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Estimating bounds for nonidentifiale parameters using potential outcomes

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ESTIMATING BOUNDS FOR NONIDENTIFIABLE PARAMETERS USING POTENTIAL OUTCOMES

by

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ABSTRACT

Conclusions from studies vary regarding the association of weight loss among obese people and measures of health and/or mortality. Total weight loss for individuals in a population may be a combination of intentional weight loss (IWL) and unintentional weight loss (UWL). Among people who have no intention to lose weight, the total weight loss observed is UWL. Among people who have intention to lose weight, the total weight loss is assumed to be UWL and IWL. Note that total weight loss among subjects intending to lose weight is observable but IWL itself is not and, therefore, the latent variable that is of interest.

This research reformulates Coffey et al. (2005) using the potential outcomes framework which help to clarify nonestimable quantities, in particular, tighten bounds for nonestimable correlation parameter and a causal parameter in a linear model under certain assumptions. Also, the positive definiteness requirement of a correlation matrix with covariate(s) is helpful in order to tighten the bounds for nonestimable quantities, and this is demostrated using the mice data example from Coffey et al. (2005). A parametric bootstrap is used to investigate sampling variability of estimated bounds for the causal parameter.

Finally, a matched pairs design is considered in order to get more information for a nonestimable parameter. Three data examples are considered; a data set from an experiment on eye treatments, the mice data set, and a data set from a study on twins. With the mice data set, the base line weight is used to assign mice to matched pairs. Some pairs are created from mice in different treatment groups, and other pairs from mice in the same treatment group. The latter helps to assess “quality of matching”.

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1. INTRODUCTION

1.1. MOTIVATION OF RESEARCH

Obesity continues to increase in the United States (Ogden et al., 2002; Flegal et al., 2002). There are many studies have shown that obesity is associated with increased mortality rate (Allison et al., 1999) and short-term weight loss improves risk factors for mortality (Weinsier, 1987), however, it has not been convincingly shown that weight loss among obese people results in reduced mortality rate. In contrary, weight loss is sometimes associated with increased mortality rate (Fontaine K.R. and Allison, 2001). Hence, weight loss among obese people is neither beneficial nor deleterious for human health. One possible explanation is that total weight loss for individuals in a population may have contributions from intentional weight loss (IWL) and unintentional weight loss (UWL). Some studies are designed to observe the intention to lose weight (Sorensen, 2003), and those that do must often implicitly assume that consequent observed weight loss was from the intention to lose weight (Yang et al., 2003). Among people who do not have intention to lose weight, it is assumed that all weight loss observed is entirely represented as unintentional. Therefore, the observed total weight loss is due only to their intention. However, among people who intend to lose weight, the total weight loss could be observed and this total, as well as any apparent effect on mortality would have contributions from UWL and IWL (Yang et al., 2003). These contributions may be in opposite directions from one another, as might be the case if UWL resulted from some underlying disease in a subset of the population being studied. Since IWL and UWL cannot be observed separately for those intending to lose weight, this makes it difficult to access their effects on mortality rate.

Again, the total weight loss for people intending to lose weight is observable but IWL itself is not. Therefore, IWL is the unobservable latent variable that is of interest. The latent variables have been described in different definitions and terminology (Bollen, 2002). Coffey et al. (2005) considered the problem of disentangling the effects of IWL on mortality from that of UWL, and developed a linear model using IWL as a latent variable and showed that the effect of IWL on mortality is a nonestimable parameter (unless some strong assumptions for other parameters). This research reformulates

Coffey et al. (2005) by using a different approach. Potential outcomes framework (Rubin, 1974) is proposed to clarify unobservable quantities and help tightening the bounds for a nonestimable correlation parameter and a causal parameter in a linear model under an assumption of random assignment to intention.

Aside from Coffey et al. (2005), there is no other paper known that considers total weight loss as a summation of UWL and IWL and that specifically try to estimate the effect of IWL on mortality or some other subsequent measure of health. There is a large body of literature on latent variable models with much of it focused on causality in observational data (cf., Berkane, 1997). Some such papers consider assignment to treatment as being dependent upon a latent variable in nonrandomized studies with resulting inferences then sensitive to hidden bias (e.g., Rosenbaum, 1991). Sensitivity analyses can be used to bound effects of treatment in such contexts (e.g. Rosenbaum, 1995; Heckman and Vytlach 1999). Here the latent variable is the causal variable that is of interest and assignment to intention is assumed to be random as was the case in Coffey et al. (2005) and is, in fact, true in the mice data example presented later. Estimation of a direct effect on a response from a variable that is not observable poses obvious problems; however, aspects of the study design combined with the fact that IWL is partially observable in total weight loss yield enough information about the variable that bounds for its effect can be estimated.

Sorensen et al. (2005) investigated the influence on mortality of intentional to lose weight for twins. Also matching can have appeal when drawing causal inferences using observational data (Rosenbaum and Rubin, 1983). Therefore, a matched pairs design is proposed in order to get the estimate bounds of the parameter of interest.

1.2. DISSERTATION OUTLINE

The effect of weight loss on mortality among obese population is questionable. As in Coffey et al. (2005), the weight loss is determined into two groups; unintentional and intentional to lose weight group. For the unintentional group, the observed weight loss is solely determined by the UWL but for intentional group, the observed total weight loss is the sum of UWL and IWL, whereas IWL is not separately observable. First, this dissertation gives the brief review and the key results of Coffey et al. (2005). Then,

Coffey et al. (2005) is reformulated by using the potential outcomes framework to clarify nonestimable parameters. The causal model is defined in terms of the parameters of interest and, under certain assumptions, the formula of the slope coefficient parameter is calculated by ordinary least squares (Graybill, 1976). Together with use of the positive definiteness requirement for a correlation matrix (Gadbury and Iyer, 2000) a set of plausible values for a nonestimable parameters is produced. Then a covariate is considered that helps tighten the bounds of the nonestimable correlation parameter and this leads to tighter bounds of the parameter of interest. Finally illustrate this approach with the mice data, which is exactly the same as in Coffey et al. (2005) and compare the result.

Next, use of parametric bootstrap procedure is implemented by simulating the data in order to assess the sampling variability of the bounds. All estimable parameters are set to be the same as in the mice experiment.

With matched pairs, the subjects in the population are paired prior to randomization using additional information, for example, twins. The mortality and covariate information are not used in this section. Section 4 focuses on matched pairs design using potential outcomes to estimate bounds of the variance of IWL. This section has two parts. First, within a pair, one subject is randomly assigned to receive one treatment; and the other is received different treatment. However, because of lack of homogeneity within pairs, the result only shows how large the nonestimable parameters might be. A modified matched pairs is then investigated in order to get the estimate bounds for parameter of interest. That is, both subjects within pairs are randomly assigned to get the same treatment. The illustration of this part is applied to three of examples which are eye, mice, and twins data. The eye experiment illustrates how the first approach applies. The mice data, with specific matching by using baseline weight at 12 months of age, and twins data are applied to both parts. The twins data is one of the interesting example since it was matched based on monozygotic and dizygotic twin pairs. Conclusions, discussion and future research work are summarized in the last section.

