treatment at each time point, (i.e. no logistic models are needed in your formula, just probabilities). *Recall that the marginal structural model is conditional on baseline comorbidity but not on other covariates.* [2 pt].

4. Using the weights for each individual, you estimate the parameters of the following marginal structural model:

$$\text{logit} \left(P(Y_{a_0 a_1} = 1 | L_0 = l_0) \right) = \beta_0 + \beta_1 a_0 + \beta_2 a_1 + \beta_3 a_0 a_1 + \beta_4 l_0 + \beta_5 a_0 l_0 + \beta_6 a_1 l_0$$

and obtain the following estimates: $\widehat{\beta}_0 = -5$, $\widehat{\beta}_1 = -0.15$, $\widehat{\beta}_2 = -0.1$, $\widehat{\beta}_3 = 0$, $\widehat{\beta}_4 = 0.1$, $\widehat{\beta}_5 = \widehat{\beta}_6 = 0.05$. Calculate and provide an interpretation of the joint effect estimate of the causal effect of interest you defined in question 1. [2 pt]