

EXAMINATION FOR INTERNAL STUDENTS

For The Following Qualification:-

M.Res.

M.Res. Health Services Research & Policy: Evidence Based Medicine with Epidemiology and Population Health

COURSE CODE : HSRP0003

DATE : 05-JUN-03

TIME : 10.00

TIME ALLOWED : 3 Hours

Paper II. Epidemiology (HSRP0003) and statistics (HSRP0002)

Answer FOUR questions only: Three questions from Section I
and
One question from Section II

Use a separate answer book for each question

Calculator : - Students are permitted to take in and use their own electronic calculator for Paper II. The College has approved the following models for use in examinations: Casio FX83WA (battery powered), Casio FX85WA (solar powered). Examiners must check the model and students must write the model used on their script.

WHERE APPROPRIATE, REFERENCE CAN BE MADE TO THE SERVICE AND CONDITIONS OF ANY NAMED COUNTRY WITH WHICH THE CANDIDATE IS FAMILIAR

Please write legibly

Section I (Answer three questions only)

1. Screening for Alzheimer's Disease

A case-control study (Poirier et al, Lancet 1993) reported that a certain gene marker was more common in 100 cases of Alzheimer's disease (AD) than in 100 age-matched healthy controls.

	AD	Controls
gene marker present	25	5
gene marker absent	75	95

QUESTION CONTINUED ON THE NEXT PAGE

TURN OVER

- a) From the table, calculate the sensitivity and specificity of the gene marker for Alzheimer's disease. 5 marks
- b) Calculate the odds ratio for being gene marker positive among AD cases compared with controls. Explain the result in everyday language in one sentence. 10 marks
- c) 1000 healthy individuals aged 50 years from the general population were followed until death. Of these individuals, 200 developed AD. Draw up a two-by-two table, similar to that on the previous page, to show the prevalence of gene test 'negatives' and 'positives' among AD cases and non-cases. (Tip: you can use the sensitivity and specificity calculated in (i) to fill in the table.) 5 marks
- e) What is the probability that an individual from the general population who is positive for the marker will actually develop AD? (This is equivalent to calculating the positive predictive value (PPV) of the gene test.) 5 marks
- f) A guest editorial in the Lancet, accompanying Poirier et al, stated
- "These results indicate that a common genetic variant... confers a high probability that an individual will develop Alzheimer's disease."
- Using your results from (a), (b) and (d), do you agree with the editorial comment? Explain your reasons for agreeing/disagreeing with the editorial's conclusion, and if you do not agree, why do you think the editorial reached a different conclusion to your own? 10 marks
- g) Note the commonly used criteria for justifying a screening programme, and write short notes on each criterion to evaluate whether the gene marker above is suitable as an Alzheimer's Disease screening test. 15 marks

CONTINUED

2. Below and overleaf there are brief outlines of four hypothetical studies. Read each one and answer the questions (2.5 marks for each answer).

a) 7,800 adults aged 35-54 answered a questionnaire about respiratory health and diet. Subjects who ate fresh fruit and vegetables at least once per day were half as likely to have productive cough in the winter compared with subjects who rarely ate fruit and vegetables.

- i What type of study is this?
- ii What was the outcome of interest?
- iii What was the exposure of interest?
- iv What do we call the measure of association between exposure and disease used in this type of study?
- v Does this study prove that the relation between exposure and outcome is a causal relationship? Briefly explain your opinion.
- vi Outline a study design that would strengthen the evidence for the protective role of fruit and vegetables.

15 marks

b) 200 cases of small cell lung cancer reported to the local cancer register were compared with 400 healthy subjects randomly selected from the general population. 80 lung cancer cases and 20 healthy subjects had a *BRAF* gene mutation.

- i What type of study is this?
- ii With the available data calculate an estimate of the association between exposure and disease.
- iii What do we call this measure of association?
- iv What does this mean in plain English?

10 marks

c) 120 children with severe asthma were randomly divided into two groups (60 in each). One group followed a new treatment regimen, the other group was given the best standard treatment used so far. After 2 months of treatment 15 of the children on the novel treatment regimen were admitted to hospital for an acute exacerbation of asthma, as were 6 children in the other group.