2. LITERATURE REVIEW

2.1. A BRIEF REVIEW OF COFFEY ET AL. (2005)

Assume that *N* subjects are observed until the time of death and denote the time until death (or some monotonic transformation thereof) as *Y*. The variable *Y* can generally be any continuous measurement of health or wellness. Let *X* be an indicator variable where $X = 0$ for subjects not intending to lose weight and $X = 1$ for subjects intending to lose weight. Denote the weight loss due to a subject's or experiment's intention as *Z* ($Z = IWL$) and the weight loss due to factors other than the intention as *W* ($W = UWL$). By definition, it is assumed that $Z = 0$ when $X = 0$. Therefore $Z|X = 1 \sim \left(\mu_Z, \sigma_Z^2\right)$ and $P\left(Z = 0|X = 0\right) = 1$.

The regression model describing the influences on lifespan is

$$Y = \beta_0 + \beta_1 W + \beta_2 ZX + \beta_3 X + e, \tag{1}$$

where the variables *Y*, *W*, *X*, and *Z* are described above. *e* is a random error with mean zero and variance σ_e^2. *W* is distributed with mean μ_W and variance σ_W^2. Also, *Z* is distributed with mean μ_Z and variance σ_Z^2. The coefficients β_0, β_1, β_2, and β_3 are constants whereas the slope coefficients β_1, β_2, and β_3 are defined as partial regression coefficients in a general linear model (Graybill, 1976) and, when estimable, are estimated by ordinary least squares.

The parameter β_1 captures the effects of UWL on *Y* and β_2 captures the effects of IWL on *Y*. Since no IWL occurs in the unintentional to lose weight, by the definition, this model assumes that there is an interaction between *Z* and *X* but no interaction between *W* and *X*. The parameter β_3 allows for the fact that there may be some effect of intending to lose weight (or more likely the actions or conditions that follow from such intention) as some data suggest (Gregg et al., 2003, 2004) which is associated with mortality. Levels of *X* were assumed to be assigned at random so that if *Z* could be observed for some

subject, then β_2 is unbiased estimator in equation (1). Note that, in human studies, this random assignment assumption could not be assumed which is left to be discussed later.

The observed total weight loss in practical is $V = W + Z$ which consists of the sum of UWL and IWL, respectively, and IWL, *Z*, is the latent variable. That is, for those not intending to lose weight, when $X = 0$, a linear regression model based on observable data is

$$Y = \beta_0 + \beta_1 W + e\,. \tag{2}$$

For those intending to lose weight, when $X = 1$, a regression model which follow from (1) is written as

$$Y = (\beta_0 + \beta_3) + \beta_1 W + \beta_2 Z + e\,. \tag{3}$$

Note that, this model assumes that both the variation of UWL and the slope of the effect of UWL is the same regardless of whether or not a subject intends to lose weight, i.e., homogeneity of variance for UWL in two groups. Since the variable *Z* in (1) is not separately observable, a regression model based on observable data does not follow from the regression model (1). This leads the linear regression equation for those intending to lose weight as

$$Y = \lambda_0 + \lambda_1 V + e\,. \tag{4}$$

Herein, λ_1 is considered as a naïve estimate relating mortality and total weight loss. Coffey et al. (2005) solved for the parameter of interest, β_2, as

$$\beta_2 = \frac{\lambda_1 \sigma_V^2 - \beta_1 \left(\sigma_W^2 + \rho_{W,Z}\sigma_W \sigma_Z\right)}{\sigma_Z^2 + \rho_{W,Z}\sigma_W \sigma_Z}\,. \tag{5}$$

The parameters β_1, λ_1, σ_V^2, and σ_W^2 are estimable in observed data but the parameters $\rho_{W,Z}$ (the simple correlation between *W* and *Z*) and σ_Z are not because the variable *Z* is not observable. Coffey et al. (2005) used (5) to get the bound of β_2 by plugging in sample estimates of the observed parameters β_1, λ_1, σ_V^2, and σ_W^2 and varying the possible values of $\rho_{W,Z}$ and σ_Z.

The results from Coffey et al. (2005) provide the plausible ranges for $\rho_{W,V}$ in (-1, 0.730) and (0.980, 1). The estimated plausible values for β_2 based on the allowable values for $\rho_{W,V}$ are $-0.15 \le \beta_2 \le 1.21$, and $5.11 \le \beta_2 \le 6.41$. However, the upper range was excluded since it was impossible to be true. Note that, bounds for β_2 in Coffey et al. (2005) are 5 times of those reported here since the results of the data example reported here are based on weigh loss measured in original units of grams, but the data example in Coffey et al. (2005) used weight loss in 5 gram increments.

2.2. OTHER LITERATURE REVIEW

Though Coffey et al. (2005) looked at a mice data set; recent studies on human have measured intention to lose weight. As in Sorensen et al. (2005), the paper analyzed the Finnish Twin Cohort which was composed of all same-sex twin pairs born in Finland before 1958 in which both twins were alive in 1967 (Kaprio, 2002) to investigate the influence on mortality of intention to lose weight among obese people. The overweight or obese was defined by body mass index (BMI=weight/height^2, kg/m^2), BMI≥25 kg/m^2. Notice that a change of 2 kg in body weight may have different implications for tall and short people, in analogy with body weight as such; Sorensen et al. (2005) analyzed weight changes as changes in BMI units rather than in kg. The data were collected since 1975. All participants were asked whether they were currently trying to lose weight because of overweight, which was interpreted as “intention to lose weight”. In addition, the lifestyle factors, such as smoking habits, alcohol drinking, physical activity, life satisfaction, work status, and income, were recorded and analyzed. Moreover, the confounding by diseases was eliminated. All of the participants were followed up until death or the end of 1999 where some subjects might have died but others were still alive.

Sorensen et al. (2005) mentioned that the health effects of weight loss are complex and it would need more research.

Also, Gregg et al. (2004) investigated the relationships between intention to lose weight, actual weight loss, and all-cause mortality among obese individuals with diabetes. The population for this study is 1401 overweight diabetic adults aged ≥ 35 years. The obese was determined by BMI ≥ 30 kg/m^2. All participants were asked for intention to lose weight, weight change, age, race, sex, education, smoking status, limitations in daily activity, past year hospitalizations, doctor visits, and insulin use. All of the participants were followed up to 9 years. Gregg et al. (2004) specified the limitation of the observational weight change on mortality which is the lack of information about weight loss intention (Yang et al., 2002). Among overweight individuals, it is difficult to examine the effect of weight loss on mortality since the weight loss among individuals includes a mixture of weight loss on purpose and unintentional weight loss that is frequently associated with poor health. Gregg et al. (2004) concluded that intention to lose weight was associated with reduced mortality regardless of whether weight loss is occurred.

