Question 1 (12 marks)

You are a GP trainee and are currently managing a 62-year-old electrician, Mr BW, who started medications for diabetes and hypertension last few months. He has never had cardiovascular events such as heart attack or stroke. He is interested in low-dose aspirin (an oral antiplatelet drug that prevents clotting) to prevent cardiovascular events after he heard about it from his mate.

You found the following systematic review that compares low-dose aspirin to standard therapy (without low-dose aspirin) for primary prevention of cardiovascular disease. 'Primary prevention' aims to avoid heart attacks and strokes entirely in people who never had such events.

> Wang M et al. Benefits and risks associated with low-dose aspirin use for the primary prevention of cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials and trial sequential analysis. Am J Cardiovascular Drugs 2022;22:657-675. **(No need to access the paper)**

You wish to help the patient and his family weigh up the benefit of low-dose aspirin (prevention of cardiovascular events) against its potential adverse effect of bleeding.

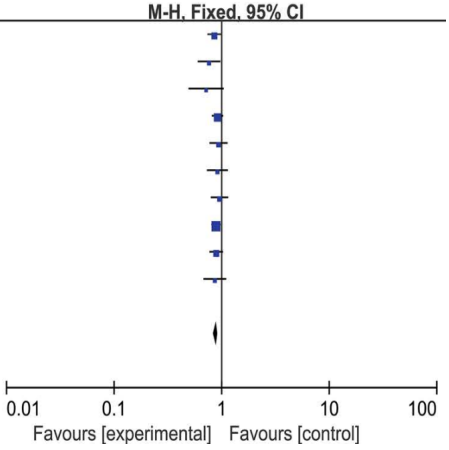
Below is a forest plot from the systematic review that looks at total cardiovascular events. For the purpose of this question, please treat 'risk ratio' as if they were relative risks.

Figure 1. Total cardiovascular events: low-dose aspirin therapy versus control

a

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
HOT 1998	315	9399	368	9391	12.7%	0.86 [0.74, 0.99]	1998
TPT 1998	105	1268	138	1272	4.7%	0.76 [0.60, 0.97]	1998
PPP 2001	45	2226	64	2269	2.2%	0.72 [0.49, 1.04]	2001
WHS 2005	477	19934	522	19942	18.0%	0.91 [0.81, 1.03]	2005
JPPP 2014	193	7220	207	7244	7.1%	0.94 [0.77, 1.14]	2015
JPAD 2016	129	1262	143	1277	4.9%	0.91 [0.73, 1.14]	2016
ARRIVE 2018	208	6270	218	6276	7.5%	0.96 [0.79, 1.15]	2018
ASCEND 2018	658	7440	743	7440	25.6%	0.89 [0.80, 0.98]	2018
ASPREE 2018	329	9525	372	9589	12.8%	0.89 [0.77, 1.03]	2018
TIPS-3 2020	116	2860	134	2853	4.6%	0.86 [0.68, 1.10]	2020
Total (95% CI)		**67404**		**67553**	**100.0%**	**0.89 [0.84, 0.93]**	
Total events	2575		2909				

Heterogeneity: Chi² = 4.19, df = 9 (P = 0.90); I² = 0%
Test for overall effect: Z = 4.55 (P < 0.00001)



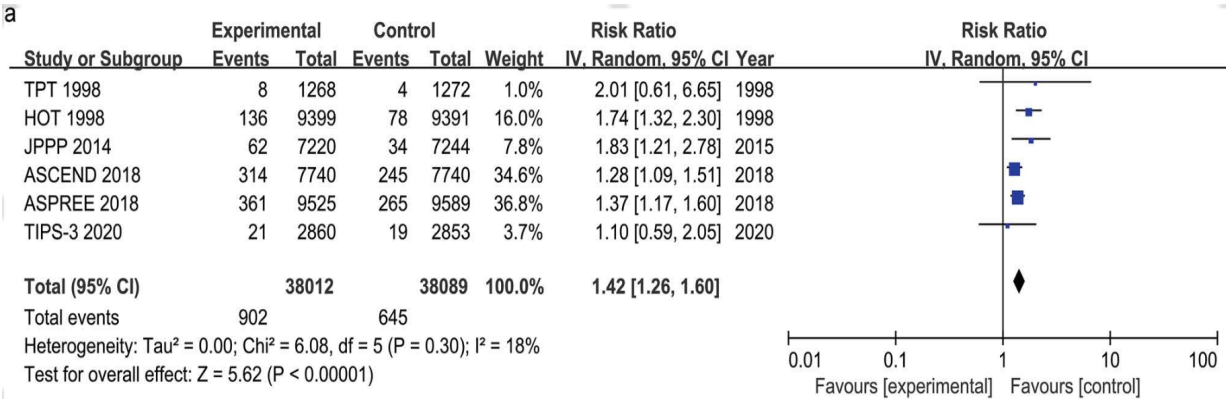
Using an online risk calculator for cardiovascular events, you have estimated that his baseline risk of cardiovascular events in the next 5 years without using aspirin is 7%.

