Multicausality: Confounding - Assignment solutions

1.

a. Reserpine is a risk factor. Overall, the incidence of breast cancer is 10.47 per 100,000 women-years in reserpine users and 6.14 per 100,000 women-years in nonusers. Moreover, among the non-obese, the rate ratio is: 6.40/4.10 = 1.6. Looking in the non-obese women avoids potential confounding by obesity if it is a risk factor.

b. Obesity is also a risk factor. The overall incidence rates for obese and non-obese women, respectively, are 8.72/100,000 women-years and 4.22/100,000 women-years. Among the women who did not take reserpine, the rate ratio is 8.30/4.10 = 2.0. Looking in the group of reserpine non-users avoids potential confounding by reserpine.

c. Reserpine use <u>is</u> associated with obesity, though that fact cannot be deduced from the stratum-specific breast cancer rates <u>alone</u>. The direct approach is to remember that the crude rates are weighted averages of stratum-specific rates, with the weights consisting of the population prevalence of the risk factors. So:

$$12.50\ P_{RO} + 8.30\ (1-P_{RO}) = 8.72 \quad \text{and}$$

$$6.40\ P_{\overline{RO}} + 4.10(1-P_{\overline{RO}}) = 4.22$$

where P_{RO} is the prevalence of reserpine use in obese subjects,
and

$P_{\overline{RO}}$ is the prevalence of reserpine use in nonobese subjects.

Solving these two equations gives $P_{RO} = 0.1$ and $P_{\overline{RO}} = 0.05$, so reserpine use is more prevalent in obese women (presumably because they are more likely to have hypertension). The relative prevalence is 2.0; the odds ratio of association between obesity and reserpine use is [(.1)(.95)]/[(.9)(.05)] = 2.1. Such an association might be characterized as "moderate."

Note that the above procedure involving weighted averages can be equally well carried out on the basis of the column rates, rather than the row rates. The odds ratio will be effectively the same.

d. The association between reserpine and breast cancer is <u>not</u> attributable to obesity (in the data for this problem). The most relevant rates to demonstrate that the association is not

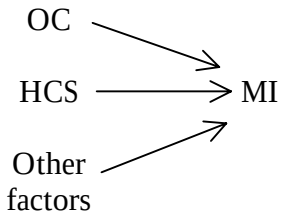
completely attributable to obesity are those comparing reserpine users and nonusers among the nonobese (6.40/4.10=1.6). Since the crude rate ratio (10.47/6.14=1.7) is ever so slightly greater than each of the stratum-specific rate ratios (1.6 in the nonobese, 1.5 in the obese) it can be argued that a slight amount of the crude association is attributable to obesity.

2.

a. Smoking is <u>not</u> likely to be a confounder, because both of the compared groups (smelters and truck stop workers) have identical proportions of smokers (55%). Smoking could therefore not account for a difference in lung disease between the two groups compared.

b. The best reason for not controlling low FEV_1 as a potential confounder is C, low FEV1 is not an independent risk factor for the development of COPD, but is rather a manifestation of COPD.

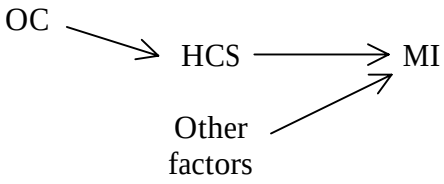
3. In the first causal model:



[arrows show hypothesized causal pathways]

HCS is a causal risk factor for MI, through a pathway independent of OC. Therefore, HCS must be controlled as a potential confounder of an OC-MI association.

In the second causal model:



[arrows show hypothesized causal pathways]

HCS is an intermediate in the causal pathway from OC to HCS. Therefore, HCS cannot logically be a confounder of the OC-MI relationship. If one controls for the effect of HCS, no residual effect will be found for OC. A more useful approach would be to investigate the

link between HCS and MI to ensure that it is causal. Then the link between OC and HCS should be explored while other influences on HCS are controlled.

4. Some possible answers:

Age: The oral contraceptive users were much younger than either the diaphragm or IUD users. In fact, there were 21% more women in the age range 25-29 using oral contraceptives than in either of the other groups -- or almost one-and-a-half times more younger women using OC's than other methods. This would bias any associations between OC use and circulatory deaths downward, since younger women are less likely to develop circulatory disease than older women.

Cigarette Smoking: The oral contraceptive users were also more likely to smoke 15 or more cigarettes a day than either diaphragm or IUD users. There were almost two-and-one half times (17% vs 7%) more 15+/day smokers among OC uses than among women using the diaphragm, and almost one-and-one-half times (17% vs 12%) more smokers among OC users than among IUD user. These differences would likely increase the risk of circulatory deaths among OC as compared to non-OC users, since cigarette smoking is significantly related to death from circulatory disease.

History of Hypertension: Although the percentages were low, the oral contraceptive users were more likely to have a history of hypertension than were other contracepting women (.91% vs .67% and .50%). This slight excess of hypertension among OC users might increase their risk of developing circulatory disease as compared to the non-users, since hypertension is one of the most significant risk factors for circulatory death.

Venous Thromboembolism: The percentage of OC users with a history of venous thromboembolism was much lower than among women using the diaphragm or the IUD. There were 5 times (4.30% vs. .87%) more women with a thromboembolism problem among diaphragm users than among OC users, and 9 times (7.96% vs. .87%) more women with a history among IUD than OC users. This difference would likely bias the risks of OC use downward, since the non-OC user group had more prevalent circulatory disease, which is more likely to lead to circulatory death.

History of Rheumatic Heart Disease: Although the percentages were small, the OC users were less likely to have had rheumatic heart disease than the non-OC users (.09% vs .26% and .32%). Since a history of rheumatic heart disease increases risk of circulatory death, the risks for OC users would be lowered by this difference.

5.

a. C -- the adjusted relative risk would be a weighted average of 2.0 and 2.1, so only 2.05 is a possible value for the adjusted relative risk.

b. Bladder cancer

	Cases	Controls	Total
3 + UTI	146 + 145 = 291	152 + 206 = 358	649
No UTI	1758 + 398 = 2,156	3642 + 979 = 4,621	6,777
Total	2,447	4,979	7,426

$$OR = \frac{ad}{bc} = \frac{(291)(4{,}621)}{(358)(2{,}156)} = 1.74$$

c. Yes, strongly. 13.9% [206/(206+296+979)] women have 3+ UTI, compared to only 3.6% [152/(152+423+3642)] men. [The question did not ask about the relative risk of bladder cancer.]

d. Yes, there is some confounding, since 1.7 is below both 2.0 and 2.1.