- i What type of study is this?
- ii With the available data calculate an estimate of the association between exposure and outcome of interest.
- iii What do we call this measure of association?
- iv What does this mean in plain English?

10 marks

QUESTION CONTINUED ON THE NEXT PAGE

TURN OVER

d) 13,329 men and women aged 65-84 years completed a questionnaire about their alcohol drinking habits. After 16 years of follow-up 833 participants had had an haemorrhagic stroke. Note that 8 grams of alcohol is equivalent to 1 unit which is 1 glass of wine, $\frac{1}{2}$ a pint of beer, or a measure of spirit such as whiskey, vodka, or gin.

	Proportion in population	Risk of haemorrhagic stroke	Relative risk
Never	23.3%	4.9%	1.00
1-10 g per day	36.8%	5.3%	
10-20 g per day	20.1%	6.2%	
20-30 g per day	7.4%	7.8%	
> 30 g per day	12.4%	10.5%	

- i What sort of study was this?
- ii With the available data calculate the missing relative risk values for subjects in each of the alcohol consumption categories.
- iii Calculate the absolute risk of haemorrhagic stroke in study participants drinking 30g + per day.
- iv Calculate the absolute risk of haemorrhagic stroke attributable to alcohol consumption in study participants drinking 30g + per day.
- v Calculate the attributable risk fraction (%) due to alcohol in this group.
- vi In plain English what does drinking >30g of alcohol per day mean in terms of the risk of these study participants having an haemorrhagic stroke?

15 marks

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3. Gulf War Syndrome

The 1991 Gulf War was followed by several reports of unexplained illness among veterans. Signs and symptoms included fatigue, joint pain, nasal congestion, diarrhoea, joint stiffness, headaches, impaired concentration and general weakness. Reports appeared often in the popular press and medical journals, provoking widespread belief that modern desert warfare involves health hazards beyond the accepted risks of death and injury associated with battle.

The MRC and Ministry of Defence are likely to issue a call for proposals to study the possible health effects of military service in the event of a second Gulf War. How would you design a study to investigate this phenomenon?

a) Please describe the study in terms of population, exposure measurements, outcome measurements, and methods for overcoming bias and confounding.

35 marks

b) Give some indication of the strengths and weaknesses of your choice of design.

15 marks

TURN OVER

4. Follow-up after surgery

It has been suggested that intensive follow-up (FU) after curative resection for colorectal cancer may improve survival. A pooled analysis of four studies found that five-year fatality was 197/666 in the intensive FU groups and 247/676 in the usual FU groups.

- a) Give two possible reasons why the pooled analysis described above might have been carried out. 5 marks
- b) What study design is ideal for this type of question, and what are the strengths of the design? 10 marks
- c) There was some evidence of heterogeneity in the study findings. Suggest some sources of heterogeneity in this context. 10 marks
- d) Calculate the 5 year risk of dying (fatality rate) in the two groups above. 5 marks
- e) Calculate the relative risk of dying in the two groups above. 5 marks
- f) Calculate the number needed to treat (NNT) to save one life. 5 marks
- g) Assuming the results of the pooled analysis were statistically significant, how might NICE be expected to act on the evidence? 10 marks

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5. Social class and coronary heart disease

The Whitehall II study recruited 10,308 (33% female) London-based civil servants aged 35-55 years at baseline (1985-1988). Participants completed a baseline questionnaire detailing job title, behavioural factors and general health questions. Based on salary and work role, the civil service defines a hierarchy of employment grades which were analysed in three levels: high (senior executives), intermediate and low (clerical and support staff). They were followed up for a mean of 5.3 years. New cases of coronary heart disease were defined using validated questionnaires.

