10.1 A. The Multicentre Aneurysm Screening Study

In Problem 5.7 we looked at 2 methods of estimating the size of abdominal aortic aneurysms (AAA): ultrasound and computed tomography (CT). The Multicentre Aneurysm Screening Study (MASS) (Ashton et al 2002)was a randomized trial of the effectiveness of ultrasound screening for AAA in reducing aneurysm-related mortality. Men aged 65-74 were randomized to either receive an invitation for an abdominal ultrasound scan or not. Aneurysm-related and overall mortality in the two randomization groups are reported below:

	N	AAA-related Deaths	%	Total Deaths	%
Invited	33,839	65	0.19%	3,750	11.08%
Not Invited	33,961	113	0.33%	3,855	11.35%
Total	67,800	178		7,605	

a. Does screening appear to be effective in reducing aneurysm-related deaths?

Yes. In fact, the 0.19% AAA-related death rate in the invited group is 42% lower (95% CI 22% to 58%; P = 0.0002) than the risk in the control group. (We will discuss relative risk reductions like this in Chapter 9, and confidence intervals and P-values in Chapter 11.)

b. You can see that in those invited for screening there were 48 fewer AAA deaths (113-65) and 105 fewer total deaths (3855-3750). Thus, there were (105-48=) 57 fewer non-AAA deaths in those invited for screening. Which of the following do you think are the most likely explanations for this: volunteer effect; lead-time bias; length-lime bias; stage migration bias; misclassification of outcome; misclassification of exposure; cointerventions; chance.

Chance is a reasonable explanation: The observed relative reduction in total mortality was only 2.4% (95% CI: 6.4% reduction to 1.8% increase; P = 0.27). Alternatively, or in addition, it is possible that invitation to screening led to *cointerventions* (e.g., treatment of hypertension) that reduced nonAAA mortality. Finally, some deaths attributed to other causes (in both groups) may actually have been due to AAA (misclassification of outcome).

A volunteer effect, lead-time bias, length-lime bias and stage migration bias would not occur in a randomized trial, and in this case the exposure is being *invited* for screening, which would be unlikely to be misclassified and in any case would not lead to differences in mortality.

The authors also did a *within groups* analysis in the invited group only, comparing those who did and did not get the ultrasound scan. Results are summarized below, same format as before:

MASS Study -- Invited Group Only					
	N	AAA Death	%	Total Death	%
Scanned	27,147	43	0.16%	2,590	9.54%
Not Scanned	6,692	22	0.33%	1,160	17.33%
Total	33,839	65		3,750	

c. The total (not just AAA-related) mortality rate in the invited patients who were not scanned was almost double that of the invited patients who were scanned (17.33% vs. 9.54%). Again, which of the following explanations are most likely responsible for this difference? Volunteer or Selection Bias; Lead-Time Bias; Length-Time Bias; Stage Migration Bias; Misclassification of Outcome; Misclassification of Exposure; Cointerventions; Chance.

The most likely explanation is volunteer or selection bias. Those interested enough in their health to attend screening may have other, better health habits. Some of those who did not attend screening may have been too sick.

Remember that lead time and length bias do not occur when the whole group receiving an intervention is compared with the whole group not receiving it. They only occur when survival of those *with disease* is compared. Misclassification of outcome is not plausible, because the outcome is total mortality. Misclassification of exposure (i.e., not being able to tell who got scanned) also seems unlikely. They may have coded it wrong in a few, but this is a huge effect. This seems like much too big a difference to be due to cointerventions, but cointerventions may have contributed a little. Chance is not a viable explanation. These numbers are huge − the P value is about 10^{-72}.

d. This was a randomized trial, so the safest way to analyze the data is by group assignment – an "Intention to Treat" analysis. Nonetheless, it is sometimes of interest to compare groups according to how they were actually treated, an "As Treated" analysis. Do you believe the "As Treated" comparison of AAA deaths (not total deaths) between the scanned and not scanned patients within the Invited group is biased? Why or why not?

The "as treated" comparison appears not to be biased because the AAA death rate in non-scanned patients (0.33%) is the same as the death rate in uninvited patients (0.33%). This suggests that for *this particular cause of death* (AAA) the volunteer bias that led to differences in total mortality was not important.