One challenge of human data is that assignment to intention is not random. This dissertation does not take up that challenge but do look at a subset of data from Sorensen et al. (2005) to determine the extent to which parameters of the distribution of Z=IWL can be estimated or bounded. In particular, matched pairs are considered. Matching has shown some value for latent variable type applications (Rosenbaum, 1989).

3. INTENTIONAL VERSUS UNINTENTIONAL WEIGHT LOSS ON MORTALITY

3.1. FORMULATING THE IWL PROBLEM WITH POTENTIAL OUTCOMES

The potential outcomes framework is used to investigate the IWL problem without considering the covariate and defined as $\left(Y^{(x)}, W^{(x)}, Z\right)$, where $x = 0$ is for subjects not intending to lose weight, $x = 1$ is for subjects intending to lose weight, *Y*, *W* and *Z* are as described before. Herein, there are five potential outcomes for a subject where $Y^{(0)}$ and $Y^{(1)}$ are the mortality of a subject who does not intend and intend to lose weight, respectively. In the same way, $W^{(0)}$ and $W^{(1)}$ are the unintentional weight loss for a subject who not intending and intending to lose weight, respectively. With the same assumptions as in Coffey et al. (2005), both variables $W^{(0)}$ and $W^{(1)}$ have the same variance, σ_W^2. Since the observed total weight loss for unintentional group is only $W^{(0)}$, that is, $Z^{(0)} = 0$, therefore, in order to simplify the notation the superscript for *Z* will be dropped out and define $Z^{(1)} = Z$ as a single outcome, however it is unobservable, for each individual. Hence the regression models from Coffey et al. (2005) in terms of potential outcomes become

$$Y^{(0)} = \beta_0 + \beta_1 W^{(0)} + \varepsilon^{(0)}, \tag{6}$$

$$Y^{(1)} = \left(\beta_0 + \beta_3\right) + \beta_1 W^{(1)} + \beta_2 Z + \varepsilon^{(1)}, \tag{7}$$

where $\varepsilon^{(0)}$ and $\varepsilon^{(1)}$ are the random error with mean zero and variance $\sigma^2_{\varepsilon^{(0)}}$ and $\sigma^2_{\varepsilon^{(1)}}$, respectively. The causal but nonestimable causal effect of IWL, where the expectation is conditional on the weight loss variables, is

$$D\left(W^{(x)}, Z\right) = E\left(Y^{(1)} - Y^{(0)}\right) = \beta_3 + \beta_1\left(W^{(1)} - W^{(0)}\right) + \beta_2 Z\,. \tag{8}$$

For 1 unit change in *Z*, by holding other variables to be constant, the effect is $D(z+1)-D(z)=\beta_2$. Therefore, the parameter β_2 is called the causal parameter and the equation (7) is the causal model.

For a given subject, either $\left(Y^{(0)},W^{(0)}\right)$ or $\left(Y^{(1)},V^{(1)}=W^{(1)}+Z\right)$ is observed depending on random assignment to either unintentional or intentional to lose weight. Again, since the observed total weight loss for unintentional group is only $W^{(0)}$, that is, $Z^{(0)}=0$ and $V^{(0)}=W^{(0)}$, therefore, the superscript of *V* will be dropped out and set $V=W^{(1)}+Z$. The parameters β_1 and λ_1 can be estimated by the regression models (2) and (4), respectively. Consider the simple linear regression model,

$$W^{(1)}=\alpha_0+\alpha_1 V+\varepsilon\,. \tag{9}$$

Since $W^{(1)}$ is not separately observable from the observed total weight loss, $V=W^{(1)}+Z$ for each subject, the parameters in equation (9) cannot be estimated. From Coffey et al. (2005) and the regression model (9), β_2 can be written as a function of one nonestimable parameter α_1, that is, $\beta_2=\dfrac{\lambda_1-\beta_1\alpha_1}{1-\alpha_1}$. With the assumption in Coffey et al. (2005) that $W^{(1)}$ and *V* are independent, it shows that $\alpha_1=0$ and also $\beta_2=\lambda_1$. This assumption is unlikely to be true. The parameter estimate of λ_1 in the linear regression model (4) is called a naïve estimate of β_2. Consider the linear regression model (9), the parameter α_1 is nonesimable because of the nonestimable correlation between *V* and $W^{(1)}$. Equation (5) shows that β_2 is a function of two nonestimable parameters which can be reformulated as the function of only one nonestimable parameter $\rho_{W,V}$, the simple correlation between *V* and $W^{(1)}$. It is clear to drop out the superscript of the correlation between *V* and $W^{(1)}$ because $V^{(0)}=W^{(0)}$ for unintentional group. In addition, as in Coffey et al. (2005), the assumption, that the marginal distributions of both $W^{(0)}$ and $W^{(1)}$ are the same with variance σ_W^2, is required. For reference, the summarization of the notation for distributional parameters of potential outcomes variables which are estimable together

with their description and any assumes restrictions on marginal and joint distributions is in Table 3.1. Moreover, Table 3.1 includes information on a covariate *U* (to be described later) and also parameter estimates from a data example explained in Section 3.3.

Table 3.1. Parameter Notation, Descriptions of Parameters Including Restrictions on Marginal and Joint Distributions, and Parameter Estimates from the Data Example

Parameter notation	Parameter description	Parameter estimate
$\mu_{Y^{(1)}}$	$E\left(Y^{(1)}\right)$	36.91
$\mu_{Y^{(0)}}$	$E\left(Y^{(0)}\right)$	33.71
μ_W	$E\left(W^{(1)}\right)=E\left(W^{(0)}\right)$	0.45
μ_V	$E\left(V^{(1)}\right)=E(V),\ V=W+Z$	14.14
μ_U	$E(U)$	41.72
$\sigma^2_{Y^{(1)}}$	$Var\left(Y^{(1)}\right)$	5.42
$\sigma^2_{Y^{(0)}}$	$Var\left(Y^{(0)}\right)$	4.71
σ^2_W	$Var\left(W^{(1)}\right)=Var\left(W^{(0)}\right)$	4.79
σ^2_V	$Var\left(V^{(1)}\right)=Var(V)$	5.20
σ^2_U	$Var(U)$	4.68
$\rho_{Y^{(1)},V}$	$Cor\left(Y^{(1)},V^{(1)}\right)=Cor\left(Y^{(1)},V\right)$	0.105
$\rho_{Y^{(0)},W}$	$Cor\left(Y^{(0)},W^{(0)}\right)$	-0.436
$\rho_{Y^{(1)},U}$	$Cor\left(Y^{(1)},U\right)$	0.126
$\rho_{Y^{(0)},U}$	$Cor\left(Y^{(0)},U\right)$	-0.272
$\rho_{W,U}$	$Cor\left(W^{(1)},U\right)=Cor\left(W^{(0)},U\right)$	0.550
$\rho_{V,U}$	$Cor\left(V^{(1)},U\right)=Cor(V,U)$	0.870

