1.)

**Methods:** To investigate the relationship between CRP and fibrinogen levels, scatterplots with lowess smooth lines were created for all subjects, subjects with prior cardiovascular disease, and subjects without prior cardiovascular disease. Prior cardiovascular disease was defined as presence of previously diagnosed angina, myocardial infarction, TIA, or stroke at study enrollment. Subjects with missing values for CRP or fibrinogen were excluded from the analysis.

**Results:**

Of the 5000 study subjects, 51 were missing values for both CRP and fibrinogen, 16 were missing values on CRP only, and 34 were missing values on fibrinogen only.

As can be seen in the first scatterplot, for the overall sample mean CRP tends to increase with increasing mean fibrinogen in a curvilinear fashion. In addition, the variance of CRP tends to increase with increasing fibrinogen levels. The variance of fibrinogen does not appear to increase with increasing CRP values. These relationships hold true in the subgroup of patients with previous CV disease (second scatterplot) and the subgroup of patients without previous CV disease (third scatterplot).

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2a.)

**Methods:** Mean fibrinogen levels for those with a previous history of CV disease were compared with those without a previous history of CV disease using a t test that assumes equal variance between groups. 95% confidence intervals were computed, also assuming equal variances between groups. A two sided p value of 0.05 or less was considered significant.

**Results:**

The mean fibrinogen level in those with previous CV disease was 334.5 mg/dL. The mean fibrinogen level in those without previous CV disease was 319.6 mg/dL. The difference in mean fibrinogen level is 14.9 mg/dL higher in the group with previous CV disease (95% confidence interval 10.4 mg/dL to 19.3 mg/dL). If the true difference between groups is between 10.4 mg/dL and 19.3 mg/dL, our data would not be surprising. At an alpha level of 0.05, this difference is statistically significant (p<0.0001); therefore, we reject the null hypothesis of no difference in mean fibrinogen level in favor of the alternative hypothesis that the mean fibrinogen level is higher in those with previous CV disease compared to those without previous CV disease.

2b.) This same analysis could be performed using simple linear regression, with the linear regression predictor variable being the presence of previous CV disease and the response variable being fibrinogen. In the regression output, the intercept corresponds to the t test (that assumes equal variances) mean fibrinogen value in those without previous CV disease, and the coefficient (and it’s associated 95% confidence interval) corresponds to the t test (that assumes equal variances) difference in means. The p value for the regression analysis also corresponds to the p value obtained from the t test.

2c.)

**Methods:** Mean fibrinogen levels for those with a previous history of CV disease were compared with those without a previous history of CV disease using a t test that allows for equal variance between groups. 95% confidence intervals were computed, also allowing for equal variances between groups. A two sided p value of 0.05 or less was considered significant.

**Results:**

The mean fibrinogen level in those with previous CV disease was 334.5 mg/dL. The mean fibrinogen level in those without previous CV disease was 319.6 mg/dL. The difference in mean fibrinogen level is 14.9 mg/dL higher in the group with previous CV disease (95% confidence interval 10.1 mg/dL to 19.7 mg/dL). If the true difference between groups is between 10.1 mg/dL and 19.7 mg/dL, our data would not be surprising. At an alpha level of 0.05, this difference is statistically significant (p<0.0001); therefore, we reject the null hypothesis of no difference in mean fibrinogen level in favor of the alternative hypothesis that the mean fibrinogen level is higher in those with previous CV disease compared to those without previous CV disease.

2d.) This same analysis could be performed using linear regression with the Huber-White sandwich estimator (robust standard errors). In the regression output, the intercept corresponds to the t test (that allows for unequal variances) mean fibrinogen value in those without previous CV disease, and the coefficient (ant it’s associated 95% confidence interval) corresponds to the t test (that allows for unequal variances) difference in means. The p value for the regression model also corresponds to the p value obtained from the t test (that allows for unequal variances).

2e.) In part a, the group with smaller sample size (those with a history of CV disease) have higher variance. The t-test that assumes equal variances is anti-conservative (meaning it returns narrower confidence intervals and smaller p values) when the smaller group has the higher variance. Therefore, I would have expected an analysis that allows for unequal variances to be more conservative (returning a wider confidence interval and higher p-value). Based on this, I would expect the analysis in part c to find a weaker association.

3.)

**Methods:** Simple linear regression with robust standard errors was used to examine the relationship between mean fibrinogen level and CRP. A two sided alpha of 0.05 was considered significant.

3a.) The intercept value of 304 mg/dL is the average fibrinogen level for subjects with CRP levels of 0.

3b.) The slope value of 5.25 mg/dL is the average increase in fibrinogen level for each 1 mg/L increase in CRP value.

3c.) For each 1 mg/L increase in CRP value, the average increase in fibrinogen value is 5.25 mg/dL (95% confidence interval 4.60 mg/dL to 5.90 mg/dL). If the true average increase in fibrinogen value is between 4.60 mg/dL and 5.90 mg/dL, our data would not be surprising. This finding is statistically significant at an alpha level of 0.05 (p < 0.0001); therefore we reject the null hypothesis of no linear trend between mean fibrinogen value and CRP value in favor of the alternative hypothesis that mean fibrinogen values increase with increasing CRP.

