Analysis of the impact of Hormone Replacement Therapy in Reducing Total Cholesterol in Postmenopausal Women

[Redacted Team Member Name 1]
[Redacted Team Member Name 2]
Jenny Wang
[Redacted Team Member Name 3]

I. Abstract

The CDC[1] notes that having high cholesterol puts a person at risk of heart disease. Furthermore, they note that with high cholesterol, a person will have around twice the risk of heart disease. As such, our analysis is exploring the impact of hormone replacement therapy (HRT) in reducing total cholesterol among postmenopausal women as a measure of risk of heart disease. Using traditional covariate selection techniques combined with subject matter expertise, we determine several health-related measures that can be used to model total cholesterol and ultimately show the impact that HRT has in reducing total cholesterol. We also consider variables that are possible effect modifiers to gauge the impact of HRT among different groups of postmenopausal women. Due to the data coming from a randomized, double-blind trial, we assume an absence of confounding. Not only do we find that undergoing HRT is a significant factor in reducing total cholesterol compared to those in the placebo group, we also find that statin use and race are statistically significant effect modifiers.

II. Statistical Methods

The data provided is from a randomized double-blind placebo-controlled study. This allows us significant power as under a well-designed randomized double-blind study, confounding is theoretically eliminated. In our building of the model to predict the percent change in total cholesterol over the 1-year study period, we considered the following two-category variables: HRT, smoking, drinking, exercise, statins, hypertension medication, diabetes, insulin, oral DM medication, race (white or non-white,) and self-reported serious medical conditions. We also considered the following continuous variables: BMI at baseline, waist-hip ratio at baseline, and age. We removed any individuals that have these (or total cholesterol) missing from the data. This removes 11 participants, less than half of a percent, so we do not expect this to affect any statistical tests.

We performed a two-sample *t*-test comparing the percent change in total cholesterol in 1 year between those undergoing HRT and those with a placebo. Next, we tested a forward selection model and a backwards selection model (using AIC) to develop a linear regression model that predicts the percent cholesterol change over 1 year. The forward selection model and backward selection model suggest using HRT, statin use, diabetes status, exercise status, age, BMI and WHR at baseline. The slope parameter estimates, *p*-values, and 95% confidence intervals [CI] were found using R (version 3.5.1). To assess if there are any significant effect modifiers among the demographic variables, we use this baseline model and added interaction terms with HRT. For comparison, we include both a foundational model without interaction terms and a final model with them. We have also assessed the fit of the two models by examining the adjusted R^2 and MSE.

III. Results

For the study, we looked 2,575 records. Of which, 1,269 belonged to the hormone treatment group and 1,306 belonged to the placebo group (**Table 1**).

Table 1. Demographic characteristics and percent change in total cholesterol, LDL, And HDL.

CHARACTERISTICS	**CASES (%)**
Total	2,575
Treatment	
Hormone treatment	1,269 (49.3%)
Placebo	1,306 (50.7%)
Race	
White	2,301 (89.3%)
African American	186 (7.2%)
Other	88 (3.4%)
Diabetes	
Yes	1,913 (74.3%)
No	662 (25.7%)
Exercise	
Yes	1,562 (60.7%)
No	1,013 (39.3%)
Statins	
Yes	1,621 (63,0%)
No	954 (37.0%)
	MEAN ± STANDARD DEVIATION
Age (years)	66.65 ± 6.65
BMI (kg/m^2)	28.54 ± 5.45***
Percent change in total cholesterol	-2.83 ± 15.55***
Percent change in LDL	-6.56 ± 23.66***
Percent change HDL	1.51 ± 9.93***

***p < 0.0001 for comparing Hormone Therapy and Placebo treatment groups using t-test.

Figure 1 shows the distribution for percent change in TC by treatment group, with patients who received hormone therapy experienced a larger percent change in TC compared to patients who received a placebo treatment. The mean percent change in TC for patients who received hormone therapy treatment was -4.49% with a standard deviation of 15.34, whereas the mean percent change in total TC for the patients who received the placebo treatment was -1.21% with a standard deviation of 15.56 (**Table 2**).