(Lancet 1997;350:235-39 Marmot, Bosma, Hemingway, Brunner, Stansfeld)

Employment grade	Age adjusted relative risk of CHD	Fully adjusted* relative risk
MEN		
High	1.00	1.00
Intermediate	1.25 (1.00-1.57)	1.21 (0.96-1.52)
Low	1.50 (0.98-2.29)	1.30 (0.85-2.01)
WOMEN		
High	1.00	1.00
Intermediate	1.12 (0.69-1.79)	1.06 (0.66-1.72)
Low	1.47 (0.92-2.35)	1.35 (0.84-2.18)

* Adjusted for age, smoking, serum cholesterol, body-mass index, hypertension, and physical activity

- a) What kind of study is this? 5 marks
- b) What is the exposure and what is the outcome? 5 marks
- c) Describe the age-adjusted relationship shown in the table above. 10 marks
- e) Why do you think the authors adjusted for age? 5 marks
- f) How do you interpret the fully adjusted risks? 10 marks
- g) What other factors might explain the social gradient? 5 marks
- h) How might you explore what other factors explain the social gradient among participants in this study? 5 marks
- i) How generalisable do you think the results are from this study to the rest of the population? 5 marks

TURN OVER

6. Association or causation?

In epidemiological studies causality is often assessed under the following headings:

- | | |
|---|----------|
| a) Temporality (timing of exposure and disease) | 10 marks |
| b) Plausibility | 10 marks |
| c) Strength of association | 10 marks |
| d) Dose-response relationship | 10 marks |
| e) Specificity (of the association) | 10 marks |

Briefly explain what is meant by each heading and why they are important in assessing cause and effect. Give illustrations and, where relevant, identify study designs most likely to provide evidence of this sort.

CONTINUED

Section II (Answer one question only)

1. In a randomised trial, 34 patients with a particular behavioural disorder were randomised to either cognitive therapy or usual care. Measurements of social functioning and clinical symptoms were taken at baseline and after 6 months. The investigators were interested to assess the effect of cognitive therapy on social functioning. Table 1 shows the Social Functioning Questionnaire (SFQ) scores in the two groups (lower scores indicate improved social functioning). Figures 1 and 2 and Table 2 relate to a parametric analysis of the social functioning data.

With reference to the various results, tables and figures below, write detailed paragraphs describing

- | | |
|--|----------|
| a) the methods used for the parametric analyses (in particular mentioning assumptions of the methods and whether these are justified, and a statement of any null hypotheses being tested) | 10 marks |
| b) the results obtained | 10 marks |
| c) the interpretation of results | 10 marks |

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Table 1: SFQ score data at baseline and follow-up by randomised group

	Usual care (N=16)		Cognitive therapy (N=18)	
	Baseline	Follow-up*	Baseline	Follow-up*
	21	12	14	11
	13	12	16	10
	11	11	15	13
	15	18	18	15
	22	21	11	7
	18	16	19	20
	17	7	13	7
	15	12	7	15
	19	18	7	10
	13	13	6	3
	13	10	18	15
	9	8	14	3
	14	11	9	2
	19	15	9	9
	16	Missing	8	9
	12	Missing	8	11
			2	7
			20	Missing
Mean (SD)	15.63 (3.7)	13.14 (4.0)	11.89 (5.18)	9.82 (4.85)
Median (interquartile range)	15.5 (13 to 18.5)	12 (7 to 21)	12 (8 to 16)	10 (2 to 20)

*Variance ratio test for follow-up SFQ scores: P=0.47

Shapiro-Francia W' test for follow-up SFQ scores: P=0.81

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Plots for follow-up SFQ scores