3d.) see table 1 below

4.)

**Methods:** Simple linear regression with robust standard errors was used to examine the relationship between mean fibrinogen level and log(2)CRP. Base 2 log was chosen to facilitate communication about the association between CRP and mean fibrinogen level. CRP values of 0 mg/L were recoded as 0.5 mg/L. A two sided alpha of 0.05 was considered significant.

4a.) The intercept value of 296 mg/dL is the average fibrinogen level for subjects with log(2) CRP levels of 0.

4b.) The slope value of 25.5 mg/dL is the average increase in fibrinogen level for each doubling in CRP value.

4c.) For each doubling in CRP value, the average increase in fibrinogen value is 25.5 mg/L (95% confidence interval 24.0 mg/dL to 27.1 mg/dL). If the true average increase in fibrinogen value per doubling of CRP is between 24.0 mg/dL and 27.1 mg/dL, our data would not be surprising. This finding is statistically significant at an alpha level of 0.05 (p < 0.0001); therefore we reject the null hypothesis of no linear trend between mean fibrinogen value and CRP value in favor of the alternative hypothesis that mean fibrinogen values increase with increasing CRP.

4d.) see table 1 below

5.)

**Methods:** Simple linear regression with robust standard errors was used to examine the relationship between log transformed fibrinogen level and CRP level. Log transformed fibrinogen levels were then exponentiated to find the geometric mean fibrinogen level. A two sided alpha of 0.05 was considered significant.

5a.) The intercept value (after exponentiation) of 301 mg/dL is the geometric mean fibrinogen level for subjects with CRP levels of 0.

5b.) The slope value of 1.0140 is the ratio of geometric mean fibrinogen levels between groups differing that differ in CRP values by 1 mg/L (with the higher CRP group being in the numerator of the ratio).

5c.) For very 1 mg/L increase in CRP level, the geometric mean fibrinogen levels increase by 1.40 % (95% confidence interval 1.22% to 1.58%). If the true geometric mean fibrinogen increase per 1 mg/L increase in CRP is 1.22% to 1.58%, our data would not be surprising. This finding is statistically significant at an alpha level of 0.05 (p < 0.0001); therefore we reject the null hypothesis of no linear trend between geometric mean fibrinogen value and CRP value in favor of the alternative hypothesis that geometric mean fibrinogen values increase with increasing CRP.

5d.) see table 1 below.

6.)

**Methods:** Simple linear regression with robust standard errors was used to examine the relationship between log transformed fibrinogen level and logtransformed CRP. Standard natural log was used for log transformation of fibrinogen, and base 2 log was chosen to log transform CRP to facilitate communication about the association between CRP and geometric mean fibrinogen. CRP values of 0 mg/L were recoded as 0.5 mg/L. A two sided alpha of 0.05 was considered significant.

6a.) The intercept value (after exponentiation) of 293 mg/dL is the average fibrinogen level for subjects with log(2) CRP levels of 0.

6b.) The slope value of 1.0801 is the ratio of geometric mean fibrinogen levels between groups that differ in CRP values by a factor of 2.

6c.) For each doubling in CRP value, geometric mean fibrinogen level increases by 8.02% (95% confidence interval 7.14% to 8.02%) . If the geometric mean fibrinogen value increases by 7.14% to 8.02% for every doubling of CRP, our data would not be surprising. This finding is statistically significant at an alpha level of 0.05 (p < 0.0001); therefore we reject the null hypothesis of no linear trend between geometric mean fibrinogen value and CRP value in favor of the alternative hypothesis that geometric mean fibrinogen values increase with increasing CRP.

6d.) see table 1 below

Table 1: Answers to problems 3-6 part D.

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| --- | --- | --- | --- | --- |
|  | **Fitted Values for Fibrinogen (mg/dL)** | | | |
| **CRP level** | **Problem 3:** (mean fibrinogen, mg/dL) | **Problem 4:** (mean fibrinogen, mg/dL) | **Problem 5:** (geometric mean fibrinogen, mg/dL) | **Problem 6:** (geometric mean fibrinogen, mg/dL) |
| **1 mg/L** | 309 | 296 | 305 | 293 |
| **2 mg/L** | 314 | 321 | 309 | 315 |
| **3 mg/L** | 320 | 336 | 313 | 328 |
| **4 mg/L** | 325 | 347 | 318 | 339 |
| **6 mg/L** | 335 | 362 | 327 | 353 |
| **8 mg/L** | 346 | 372 | 336 | 364 |
| **9 mg/L** | 351 | 377 | 341 | 369 |
| **12 mg/L** | 367 | 387 | 355 | 380 |