The causal model (7) can be rewritten as

$$Y^{(1)} = (\beta_0 + \beta_3) + (\beta_1 - \beta_2)W^{(1)} + \beta_2 V + \varepsilon^{(1)}. \tag{10}$$

Now consider the regression model (6) and the causal model (10). In the regression model (6), $(Y^{(0)}, W^{(0)})$ are observable for unintentional group but in the causal model (10), for intentional group, $W^{(1)}$ is not observable. It is previously assumed that β_1 is the same in models (6) and (10), that is, there was no *W* and *X* interaction or homogeneity of variance of UWL in the two groups. Applying these two equations (see details in Appendix A), $\rho_{W^{(1)},Z}\sigma_Z = \sigma_V \rho_{W,V} - \sigma_W$ and $\sigma_Z^2 = \sigma_V^2 + \sigma_W^2 - 2\sigma_V \sigma_W \rho_{W,V}$ leads equation (5) as

$$\beta_2 = \frac{\sigma_{Y^{(1)}} \rho_{Y^{(1)},V} - \sigma_{Y^{(0)}} \rho_{Y^{(0)},W} \rho_{W,V}}{\sigma_V - \sigma_W \rho_{W,V}}. \tag{11}$$

All the parameters in equation (11) are estimable except the simple correlation between *V* and $W^{(1)}$, $\rho_{W,V}$. Vary the possible value of nonestimable $\rho_{W,V}$ from -1 to 1 in order to get the bounds for the parameter of interest, β_2.

There is another constraint that could tighten the bounds for β_2. Gadbury and Iyer (2000) used the positive definiteness requirement for a correlation matrix to produce a set of plausible values for a nonestimable parameters. Consider the correlation matrix of the random vector $(Y^{(1)}, Y^{(0)}, W^{(1)}, V)'$ with six correlation parameters. Four of them are nonestimable which are $\rho_{Y^{(1)},Y^{(0)}}$, $\rho_{Y^{(1)},W}$, $\rho_{Y^{(0)},V}$, and $\rho_{W,V}$. Applying the use of positive definiteness which is not useful since this set of matrix produces only 3 equations but 4 unknowns or nonestimable parameters. Therefore, consider the random vector of only three variables, $(Y^{(1)}, W^{(1)}, V)'$ and see that these 3 variables are, in fact, those of interest in the causal model (10). Let *R* be the 3-dimensional correlation matrix and there are only 2 nonestimable parameters which are $\rho_{Y^{(1)},W^{(1)}}$ and $\rho_{W,V}$. However, with the assumptions

stated as before, both of nonestimable parameters are functionally related. Equation (6) gives a formula β_1 and equation (10) gives two different formulas for β_2, which are,

$$\beta_2^{(1)} = \frac{\sigma_{Y^{(1)}}\left[\rho_{Y^{(1)},V} - \rho_{Y^{(1)},W^{(1)}}\rho_{W,V}\right]}{\sigma_V\left(1-\rho_{W,V}^2\right)},$$

$$\beta_2^{(2)} = \frac{1}{\sigma_W}\left[\sigma_{Y^{(0)}}\rho_{Y^{(0)},W^{(0)}} - \frac{\sigma_{Y^{(1)}}\left[\rho_{Y^{(1)},W^{(1)}} - \rho_{Y^{(1)},V}\rho_{W,V}\right]}{\left(1-\rho_{W,V}^2\right)}\right].$$

The derivation detail is in Appendix A. Equating these two of β_2 providing β_1 produces the equation of β_2 as given in equation (11). See details in Appendix A. One result is an equation of the correlation between the two nonestimable parameters $Y^{(1)}$ and $W^{(1)}$ as

$$\rho_{Y^{(1)},W^{(1)}} = \frac{\sigma_{Y^{(0)}}\sigma_V\rho_{Y^{(0)},W}\left(1-\rho_{W,V}^2\right)+\sigma_{Y^{(1)}}\rho_{Y^{(1)},V}\left(\sigma_V\rho_{W,V}-\sigma_W\right)}{\sigma_{Y^{(1)}}\left(\sigma_V-\sigma_W\rho_{W,V}\right)}. \tag{12}$$

Plugging the formula (12), which is a function of only nonestimable $\rho_{W,V}$, into the correlation matrix for $\left(Y^{(1)},W^{(1)},V\right)'$,

$$R = \begin{pmatrix} 1 & h\left(\rho_{W,V}\right) & \rho_{Y^{(1)},V} \\ h\left(\rho_{W,V}\right) & 1 & \rho_{W,V} \\ \rho_{Y^{(1)},V} & \rho_{W,V} & 1 \end{pmatrix}, \tag{13}$$

where $h(\rho_{W,V})$ is in the form (12). Let $e_{\min}$ be the minimum eigenvalue of the correlation matrix *R*. With the positive definiteness constraint, $e_{\min} > 0$, this can tighten the range of plausible values of $\rho_{W,V}$. The range for $\rho_{W,V}$ results in tighter bounds for β_2 that can be estimated from observable data.

3.2. THE ROLE OF A COVARIATE IN TIGHTENING BOUNDS

Let *U* be a covariate and observed on all subjects in an experiment. Note that *U* is not affected by the assigned treatment, herein, the intention to lose weight. An example of a covariate could be baseline weight before assigning the treatment. It is questionable on whether the causal model is given by model (10) defined without the covariate, or by a similar model with the covariate. However, the capability of the covariate to tighten the bounds for $\rho_{W,V}$ depends on how well it predicts *W* and/or *V*, in which case colinearity problems are encountered when it is included in the causal model. Which causal model is ultimately preferred depends on the ability of *U* to predict $Y^{(1)}$ given *W* and *V* are in the model. This section presents a method to estimate bounds for β_2 in a causal model with and without a covariate in the model. The issue of colinearity is considered later with a data example in Section 3.3.

3.2.1. Using a Covariate to Tighten the Range for $\rho_{W,V}$. Consider the 4-dimensional correlation matrix for the random vector $\left(Y^{(1)}, W^{(1)}, V, U\right)'$,

$$\Sigma = \begin{pmatrix} 1 & \rho_{Y^{(1)},W^{(1)}} & \rho_{Y^{(1)},V} & \rho_{Y^{(1)},U} \\ \rho_{Y^{(1)},W^{(1)}} & 1 & \rho_{W,V} & \rho_{W,U} \\ \rho_{Y^{(1)},V} & \rho_{W,V} & 1 & \rho_{V,U} \\ \rho_{Y^{(1)},U} & \rho_{W,U} & \rho_{V,U} & 1 \end{pmatrix}. \tag{14}$$