Figure 1

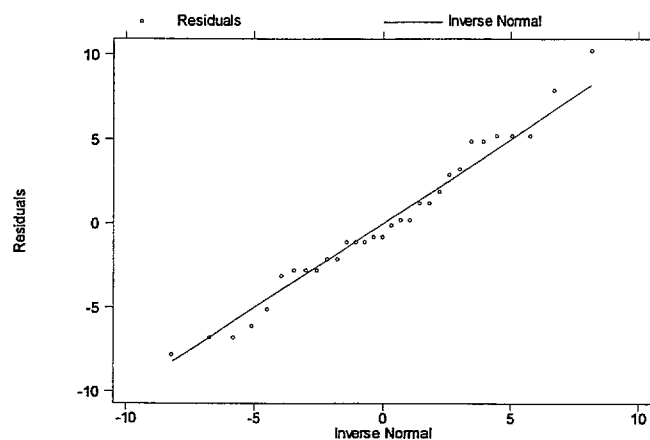


Figure 2

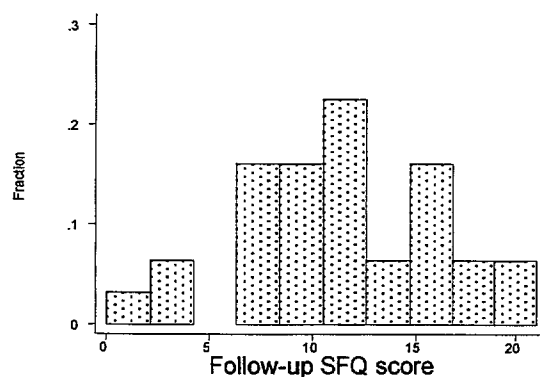


Table 2: Results from parametric analyses of follow-up SFQ score

	Treatment effect estimate* (95% confidence interval)	P-value (2-tailed)
Unadjusted	3.32 (0.01 to 6.63)	0.050 (t-test)
Adjusted for baseline SFQ score	0.88 (-2.31 to 4.07)	0.58 (regression)

*usual care- cognitive therapy

QUESTION CONTINUED ON THE NEXT PAGE

TURN OVER

d) A non parametric analysis gave the following results :

Treatment effect estimate (95% confidence interval): 3 (0 to 7),
Mann-Whitney test: P-value = 0.04

How was the treatment effect estimate calculated? Interpret the non parametric results. When is it appropriate to use such a non parametric approach? Should this be preferred for the SFQ analysis?

10 marks

e) One of the research team suggested dichotomising the Social Functioning Scale to provide 2 groups, those with an improved social functioning after intervention and those without an improved social functioning. With this as the outcome of interest briefly describe the analysis you might use to compare the randomised groups (mention the estimate and type of test).

10 marks

CONTINUED

2. A clinical trial was carried out to assess whether Peppermint oil was effective for relieving the symptoms of irritable bowel syndrome (IBS). It was reported that out of 19 sufferers given the oil, 13 (68%) found relief compared to only 6 (26%) from the other group of 23 patients who were not given the oil. Based on a statistical analysis, the researchers concluded that peppermint oil has a relaxing effect on the bowel spasms which cause the symptoms of IBS.
- a) Construct an appropriate 2x2 table to summarise the results from the trial. 5 marks
 - b) Calculate the estimated treatment effect? 5 marks
 - c) What statistical methods would you use to make a comparison of the two groups? 5 marks
 - d) What would you expect to see in the results of your analysis if the conclusion given above is correct? 5 marks
 - e) What further information about the design of the study would you require in order to assess the reliability of the trial results? 5 marks

In a study of 24 men it was of particular interest to examine the relationship between body mass index (measured in Kg/m^2) (BMI) and diastolic blood pressure (DBP) (measured in mmHg).

- f) What do correlation coefficients tell us about the relationship between two such variables? 5 marks
- g) In this study, the Pearson correlation coefficient was found to be 0.49. What does this say about the relationship of interest? 5 marks
- h) A linear regression model of the form $\text{DBP} = \alpha + \beta \text{BMI}$ was fitted. Estimates of α and β were 64.5 and 1.05 respectively. What do these estimates tell us about the relationship between DBP and BMI? 5 marks

QUESTION CONTINUED ON THE NEXT PAGE

TURN OVER

- i) Using the model described in h), what would be the predicted DBP for a man with a BMI of 20kg/m^2 ? 5 marks
- j) The 95% confidence interval and P-value for estimate β were 0.27 to 1.83 and $P=0.02$ respectively. What do you conclude about the relationship between DBP and BMI? 5 marks

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3. The following (fictitious) data concern survival of patients following an HIV positive diagnosis:

Age at diagnosis	Outcome	Age at outcome
25	Death	42
28	Death	37
37	Alive at end of follow up	57
39	Alive at end of follow up	50
42	Death	55
46	Death	49
51	Alive at end of follow up	71
58	Alive at end of follow up	72

- a) Explain how the numbers in the last two columns of the life table below are calculated.