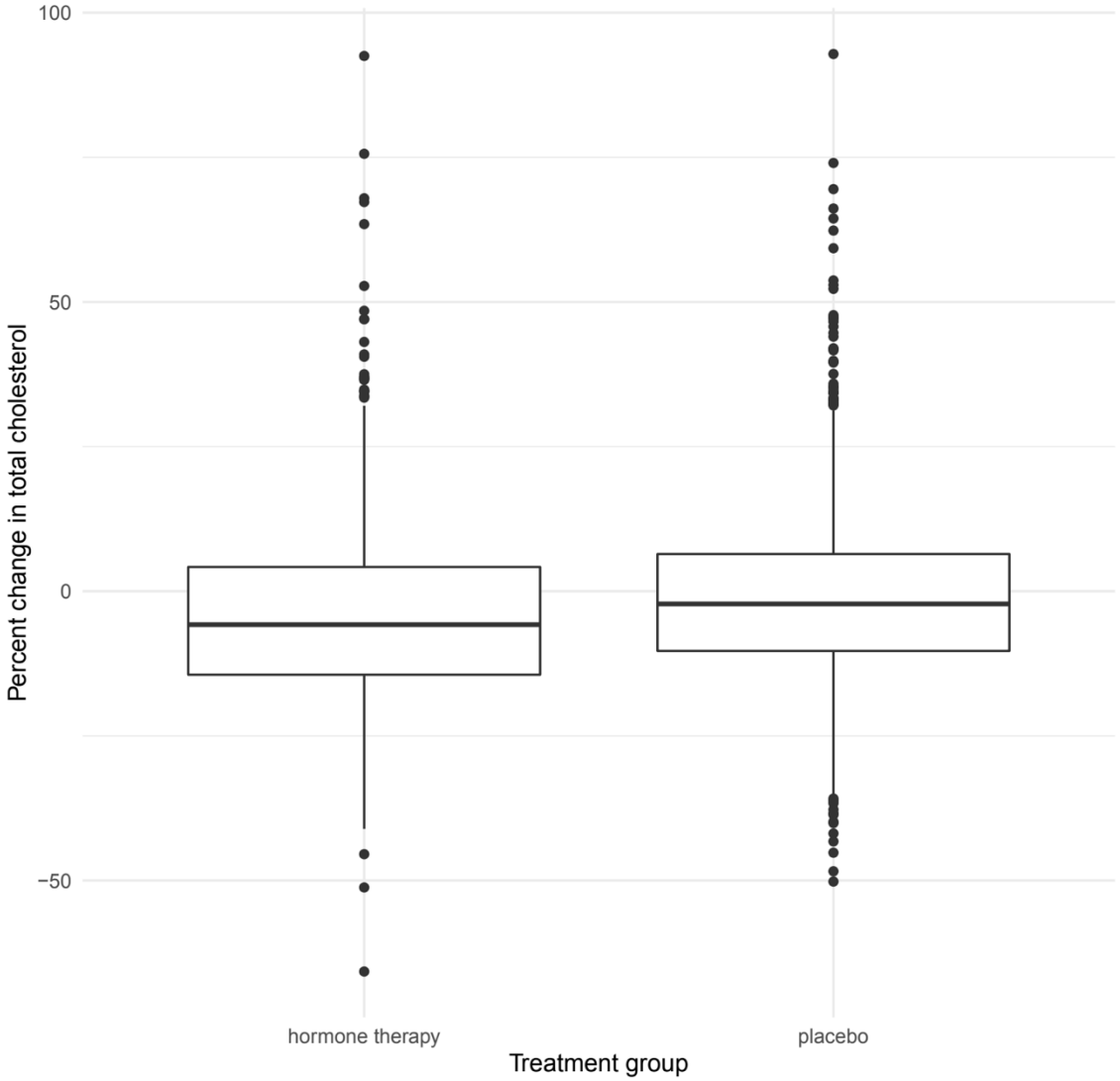

Figure 1. Boxplots for percent change in total cholesterol by treatment group.