7.) See following table:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Fitted Values for Fibrinogen (mg/dL)** | | | |
| **Comparisons across CRP level** | **Problem 3:** (mean fibrinogen, mg/dL) | **Problem 4:** (mean fibrinogen, mg/dL) | **Problem 5:** (geometric mean, mg/dL) | **Problem 6:** (geometric mean, mg/dL) |
| ***Differences*** | | | | |
| **2 mg/L – 1 mg/L** | 5.24 | 25.5 | 4.27 | 22.2 |
| **3 mg/L – 2 mg/L** | 5.24 | 14.9 | 4.33 | 13.7 |
| **4 mg/L – 1 mg/L** | 15.7 | 51.1 | 13.0 | 46.0 |
| **4 mg/L – 2 mg/L** | 10.5 | 25.5 | 8.73 | 23.9 |
| **6 mg/L – 3 mg/L** | 15.7 | 25.5 | 13.4 | 24.9 |
| **8 mg/L – 4 mg/L** | 21.0 | 25.5 | 18.2 | 25.7 |
| **9 mg/L – 6 mg/L** | 15.7 | 14.9 | 13.9 | 15.4 |
| **9 mg/L – 8 mg/L** | 5.24 | 4.34 | 4.71 | 4.55 |
| **12 mg/L – 6 mg/L** | 31.4 | 25.5 | 28.4 | 26.8 |
| ***Ratios*** | | | | |
| **2 mg/L / 1 mg/L** | 1.0170 | 1.0864 | 1.0140 | 1.0758 |
| **3 mg/L / 2 mg/L** | 1.0167 | 1.0465 | 1.0140 | 1.0437 |
| **4 mg/L / 1 mg/L** | 1.0509 | 1.1727 | 1.0426 | 1.1573 |
| **4 mg/L / 2 mg/L** | 1.0334 | 1.0795 | 1.0282 | 1.0758 |
| **6 mg/L / 3 mg/L** | 1.0492 | 1.0760 | 1.0426 | 1.0758 |
| **8 mg/L / 4 mg/L** | 1.0646 | 1.0736 | 1.0573 | 1.0758 |
| **9 mg/L / 6 mg/L** | 1.0469 | 1.0413 | 1.0426 | 1.0437 |
| **9 mg/L / 8 mg/L** | 1.0152 | 1.0117 | 1.0140 | 1.0125 |
| **12 mg/L / 6 mg/L** | 1.0938 | 1.0871 | 1.0871 | 1.0758 |

8a.) The analysis from problem #3 gives constant differences in the fitted values when comparing two groups that differed by an absolute increase in *c* units in CRP levels. For comparisons where c=1 (which includes 2mg/L-1mg/L, 3mg/L-2mg/L, and 9mg/L-8mg/L), the difference is 5.24 mg/dL in fibrinogen. For comparisons where c=3 (which includes 4mg/L-1mg/L, 6mg/L-3mg/L, and 9mg/L-6mg/L), the difference is 15.7 mg/dL in fibrinogen.

8b.) The analysis from problem #5 gave constant ratios of the fitted values when comparing two groups that differed by an absolute increase in *c* units in CRP levels. For comparisons where c=1 (which includes 2mg/L-1mg/L, 3mg/L-2mg/L, and 9mg/L-8mg/L), the ratio is 1.0140. For comparisons where c=3 (which includes 4mg/L-1mg/L, 6mg/L-3mg/L, and 9mg/L-6mg/L), the ratio is 1.0426.

8c.) The analysis from problem #4 gave constant differences in the fitted values when comparing two groups that differed by a relative *c*-fold increase in CRP levels. For comparisons where c=1.5 (which include 3mg/L vs 2mg/L and 9mg/L vs 6mg/L), this difference is 14.9 mg/dL in fibrinogen. For comparisons where c=2 (which includes 2mg/L vs 1 mg/L, 4mg/L vs 2mg/L, 6mg/L vs 3mg/L, 8mg/L vs 4 mg/L, and 12mg/L vs 6 mg/L), this difference is 25.5 mg/dL in fibrinogen.

8d.) The analysis from problem #6 gave constant ratios in the fitted values when comparing two groups that differed by a relative *c*-fold increase in CRP levels. For comparisons where c=1.5 (which include 3mg/L vs 2mg/L and 9mg/L vs 6mg/L), this ratio is 1.0437. For comparisons where c=2 (which includes 2mg/L vs 1 mg/L, 4mg/L vs 2mg/L, 6mg/L vs 3mg/L, 8mg/L vs 4 mg/L, and 12mg/L vs 6 mg/L), this ratio is 1.0758.

9.) To determine which analysis to use, I would ask an expert in the field if it was scientifically more plausible that the biologic effect of both CRP and fibrinogen is additive or multiplicative. If the biologic effect of CRP is likely additive (ie same effect as you go from 1 to 2 as when you go from 10 to 11), I would use an analysis that does not log transform CRP; if the biologic effect is likely multiplicative (ie same effect as you go from 2 to 4 as when you go from 4 to 8), then I would use an analysis that log transforms CRP. I would make the same determination for fibrinogen based on whether the biologic effect of fibrinogen is likely to be additive or multiplicative.