5 marks

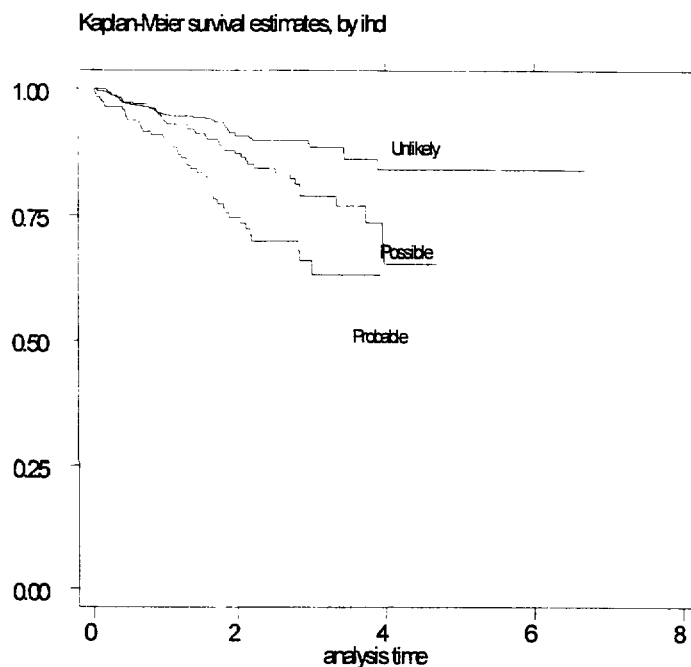
Interval from diagnosis (years)	No living at start of interval (n)	Death (d)	Censoring (c)	Probability of survival	Cumulative probability of survival/
[3,9)	8	1	0	0.875	0.875
[9,11)	7	1	0	0.857	0.750
[11,13)	6	0	1	1	0.750
[13,14)	5	1	0	0.8	0.600
[14,17)	4	0	1	1	0.600
[17,20)	3	1	0	0.666	0.400
[20, --)	2	0	2	1	0.400

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A study collected waiting times for abdominal aortic aneurysm surgery. Patients can experience three outcomes 1) death, 2) surgery or 3) end of follow up (i.e. alive and without having had surgery by the end of the study). Most patients have to wait until they are fit enough to undergo surgery, and unfortunately many die in the interim. Of the 1214 individuals in the study there were 160 deaths (13.2%), 295 (24.3%) went for surgery and 759 (62.5%) reached the end of follow up. Data were also collected on whether there was evidence of ischaemic heart disease (IHD) from ECG and the aneurysm size (measured in cm).

- b) If time till death (i.e. survival) is our main interest, then the other 2 outcomes are censoring events. Is the censoring mechanism “informative” in this study? 5 marks
- c) The incidence rate (of death) is 0.075. Estimate the total time at risk (in years) for patients in the study. 5 marks
- d) The figure below shows the Kaplan Meier graph for patients that had unlikely, possible and probable evidence of IHD. What does the graph suggest about the survival for the different groups? 5 marks



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- e) What test could one use to formally assess whether there is evidence of a difference in survival between these groups?
The P-value from this test is $P < 0.001$, interpret this. 6 marks
- f) The hazard ratios for possible and probable IHD relative to unlikely IHD are 1.7 (95% confidence interval: 1.1 to 2.6) and 3.2 (95% confidence interval: 2.1 to 4.9). Interpret these results. 8 mark
- g) What regression technique could be used to obtain such hazard ratios? What important assumption underlies this method and how could this be visually assessed from a plot of the survival curves ? 8 marks
- h) Incorporating aneurysm size into the regression model provides the following hazard ratios for possible and probable IHD compared to unlikely IHD, 1.5 (95% confidence interval 0.99 to 2.31), 2.8 (95% confidence interval 1.8 to 4.2). The hazard ratio for the aneurysm variable is 1.5 (95% confidence interval 1.3 to 1.8). Interpret these results. 8 marks

END OF PAPER