Since the covariate *U* is observable for all subjects, four out of six correlation parameters in matrix (14) are all estimable except $\rho_{Y^{(1)},W^{(1)}}$ and $\rho_{W,V}$, which are the same as previous section. Partition the correlation matrix as

$$\Sigma = \begin{pmatrix} R & S_{12} \\ S_{21} & S_{22} \end{pmatrix}, \tag{15}$$

where *R* is the same matrix as (13) and $\rho_{Y^{(1)},W^{(1)}} = h\left(\rho_{W,V}\right)$ is the function in term of $\rho_{W,V}$ using the multivariate distribution without the covariate. $\rho_{W,V}$ is now a constraint

for making the matrix *R* positive definite, i.e., $R > 0$. In general, the notation $S_{12} = S_{21}'$ is used for general case with multiple covariates observed for a subject and these terms represent the correlation between each covariate and the first three variables $\left(Y^{(1)}, W^{(1)}, V\right)$. The matrix S_{22} is the correlation matrix of the vector of covariates and equal to 1 in the case of only one covariate. The constraint of that the matrix *R* is positive definite, $R > 0$, combined with the identity $\left|\Sigma\right| = \left|R\right|\left|S_{22} - S_{21}R^{-1}S_{12}\right| > 0$ gives more information to tighten the range for $\rho_{W,V}$. With only one covariate, it is simplified to $S_{21}R^{-1}S_{12} < 1$.

3.2.2. A Causal Model With a Covariate. The regression model with a covariate is

$$Y = \beta_0 + \beta_1 W + \beta_2 ZX + \beta_3 U + \beta_4 X + \beta_5 UX + \varepsilon . \tag{16}$$

The treatment-covariate interaction term in model (16) implies that the slope parameters on the covariate, *U*, are not necessarily to be the same for both groups. It is explicitly seen when consider the model (16) into two groups, UWL and IWL, and the total weight loss for IWL group is $V = W^{(1)} + Z$, as

$$Y^{(0)} = \beta_0 + \beta_1 W^{(0)} + \beta_3 U + \varepsilon^{(0)}, \tag{17}$$

$$Y^{(1)} = \left(\beta_0 + \beta_4\right) + \left(\beta_1 - \beta_2\right) W^{(1)} + \beta_2 V + \left(\beta_3 + \beta_5\right) U + \varepsilon^{(1)}. \tag{18}$$

As before, the causal but nonestimable causal effect of IWL is

$$D\left(Z, W^{(x)}, U\right) = E(Y^{(1)} - Y^{(0)}) = \beta_4 + \beta_1\left(W^{(1)} - W^{(0)}\right) + \beta_2 Z + \beta_5 U .$$

For 1 unit change in *Z*, holding other variables constant, the effect is $D\left(z+1\right) - D(z) = \beta_2$. Therefore β_2 is the causal parameter and equation (18) is the causal model.

Similarly with no covariate case, the model (17) gives the equation of β_1 and model (18) gives two forms of β_2, which are,

$$\beta_2^{(1)} = \frac{\sigma_{Y^{(1)}}}{\sigma_V}\left[\frac{\rho_{Y^{(1)},W^{(1)}}\left(\rho_{W,U}\rho_{V,U}-\rho_{W,V}\right)+\rho_{Y^{(1)},V}\left(1-\rho_{W,U}^2\right)+\rho_{Y^{(1)},U}\left(\rho_{W,V}\rho_{W,U}-\rho_{V,U}\right)}{1-\rho_{W,U}^2-\rho_{V,U}^2-\rho_{W,V}^2+2\rho_{W,V}\rho_{W,U}\rho_{V,U}}\right], \quad (19)$$

$$\beta_2^{(2)} = \frac{\sigma_{Y^{(0)}}\left|\rho_{Y^{(0)},W^{(0)}}-\rho_{Y^{(0)},U}\rho_{W,U}\right|}{\sigma_W\left(1-\rho_{W,U}^2\right)}$$

$$-\frac{\sigma_{Y^{(1)}}}{\sigma_W}\left[\frac{\rho_{Y^{(1)},W^{(1)}}\left(1-\rho_{V,U}^2\right)+\rho_{Y^{(1)},V}\left(\rho_{W,U}\rho_{V,U}-\rho_{W,V}\right)+\rho_{Y^{(1)},U}\left(\rho_{W,V}\rho_{V,U}-\rho_{W,U}\right)}{1-\rho_{W,U}^2-\rho_{V,U}^2-\rho_{W,V}^2+2\rho_{W,U}\rho_{V,U}\rho_{W,V}}\right].$$

The derivation detail is in Appendix B. With the same approach, equate those two forms of β_2 provides a functional relationship $\rho_{Y^{(1)},W^{(1)}} = g\left(\rho_{W,V}\right)$ which is (also, see details in Appendix B),

$$\rho_{Y^{(1)},W^{(1)}} = \left[\frac{\sigma_{Y^{(1)}}\left(\rho_{W,U}\rho_{V,U}-\rho_{W,V}\right)}{\sigma_V D}+\frac{\sigma_{Y^{(1)}}\left(1-\rho_{V,U}^2\right)}{\sigma_W D}\right]^{-1}\left[\beta_1-\frac{\sigma_{Y^{(1)}}E_2}{\sigma_W D}-\frac{\sigma_{Y^{(1)}}E_1}{\sigma_V D}\right], \quad (20)$$

where,
$$E_1 = \rho_{Y^{(1)},V}\left(1-\rho_{W,U}^2\right)+\rho_{Y^{(1)},U}\left(\rho_{W,V}\rho_{W,U}-\rho_{V,U}\right),$$
$$D = 1-\rho_{W,U}^2-\rho_{V,U}^2-\rho_{W,V}^2+2\rho_{W,V}\rho_{W,U}\rho_{V,U},$$
$$E_2 = \rho_{Y^{(1)},V}\left(\rho_{W,U}\rho_{V,U}-\rho_{W,V}\right)+\rho_{Y^{(1)},U}\left(\rho_{W,V}\rho_{V,U}-\rho_{W,U}\right),$$

and the equation of parameter of interest, β_2, is now a function of only one nonestimable correlation $\rho_{W,V}$. The derivation of β_2 is somewhat tedious, though straightforward, and given in Appendix B. The constraints on $\rho_{W,V}$ result from the positive definiteness requirement for the matrix Σ as in (14) and these constraints is used to bound β_2 in the model (18).

3.2.3. Putting it All Together Using a Covariate. The nonestimable correlation, $\rho_{W,V}$, is an unknown, but fixed parameter. With certain conditions, $\rho_{W,V}$ is bounded by a continuous interval.

Proposition 1. Consider a population correlation matrix consisting of an unknown nonestimable correlation, $\rho_{W,V}$, and other distinct but fixed known correlations. Assume that there is at least one value of $\rho_{W,V}$ such that the population correlation matrix is positive definite. Then plausible values of $\rho_{W,V}$ are bounded by a continuous interval.