a) What do you estimate his risk of cardiovascular events would be in the next 5 years if he receives low-dose aspirin instead? **(2 marks)**

b) Based on your answer to a), what is the absolute change in the risk of cardiovascular events if he receives low-dose aspirin? **(2 marks)**

Below is another forest plot from the same review that looks at the risk of major bleeding, for example, from blood vessels in head, stomach or intestine.

Figure 2. Major bleeding: low-dose aspirin therapy versus control



Mr BW does not have any specific risk factors for bleeding and you have estimated that his baseline risk of having a major bleed in the next 5 years without taking low-dose aspiring is 2%.

c) What do you estimate his risk of major bleeding would be in the next 5 years if he receives low-dose aspirin instead? **(2 marks)**

d) Based on your answer to c), what is the absolute change in the risk of major bleeding if he receives low-dose aspirin? **(2 marks)**

e) Explain the benefits and harms you have estimated above to Mr BW and his family in simple non-technical terms **(4 marks)**

Please show any relevant working where applicable.

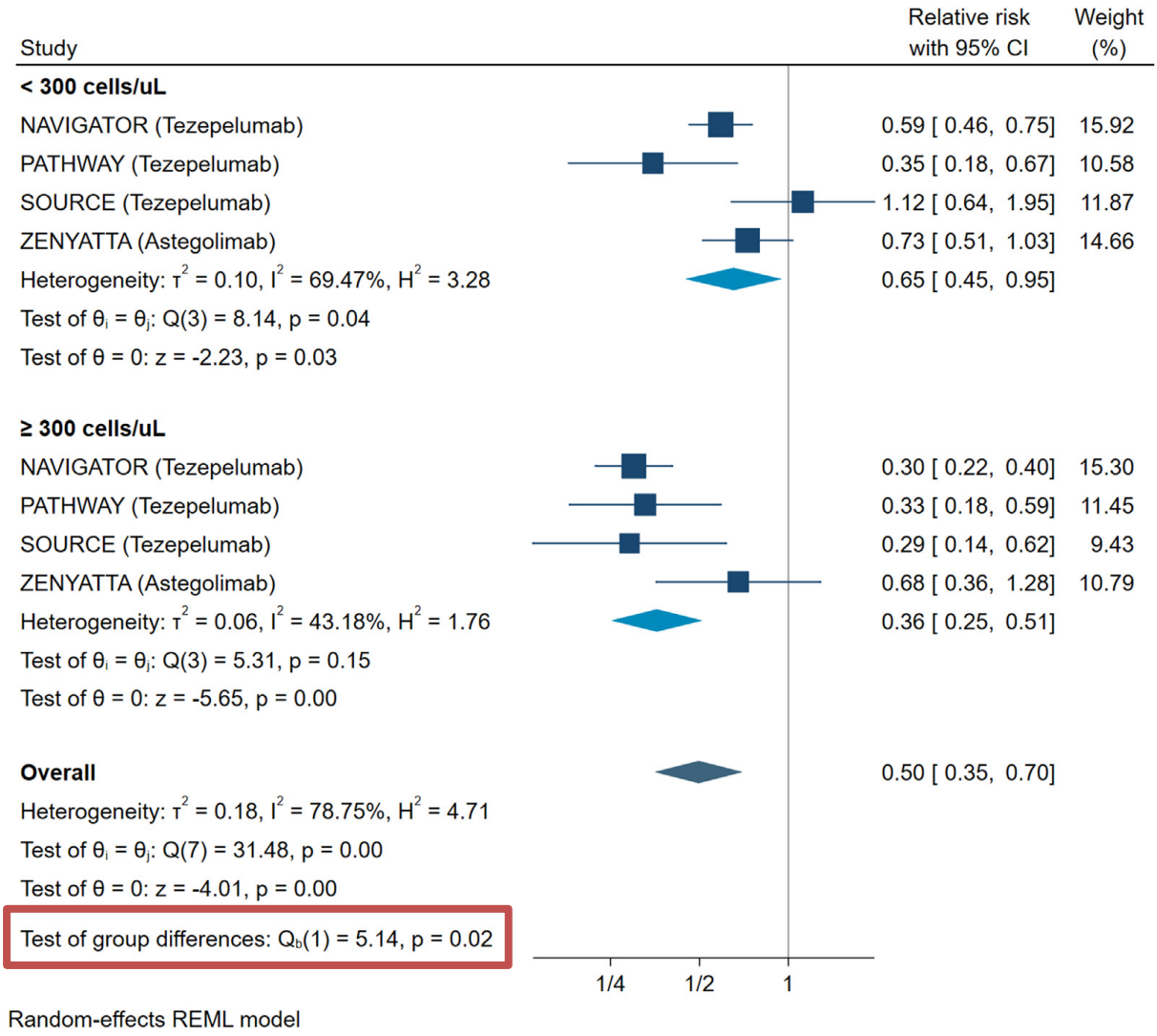
(Answer length for question 1 can be no longer than 300 words. Any part of the answer over this limit will not be marked. **Do not repeat the question from the assignment** just provide your answers clearly labelled e.g. 2(a).)