The plot of observed values with a superimposed fit from the model chosen using forward selection is shown in **Figure 2.** The forward selection process helped to select a model that incorporated treatment, statins, exercise, diabetes, BMI, and age as variables; the predicted values from this model are plotted as two separate lines, one for each treatment group.

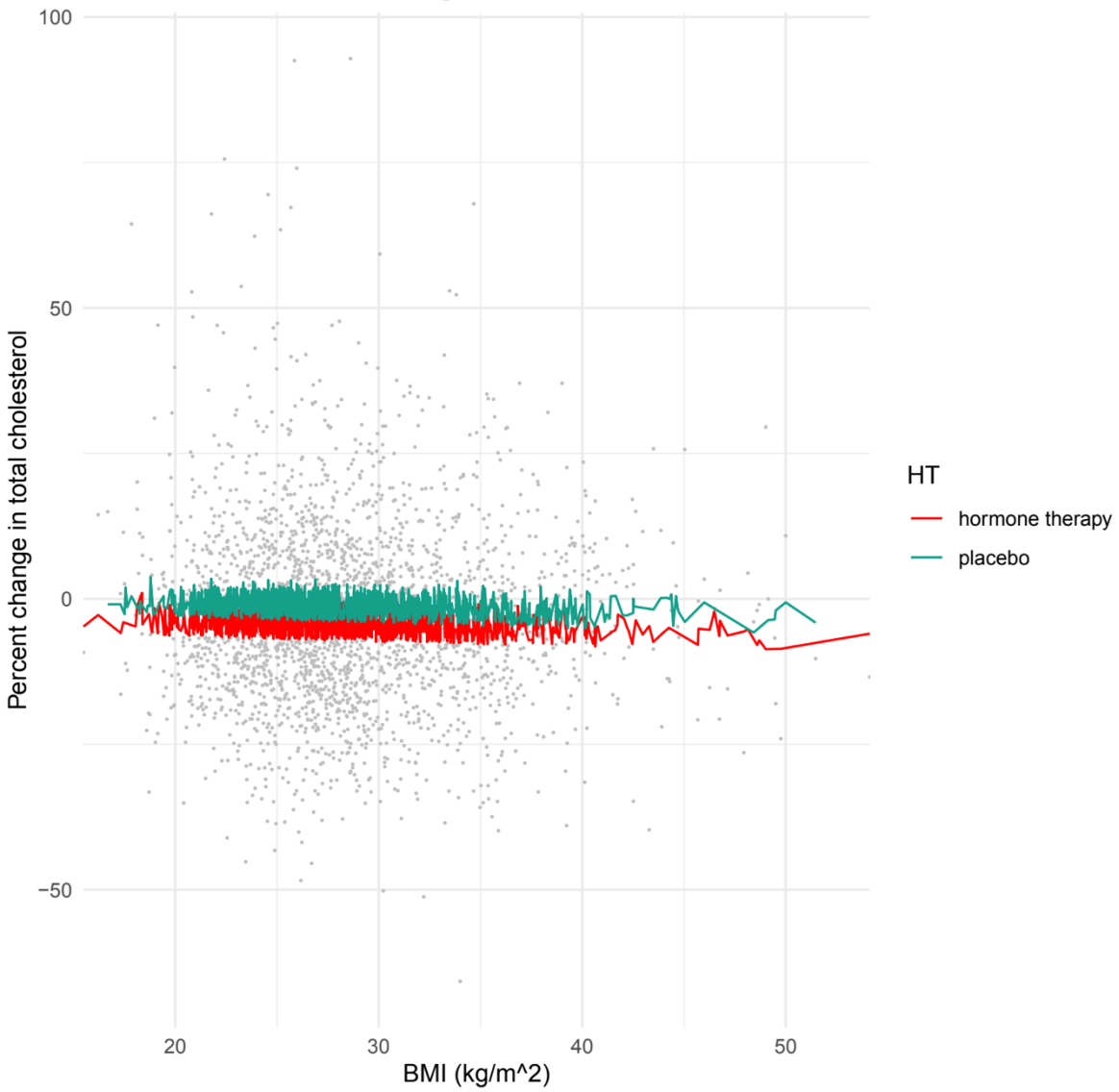

Figure 2. Predicted vs. actual percent change in total cholesterol against BMI.

Univariable analysis was performed to determine independent predictors of percent change in total cholesterol over 1 year (**Table 2**). Independent predictors of percent change in total cholesterol included HRT, statin use, exercise, and diabetes status. The final model included 2,575 subjects with an adjusted R^2 of 0.022 and MSE of 15.34. Holding all other covariates constant, HRT is associated with a 4.631% decrease in total cholesterol for patients not on statins and a 0.314% decrease for patients on statins ($p < 0.001$). From these results, we can see that HRT is significantly associated with decreased total cholesterol. The effect modification by statins use was an important consideration, as patients with high baseline cholesterol are often prescribed statins to control their cholesterol levels. From our analysis, for patients on statins, most of the effect of cholesterol decrease is explained by statins use as opposed to HRT. However, HRT still had a slight effect in reducing total cholesterol in these subjects. **Table 3** shows the effect modification of various covariates with HRT. From this table we can see that potential effect modifiers of HRT on change in total cholesterol are statin use and race. With our final model with effect modification by statin use and race, we were able to effectively predict total cholesterol change as a measure of heart disease. Our findings indicate that HRT has a significant effect on total cholesterol change.