Proof. Let a random vector be given by (V,W,U) where *U* is a vector of variables. Partition the correlation matrix as $\begin{pmatrix} A & B \\ B' & S_U \end{pmatrix}$ where $A = \begin{pmatrix} 1 & \rho_{W,V} \\ \rho_{W,V} & 1 \end{pmatrix}$, S_U is a correlation matrix of *U*, and $B = \begin{pmatrix} S_{V,U} \\ S_{W,U} \end{pmatrix}$, that is, the correlation of *V* and *W*, respectively, with variables in *U*. The positive definite requirement of a correlation matrix implies that $\left|A - BS_U^{-1}B'\right| > 0$. With $BS_U^{-1}B' = \begin{pmatrix} m_{11} & m_{12} \\ m_{21} & m_{22} \end{pmatrix}$, where $m_{12} = m_{21}$, hence, $\rho_{W,V}$ is bounded by $m_{12} \pm \sqrt{(1-m_{11})(1-m_{22})}$.

□

The proposition is important to state since it is difficult to interpret the bounds for $\rho_{W,V}$ when they do not contain a continuous interval. In the application described here, the conditions of the proposition are not met because of a restriction enforced by the assumption that the coefficient parameter β_1 was the same for both UWL and IWL groups. This assumption not only helped to tighten the bounds for $\rho_{W,V}$, but also led the two nonestimable parameters, $\rho_{W,V}$ and $\rho_{Y^{(1)},W^{(1)}}$, to be functionally related by either equation (12) which is used to bound $\rho_{W,V}$ in Section 3.1, or by equation (20) which is used to bound $\rho_{W,V}$ in Section 3.2. Consequently, plausible values of $\rho_{W,V}$ may or may not lie in a continuous interval but this due to an assumption made herein. Therefore, it is interesting to find a reasonable method to combine information obtained from population

models with and without covariate that produces a continuous set of plausible values for $\rho_{W,V}$.

Let P_1 be the estimated set of plausible values for $\rho_{W,V}$ from Section 3.1, and P_2 be the estimated set of plausible values for $\rho_{W,V}$ from Section 3.2. Since $\rho_{W,V}$ is a fixed population parameter, all of the information available in both the marginal tri-variate distribution of $\left(Y^{(1)}, W^{(1)}, V\right)'$ and in the 4-dimensional distribution of $\left(Y^{(1)}, W^{(1)}, V, U\right)'$ is used. Thus the plausible values of $\rho_{W,V}$ could be defined as the set P,

$$\rho_{W,V} \in \mathrm{P} = \left(\mathrm{P}_1 \cap \mathrm{P}_2\right). \tag{21}$$

After the set P has been obtained as in equation (21), bounds for β_2 can be estimated using either equation (11) or equation (19), depending on whether or not the covariate has been conditioned on the estimated causal effect. Henceforth, when the lower and upper values bound a continuous interval, the estimated bounds will be referred as valid bounds.

3.3. ILLUSTRATION ON A DATA SET

The illustration of this approach is applied with the same example described in Coffey et al. (2005). The data were drawn from the field of rodent caloric restriction studies where animals are regularly observed until all are dead. Briefly, 135 male mice of the B10C3F$_1$ strain were fed *ad libitum* until 12 months of age at which point they were randomized, individual housed, and provided an intake of either an amount sufficient to maintain body weight (a control diet is the unintentional condition, X=0,160 kcal/mouse/wk) or an intake of 90 kcal (a restricted group is the intentional condition, X=1). To avoid malnutrition, both groups consumed a diet enriched in content of protein, vitamins and minerals, therefore, the intakes of these dietary essentials were matched between groups. All mice were followed until death and the treatments were randomly assigned at the age of 12 months. The baseline weight at 12 months of age is set to be a covariate U.

At 23 months of age, the weight loss was observed for each mouse. Four mice were omitted since they were not alive at the 23 month. The remaining 131 mice were followed until death. *Y* represents the lifespan or mortality which was recorded for 64 mice in the UWL group and 67 in the IWL group.

3.3.1. Analysis Without the Covariate. Figure 3.1 shows the scatter plot of total weight loss at 23 months and lifespan, also, with a fitted simple regression estimated for both IWL and UWL groups, $\left(V, Y^{(1)}\right)$ and $\left(W^{(0)}, Y^{(0)}\right)$. Circle and the plus sign represent for IWL and UWL group, respectively. The solid line stands for IWL group and the other for UWL group.

It is obviously seen that the IWL group seemed to have more weight loss and slightly positive relationship with the mortality. On the other hand, the UWL group had a negative association between *W* and $Y^{(0)}$. The sample estimable parameters of this mice experiment are given in Table 3.1. The correlation matrix *R*, defined in matrix (13), with the positive definite requirement provides the plausible values for $\rho_{W,V}$ into two intervals (-1, 0.730) and (0.980, 1). These plausible ranges of values for $\rho_{W,V}$ were obtained numerically such that the minimum eigenvalue, $e_{\min}$, of the matrix *R* is positive. The values of $\rho_{W,V}$ in the interval (0.980, 1) have the minimum eigenvalues near singularity. The interval is not continuous because the functional relationship, $\rho_{Y^{(1)},W^{(1)}} = h\left(\rho_{W,V}\right)$ given by equation (12), is nonlinearity which created a complex functional relationship, i.e., higher order between $e_{\min}$ and $\rho_{W,V}$. The estimated plausible values for β_2 based on the allowable values for $\rho_{W,V}$ are $-0.15 \le \beta_2 \le 1.21$, and $5.11 \le \beta_2 \le 6.41$. Coffey et al. (2005) excluded the upper range as implausible based on knowledge of the particular application, however, there was no mathematical justification for eliminating this range. Note that, bounds for β_2 in Coffey et al. (2005) are 5 times of those reported here since the results of the data example reported here are based on weigh loss measured in original units of grams, but the data example in Coffey et al. (2005) used weight loss in 5 gram increments.