Question 2 (8 marks)

Eosinophils are a type of white blood cells that increase when your body is having an allergic reaction or fighting an infection, and some asthma patients have increased eosinophil counts in the airway and the blood and their symptoms tend to be severe.

Below is a subgroup analysis from a systematic review about a potential treatment for asthma, 'anti-epithelial-derived cytokines', comparing its effect of decreasing asthma exacerbations (worsening of asthma) in patients with high blood eosinophil counts [≥ 300 cells/uL] versus those with low blood eosinophil counts [< 300 cells/uL].

> Su J et al. Anti-epithelial-derived cytokines for severe asthma: systematic review and meta-analysis. Journal of Allergy and Clinical Immunology 2023;151(6):1566-1576
> **(No need to access the paper)**



Interpret the forest plot above, including the subgroup analysis, and explain it to a clinical colleague who has not studied epidemiology.

(Please note that you should base your answer on the information in the linked paper only. You will not receive any marks for commenting on extra material that the authors refer to in previously published papers or in supplementary material available online.)

(Answer length for question 2 can be no longer than 400 words. Any part of the answer over this limit will not be marked. **Do not repeat the question from the assignment** but just provide your answer. Do not copy and paste any part of the paper such as figures or tables into your assignment.)

Question 3 (30 marks)

Critically appraise the following article by answering questions a) to g) below **based on how you have been taught to appraise risk of bias in studies of this type in this unit of study.**

Andersen_Ranberg NC et al. Haloperidol for the treatment of delirium in ICU patients. N Engl J Med 2022;387:2425-35
https://www.nejm.org/doi/full/10.1056/NEJMoa2211868

Please note that you should base your answer on the information in main text of the linked paper only. You will not receive any marks for commenting on extra material that the authors refer to such as the Supplements, previously published papers, or other materials available online.

Realistically, many of you will resort to ChatGPT to do critical appraisal in the future. So, we have provided ChatGPT responses for each critical appraisal questions below to use as a starting point/draft **only if you like**. We asked ChatGPT to "read the following paper and answer questions a) to g) below (copy and paste full text of the paper) (copy and paste questions a) to g))".

You should still read the relevant parts of the paper and exercise your own judgement to correct the ChatGPT responses. You may give further prompts to ChatGPT (copy and paste the entire paper before asking more questions to ChatGPT), in which case you need to declare the specific prompts you used. Please make a section called 'Appendix' in the end of your responses to Question 3 to list the specific questions you have asked ChatGPT for each question (a) to (g) and this will NOT be included in the word count limit. If you think Chat GPT response for a specific question is perfect and there is no room for improvement, you can state so, but be careful because they sometimes do not answer the question being asked at all!

a) i. Was the assignment to treatment or control groups randomised? Was an appropriate method of randomisation used? Provide a one-word answer to the question (Yes/No/Unclear) AND your assessment of the risk of bias (Low/High/Unclear)
ii. Explain and justify your answer to part i.
(3 marks)