Table 2. Univariable linear regression of percent change in total cholesterol with patient risk factors.

Variable	Percent change in total cholesterol	
	Foundation model (no interaction)	Final model (interaction)
Patients, n	2,575	2,575
Adjusted R^2	0.022	0.028
MSE	15.37	15.34
HRT		
Placebo	Reference	Reference
Hormone treatment		
β-estimate (P)	-3.246 (3.70e-08)	-4.631 (3.52e-09)
95% CI	-4.434 to -2.057	-6.163 to -3.099
Statins		
No	Reference	Reference
Yes		
β-estimate (P)	2.963 (9.33e-08)	0.828 (0.344)
95% CI	1.732 to 4.194	-0.888 to 2.545
Exercise		
No	Reference	Reference
Yes		
β-estimate (P)	1.360 (0.029)	1.246 (0.045)
95% CI	0.139 to 2.581	0.026 to 2.466
Diabetes		
No		Reference
Yes		
β-estimate (P)	1.281 (0.067)	1.412 (0.043)
95% CI	-0.085, 2.646	0.046 to 2.778
HT: statins	–	
No	Reference	Reference
Yes		
β-estimate (P)		4.317 (0.0006)
95% CI		1.856 to 6.778
HT: race	–	
White		Reference
Non-white		
β-estimate (P)		1.884 (0.166)
95% CI		-4.548 to 0.781

Table 3. Summary of linear model based on variable selection model with additional interaction terms added.

Interaction Term added	Estimated Coefficient of HRT* interaction term	P-value of Interaction term
Smoking	0.017	0.344
Drinking	0.011	0.366
Exercise	< 0.001	0.985
Statin Use	0.042	0.0007
Hypertension	0.008	0.622
Diabetes	- 0.0011	0.934
Insulin Use	- 0.0063	0.761
Oral DM Medication	- 0.027	0.185
Race	- 0.0447	0.022
Age	< 0.0001	0.975
BMI at baseline	- 0.0017	0.128
WHR at baseline	- 0.024	0.749
Serious Medical Condition	0.017	0.175

IV. References

1. https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_cholesterol.htm