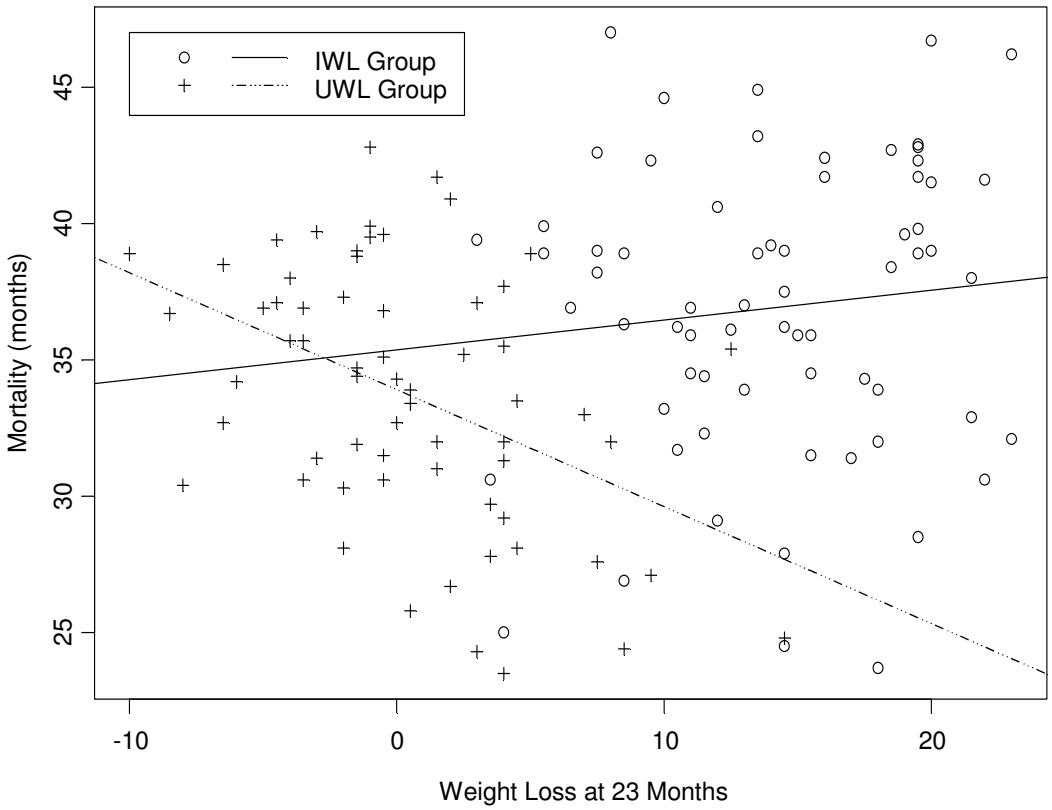

Figure 3.1. Scatter Plot of Mortality versus Observed Total Weight Loss with Fitted Regression Lines for the Two Groups

Based on the result in Section 3.2, the estimated bounds is valid only if the lower and upper values bound a continuous interval. These two plausible intervals for β_2 are not considered valid. Unless one is willing to assume a more restricted range for $\rho_{W,V}$, there is little else that can be done to tighten the bounds for β_2 without more information.

3.3.2. Illustration on the Data Set Using Baseline Weight as a Covariate. The covariate *U* is baseline weight, in grams, at the age of 12 months which was recorded prior to the treatment assignment and not effect by the assigned treatment. First, the 3-dimensional correlation matrix $\left(W^{(1)},V,U\right)$, with positive definiteness requirement, provides estimated bounds for the nonestimable correlation, $0.067 \le \rho_{W,V} \le 0.890$.

Next, the 4-dimensional correlation matrix $\left(Y^{(1)}, W^{(1)}, V, U\right)$ with use of partitioned Σ defined in equation (15) provides estimated bounds, $0.203 \leq \rho_{\mathrm{W,V}} \leq 0.720$.

Section 3.1 used the relationship between $\rho_{Y^{(1)},W^{(1)}}$ and $\rho_{W,V}$ with covariate, as in equation (20), together with the positive definiteness restriction of the matrix Σ in equation (14) provides a set of plausible $\rho_{W,V}$ which is the union of the two intervals, (0.069, 0.676) and (0.792, 0.890). The intervals are discontinuous because of the nonlinearity functional relationship $\rho_{Y^{(1)},W^{(1)}} = g\left(\rho_{W,V}\right)$ described in Section 3.2 and the equation is given in equation (20).

There are two estimated sets of plausible values for $\rho_{W,V}$, which are $\mathrm{P}_1 = (0.203, 0.720)$ and $\mathrm{P}_2 = \left[(0.069, 0.676) \cup (0.792, 0.890)\right]$. As discussed in Section 3.2, the intersection of these two sets gives estimated bounds for nonestimable correlation $0.203 \leq \rho_{\mathrm{W,V}} \leq 0.676$. Using this interval as a range for values of $\rho_{W,V}$ leads to obtain bounds for the causal parameter β_2.

Let β_2^{No} be the parameter β_2 in the model without covariate as in model (11). The estimated bounds are given by $0.233 \leq \beta_2^{No} \leq 0.996$. The naïve estimate of total weight loss on mortality, i.e., λ_1 in equation (4), is 0.109, which is lower than the estimated minimum for β_2^{No}. This implies that the variable *Z* has positive effects on mortality and the effects are greater than what is observed to be the effect of total weight loss on mortality.

Similarly, let β_2^{Yes} be the parameter β_2 in the model with covariate as explained in Section 3.1. Using equation (19) in, the estimated bounds are given by $-0.216 \leq \beta_2^{Yes} \leq 1.125$. The naïve estimate of total weight loss on mortality including the covariate is -0.020 which is near the lower bound of the estimates for β_2^{Yes}. The interval of plausible estimates for β_2^{Yes} is wider than β_2^{No}. This could happen because, for this mice example, baseline weight is not statistically significant when included in the two regression models (2) and (4). Hence, additional correlation parameters are being estimated for a variable that is not a significant predictor of mortality, given that the

weight loss variable is in the model. Baseline weight is a significant predictor of *W* and *V*, which explains its usefulness in tightening the bound of plausible values for parameter of interest, $\rho_{W,V}$, but it presents colinearity problems when included in the causal model. More discussion is in Section 5.

3.3.3. Assessing the Sampling Variability of the Bounds Using a Modified Parametric Bootstrap Procedure. A parametric bootstrap (Efron and Tibshirani, 1993) procedure was proposed to test the sampling variability of the estimated bounds for $\rho_{W,V}$, β_2^{No}, and β_2^{Yes}. A multivariate normal distribution was applied to simulate data from the two models in (17) and (18). Equation (17) corresponds to data from a random vector $\left(Y^{(0)},W^{(0)},U\right)'$ and, similarly, equation (18) from a random vector $\left(Y^{(1)},W^{(1)},V,U\right)'$. All estimable parameters were set as the sample estimates from the mice experiment and the nonestimable $\rho_{W,V}$ was set to specific values within the interval specified by the estimated bounds, in particular, 0.3, 0.4, 0.5, and 0.6. Values of $\rho_{W,V}$, that is outside the range specified by the estimated bounds, did not have the positive definiteness requirement for the correlation matrix, therefore, those values would not be considered in the simulation model. Table 3.1 provides the estimable parameters and their estimates from the mice data set.

Herein, the sample sizes, *N* = 100, 500, 1000, and 10000, were considered and divided into the unintentional and intentional groups of sizes *N*/2. The parameter $\rho_{Y^{(1)},W^{(1)}}$ is computed using the relationship in equation (20) for each value of $\rho_{W,V}$. Use the simulation with all of above setting as a function of sample size and values of $\rho_{W,V}$ to see the estimated bounds and their sampling variance.

The simulation results for $\rho_{W,V}$, β_2^{No}, and β_2^{Yes} are shown in Tables 3.2-3.4, respectively. The entries in the table show the sample size, *N*, the true value of the parameter using in the simulation, and the lower and upper bounds of the simulation estimate for the mean and standard deviation of the sampling distribution.