Chat GPT response:

i. Yes/Low

ii. Yes, the assignment to treatment or control groups was randomized. The study mentions centralized randomization performed with a computer-generated assignment sequence and randomly varying block sizes. This approach helps ensure that each participant has an equal chance of being assigned to either the haloperidol or placebo group. The risk of bias is low as randomization helps minimize the impact of confounding variables.

b) i. Was there allocation concealment? Provide a one-word answer to the question (Yes/No/Unclear) AND your assessment of the risk of bias (Low/High/Unclear)
ii. Explain and justify your answer to part i.
(5 marks)

Chat GPT response:

i. Yes/Low

ii. Yes, there was allocation concealment. The study states that randomization was performed at a central location using a computer-generated assignment sequence with randomly varying block sizes. This centralized process helps ensure that those involved in the trial (clinicians, patients, investigators, outcome assessors, statisticians) were unaware of the group assignments. The risk of bias is low as this method minimizes the potential for selection bias.

c) i. Were the two (or more) study groups similar in terms of prognostic factors at baseline? Provide a one-word answer to the question (Yes/No/Unclear) AND your assessment of the risk of bias (Low/High/Unclear)
ii. Explain and justify your answer to part i.
(5 marks)

Chat GPT response:

i. No/Unclear

ii. The baseline characteristics of the two study groups were not extensively discussed in the provided text. While the text mentions that patient characteristics at baseline were reasonably balanced between the trial groups, the specific details of the baseline characteristics are not provided in this summary. Therefore, the answer is "Unclear."

d) i. Was the study blinded? Provide a one-word answer to the question (Yes/No/Unclear) AND your assessment of the risk of bias (Low/High/Unclear)
ii. Explain and justify your answer to part i.
(5 marks)

Chat GPT response:
i. Yes/Low
ii. Yes, the study was blinded. The paper mentions a blinded, placebo-controlled design, and the interventions (haloperidol and placebo) were administered in identical ampules with identical labelling. The risk of bias is low as blinding helps minimize performance and detection bias.

e) i. Is there any incomplete data? Provide a one-word answer to the question (Yes/No/Unclear) AND your assessment of the risk of bias (Low/High/Unclear) You may focus on the primary outcome.
ii. Explain and justify your answer to part i.
(5 marks)

Chat GPT response:
i. Yes/Low
ii. Yes, there is some incomplete data, but the risk of bias is low. The paper mentions that primary outcome data were available for 963 patients (97.6%), and data on 90-day mortality and secondary outcomes were available for 987 patients (98.7%). The number of patients with missing data is low for all outcomes and considered negligible. No imputation for missing data was performed.

f) i. Was the analysis of results appropriate? Provide a one-word answer to the question (Yes/No/Unclear) AND your assessment of the risk of bias (Low/High/Unclear)
ii. Explain and justify your answer to part i.
(5 marks)

Chat GPT response:
i. Yes/Low
ii. Yes, the analysis of results was appropriate. The paper describes the statistical analysis plan, and analyses were adjusted for stratification variables. The intention-to-treat analysis, per-protocol analysis, and sensitivity analysis were conducted. The statistical methods are well-described, and appropriate tests were used. The risk of bias is low.

g) Would you be happy to use this paper to guide your clinical decision making? Why or why not? **(2 marks)**

Note for part g):

1. You should base your justification on the strengths and weakness of the paper in terms of risk of bias rather than any issues of generalisability or level of evidence (i.e. that you would prefer to use a systematic review – for this exercise assume that there is no higher level of evidence available)
2. Using the paper to guide your clinical decision making does NOT mean that you will be giving the particular treatment but rather that you would be happy to base your decision about whether or not to use this particular treatment on this paper.

> Chat GPT response:
> *Yes I would be cautious in using this paper to guide clinical decision-making. While the study design is robust with randomization, blinding, and appropriate analysis, the results show no significant difference in the primary outcome (number of days alive and out of the hospital at 90 days) between the haloperidol and placebo groups. Additionally, the confidence interval for the adjusted mean difference includes zero, indicating the possibility of no effect. The inconclusive nature of the primary outcome raises concerns about the effectiveness of haloperidol in this context. Further research or consideration of additional evidence may be necessary before making definitive clinical decisions.*

(Answer length for Question 3 can be no longer than 1300 words (excluding your own Chat GPT prompts in the appendix). Any part of the answer over this limit will not be marked. Do NOT copy and paste any part of the paper such as the figures or tables into your assignment. Do not repeat the question from the assignment just provide your answers clearly labelled e.g. 3a) ii.)

This is the end of the assignment.