CYP1A2 is one of the most important drug-metabolizing compounds. Caffeine is predominantly metabolized by CYP1A2. The body metabolizes caffeine through stages to different caffeine metabolites.

Researchers interested in genetic and environmental factors that affect caffeine metabolism conducted an experiment with 378 Danish twins, some of whom were monozygotic and some of whom were dizygotic. The genes of monozygotic twins are identical while the genes of dizygotic twins are just as similar as non-twin siblings. All twins were volunteers. Environmental factors thought to be important include sex, tobacco use, and oral contraceptive use. There are likely many other important factors.

Subjects did not consume any products with caffeine for 40 hours prior to data collection. At the beginning of the experiment, each subject ingested 200mg of caffeine. CYP1A2 activity was estimated by the *caffeine ratio*, the ratio of the sum of concentrations of three caffeine metabolites over another in urine six hours after ingestion of the caffeine.

The table displays a summary of caffeine ratio measurements for various groups. A graph of caffeine ratio for all subjects was unimodal and approximately symmetric with mean $\pm$ SD of $5.9 \pm 3.4$. Caffeine ratios within each group did not include extreme outliers or skewness. These summary statistics include both monozygotic and dizygotic twins.

| | Men | | Women that do not take oral contraceptives | | Women that do take oral contraceptives | |
|---|---|---|---|---|---|---|
| | Non-smokers | Smokers | Non-smokers | Smokers | Non-smokers | Smokers |
| Number | 154 | 33 | 120 | 40 | 24 | 7 |
| Mean ($\pm$ SD) | $6.1 \pm 3.0$ | $8.7 \pm 4.6$ | $4.9 \pm 2.5$ | $7.8 \pm 4.5$ | $3.6 \pm 1.4$ | $3.9 \pm 0.9$ |

(a) The researchers compared caffeine ratios between men and women not taking oral contraceptives separately for both smokers and nonsmokers. For nonsmokers a 95% confidence interval for the difference in caffeine ratios was $1.2 \pm 0.7$. Find a comparable confidence interval for smokers.

(b) Alternatively, one could compare the means of all six groups in a single analysis. What method would be appropriate for that comparison? What reference distribution (including degrees of freedom) would be appropriate to use to find a $p$-value?

(c) A hypothesis test could be used to assess the evidence that caffeine ratios were lower among women nonsmokers using oral contraceptives than among women nonsmokers who do not use oral contraceptives. Use the tabulated data to carry out such a hypothesis test. Interpret the results in the context of the problem.

(d) The researchers reported results from a large number of comparisons. Briefly discuss a method from the course that could have been used (but was not) to account for multiple comparisons.

(e) The subjects in the study are all twins and are all volunteers from Denmark. The analysis you have carried out to this point ignores this. What difficulties does this present for generalizing the results to different groups of people?

(f) To test for a genetic contribution to caffeine metabolism, the researchers found a correlation coefficient of 0.798 for monozygotic twins and 0.394 for dizygotic twins. Using a test beyond the scope of this course, they found that the difference in correlation coefficients was statistically significant ($p = 0.0015$). Interpret this result in the context of the problem.