1. **Table 1. Difference in risk of CVD death within 4 years between women who received estrogen therapy and those who did not**

	Risk Difference (95% CI)	p-value
Unadjusted	-0.0256 (-0.0378, -0.0134)	0.0111*
Adjusted for prior CVD	-0.0122 (-0.0224, -0.0020)	0.0190*
Adjusted for prior CVD and age	-0.0035 (-0.0118, 0.0048)	0.4114

* Risk difference is significantly different from 1 ($p < 0.05$).
Differences and statistical significance were determined using tabular methods and linear binomial regression models.

a. There were approximately 26 fewer deaths from CVD within 4 years in each 1,000 women who received estrogen therapy compared to those who did not receive therapy (RD = -0.0256, $CI_{95\%}$= -0.0378, -0.0134) (Table 1). This crude association is statistically significant.

b. Prior CVD is not an effect modifier of the association between CVD death and estrogen therapy based non-significance of the interaction between death and prior CVD in a linear binomial model of the risk (χ^2=2.30, df=1, p=0.1291).

c. It appears that history of prior CVD is confounding the association between CVD death and estrogen therapy. Although no statistical test can prove the presence of confounding, certain characteristics of the analysis suggest that confounding is occurring. Specifically, the parameter estimating the association between CVD death and estrogen therapy is markedly attenuated (52% closer to the null value of 0), while the association between CVD death and prior CVD is highly statistically significant (χ^2=36.01, df=1, p<0.0001).

d. There were approximately 12 fewer deaths from CVD within 4 years in each 1,000 women who received estrogen therapy compared to those who did not receive therapy after adjusting for prior CVD (RD = -0.0122, $CI_{95\%}$= -0.0224, -0.0020) (Table 1). This association is statistically significant.

e. Age appears to be further confounding the association between CVD death and estrogen therapy. Confounding is suspected because the parameter estimating the age- and prior CVD-adjusted association between CVD death and estrogen shows substantial attenuation (71%) compared to the estimate that was adjusted for prior CVD alone, while the association between CVD death and dichotomized age is highly statistically significant (χ^2=16.29, df=1, p<0.0001).

f. There is no statistically significant difference in death from CVD within 4 years between women who received estrogen therapy compared to those who did not receive therapy after adjusting for prior CVD and dichotomous age (RD = -0.0035, $CI_{95\%}$= -0.0118, 0.0048) (Table 1).

2. **Table 2. Odds ratio for CVD death within 4 years comparing women who received estrogen therapy to those who did not**

	Odds Ratio (95% CI)	p-value
Unadjusted	0.250 (0.079, 0.794)	0.0188*
Adjusted for prior CVD	0.338 (0.106, 1.084)	0.0682
Adjusted for prior CVD and age	0.427 (0.132, 1.379)	0.1548

* Odds ratio is significantly different from 1 ($p < 0.05$).
Odds ratios and statistical significance were determined using logistic regression models.

a. Odds of death from CVD within 4 years is 75% less in women who received estrogen therapy compared to those who did not receive therapy (OR = 0.250, $CI_{95\%}$= 0.079, 0.794) (Table 2). This crude association is statistically significant.

b. Previous CVD is not an effect modifier of the association between CVD death and estrogen therapy (χ^2=0.0089, df=1, p=0.9247).

c. It appears that a history of prior CVD is confounding the association between CVD death and estrogen therapy. Similar to question 1c, confounding can be suspected based on attenuation in the parameter estimating the association between CVD death and estrogen therapy (34%) and significance of the association between CVD death and prior CVD (χ^2=66.77, df=1, p<0.0001).

d. The odds of death from CVD within 4 years is 66% less in women who received estrogen therapy compared to those who did not receive therapy after adjusting for prior CVD, however this association is not statistically significant (OR = 0.338, $CI_{95\%}$= 0.106, 1.084) (Table 2).

e. Age appears to be further confounding the association between CVD death and estrogen therapy. Confounding is suspected because the parameter estimating the association between CVD death and estrogen shows a substantial change (22%) from the estimate that was adjusted for prior CVD alone, while the parameter estimate for age is highly statistically significant (χ^2=30.5934, df=1, p<0.0001).

f. The odds of death from CVD within 4 years is 57% less in women who received estrogen therapy compared to those who did not receive therapy after adjusting for prior CVD, however this association is not statistically significant (OR = 0.427, $CI_{95\%}$= 0.132, 1.379) (Table 2).

3. Table 3. Risk ratio for CVD death within 4 years comparing women who received estrogen therapy to those who did not

	Risk Ratio (95% CI)	p-value
Unadjusted	0.257 (0.082, 0.806)	0.0199*
Adjusted for prior CVD	0.349 (0.111, 1.097)	0.0716
Adjusted for prior CVD and age	0.435 (0.138, 1.370)	0.1549

* Risk ratio is significantly different from 1 ($p < 0.05$).
Risk ratios and statistical significance were determined using log-binomial and Poisson regression models.

a. Risk of death from CVD within 4 years is 74% less in women who received estrogen therapy compared to those who did not receive therapy (RR = 0.257, $CI_{95\%}$= 0.082, 0.806) (Table 3). This crude association is statistically significant.

b. Previous CVD is not an effect modifier of the association between CVD death and estrogen therapy (χ^2=0.00, df=1, p=0.9612).

c. It appears that a history of prior CVD is confounding the association between CVD death and estrogen therapy. The parameter estimating the association between CVD death and estrogen therapy is attenuated (22%), while the association between CVD death and prior CVD is highly statistically significant (χ^2=67.42, df=1, p<0.0001).

d. The risk of death from CVD within 4 years is 65% less in women who received estrogen therapy compared to those who did not receive therapy after adjusting for prior CVD, however this association is not statistically significant (OR = 0.349, $CI_{95\%}$= 0.111, 1.097) (Table 3).

e. Age appears to be further confounding the association between CVD death and estrogen therapy. The parameter estimate for estrogen is attenuated (25%) compared to the estimate that was adjusted for prior CVD alone, while the association between CVD death and age is highly statistically significant (χ^2=6.01, df=1, p<0.0001).

f. The risk of death from CVD within 4 years is 56% less in women who received estrogen therapy compared to those who did not receive therapy after adjusting for prior CVD, however this association is not statistically significant (OR = 0.435, $CI_{95\%}$= 0.138, 1.370) (Table 2).

4. Overall, the conclusions drawn from these three measures of association were very similar. While the crude association between estrogen therapy and 4-year death from CVD was found to be statistically significant in all cases, adjustment for prior CVD and age attenuated the effect for each measure. Because each of these predictors are also associated with the outcome and casual association between each predictor and the outcome is known or plausible, both prior CVD and age are confounders in our investigation of the association between estrogen therapy and death.

No evidence of effect modification by prior CVD disease was detected for any measure. This can be expected when there is no association between the POI (estrogen) and the outcome (CVD death), i.e. the null case.

The risk ratio has the most straightforward interpretation, however because probabilities are constrained to the range, 0 to 1, problems in estimation can occur. While there are ways to overcome this constrain, using odds ratio as a measure avoids this problem altogether because odds is not similarly constrained, however interpretation of the odds ratio is much less straightforward to many non-experts. When the probability of the event is small, the two measures are very similar as we see in this example. Risk differences can also be somewhat more difficult to interpret than risk ratio, however a bigger problem is that when the risks are very small the risk differences is very small. In general, the choice of a measure will depend on your scientific question. When one is interested in absolute risk reduction, risk difference is likely to be the measure of choice.