Table 3.2. The Estimated Bounds for the Mean and Standard Deviation of $\rho_{W,V}$ Including the Number of Sample Correlation Matrices which are Positive Definite and the Number of Simulations Creating the Valid Bounds from 200 Parametric Bootstrap Simulations

N		100		500		1000		10000	
$\rho_{W,V}$		min	max	min	max	min	max	min	max
0.3	mean	0.215	0.606	0.214	0.630	0.220	0.647	0.204	0.674
	sd	0.182	0.127	0.091	0.061	0.069	0.054	0.027	0.014
	(n_p, n_c)	(148, 72)		(169, 114)		(190, 147)		(200, 200)	
0.4	mean	0.200	0.620	0.218	0.640	0.220	0.645	0.205	0.674
	sd	0.207	0.127	0.083	0.066	0.070	0.054	0.023	0.011
	(n_p, n_c)	(151, 66)		(175, 120)		(191, 153)		(200, 200)	
0.5	mean	0.170	0.606	0.225	0.645	0.224	0.647	0.206	0.674
	sd	0.186	0.127	0.097	0.059	0.080	0.059	0.024	0.012
	(n_p, n_c)	(139, 68)		(174, 128)		(186, 144)		(200, 199)	
0.6	mean	0.148	0.592	0.221	0.634	0.221	0.651	0.204	0.675
	sd	0.142	0.117	0.102	0.069	0.078	0.047	0.023	0.011
	(n_p, n_c)	(141, 68)		(178, 126)		(188, 148)		(200, 200)	

As shown in Table 3.2, there are two numbers, n_p and n_c, for each simulation case. Nevertheless, the population correlation matrix that simulated the data was positive definite, because of the sampling variability, the estimate matrix of the simulation might not be positive definite. Hence, the number n_p represents the number of sample correlation matrices which are positive definite out of 200 simulations. Of the number of the positive definite matrices with the approach in Section 3.2.3, it did not always produce a continuous interval for $\rho_{W,V}$. Often the correlation matrix was positive definite for values of $\rho_{W,V}$ close to 1, however, the matrix was very near singular in these cases.

Table 3.3. The Estimated Bounds for the Mean and Standard Deviation of β_2^{No} from 200 Parametric Bootstrap Simulations

N			100		500		1000		10000	
$\rho_{W,V}$	β_2^{No}		min	max	min	max	min	max	min	max
0.3	0.315	mean	0.206	0.814	0.272	0.919	0.262	0.946	0.235	0.993
		sd	0.393	0.420	0.121	0.148	0.088	0.123	0.034	0.054
0.4	0.423	mean	0.189	0.836	0.263	0.924	0.262	0.945	0.234	0.989
		sd	0.411	0.509	0.101	0.153	0.087	0.114	0.030	0.051
0.5	0.569	mean	0.182	0.807	0.280	0.963	0.263	0.938	0.237	0.989
		sd	0.429	0.516	0.115	0.149	0.102	0.124	0.032	0.053
0.6	0.774	mean	0.192	0.789	0.275	0.918	0.265	0.951	0.233	0.989
		sd	0.161	0.275	0.122	0.168	0.097	0.117	0.029	0.047

Table 3.4. The Estimated Bounds for the Mean and Standard Deviation of β_2^{Yes} from 200 Parametric Bootstrap Simulations

N			100		500		1000		10000	
$\rho_{W,V}$	β_2^{Yes}		min	max	min	max	min	max	min	max
0.3	-0.175	mean	-0.212	0.580	-0.183	0.796	-0.207	0.862	-0.216	1.088
		sd	0.256	0.525	0.065	0.412	0.049	0.367	0.016	0.096
0.4	-0.108	mean	-0.233	0.555	-0.194	0.850	-0.201	0.864	-0.218	1.088
		sd	0.294	0.625	0.063	0.428	0.049	0.375	0.017	0.074
0.5	0.015	mean	-0.250	0.810	-0.197	0.848	-0.201	0.860	-0.215	1.085
		sd	0.336	0.909	0.067	0.423	0.0510	0.396	0.018	0.079
0.6	0.310	mean	-0.222	0.749	-0.199	0.842	-0.206	0.886	-0.216	1.095
		sd	0.260	0.508	0.072	0.425	0.043	0.380	0.016	0.064

Therefore, the number n_c represents the number of simulations that the estimated bounds yield to a continuous interval between the estimated bounds. The mean and sd represent the mean and standard deviations of the sampling distributions for the lower and upper bounds which were computed from the number n_c estimated valid bounds in all Tables 3.2-3.4.

The simulations provide comprehensive insight of the sampling variability of the bounds at small values of *N*. In most cases, the estimated bounds for the mean of the sampling distributions contain the true parameter values, except only the bounds for $\rho_{W,V}$ when its true value is 0.6 and the sample size, *N*, is 100. The bounds involve estimates of several population correlations and standard deviations. The results show that the larger of the sample size *N*, particularly more than 1000, the smaller of the sampling variability is. This would reflect some caution in interpreting the accuracy of the bounds in the mice experiment with 131 sample size.

The width of the bounds does not depend on the true value of $\rho_{W,V}$ since $\rho_{W,V}$ is nonestimable in observed data. Note that, the parametric bootstrap simulation procedure simulated data using parameter estimates from the data example as model parameter values in the simulated model, therefore, the true value of $\rho_{W,V}$ was restricted to be between the bounds computed from the data. Also, the width of the bounds does not depend on how large the sample size, *N*, is. The larger the sample size, *N*, results the smaller the sampling variability of the bounds. If one could find the covariate that are extremely predictive of the weight loss variable *W* and/or *V*, then it would narrower the interval between the bounds.

4. MATCHED PAIRS DESIGN

4.1. INTRODUCTION

Matched pairs design is a type of experimental design using a sample size of $N = 2n$. The subjects in the population are paired prior to randomization using a relevant factor or additional information that may be available on the subjects. This information could be in the form of covariates, or other more subjective information, for example, twins, husband and wife, or same geographical location. There are two treatments in a matched pairs design and the two subjects are paired in such a way that their responses to either treatment may be assumed to be the same. Thus, one subject's observed outcome to a particular treatment can serve as a prediction for the missing potential outcome for the other subject within the pair that received the other treatment. In usual matched pairs designs, one subject within a pair is randomly selected to receive one treatment with the other receiving the second treatment. The resulting observed data could provide for estimation of an average treatment effect and its standard error. Also considered herein is a modified matched pairs design where, for some pairs, the same treatment is applied to both subjects. This allows for some assessment of the quality of matching.

This section focuses on estimating bounds for the correlation between W and V that was considered earlier and also the variance of Z, the two parameters that were not estimable from the results in Coffey et al., (2005). The mortality variable is not considered here but, instead, only the variables W, V, (and Z) are considered as is a covariate, U. The covariate is used as a matching variable and its use in matching is compared to its use as covariate in a linear regression model, i.e., the way it was used in the previous section. Data on twins are also used where their matching has essentially been done on information related to genetics and living environment.

The true variance of IWL is defined as S_Z^2. This can be thought of as a variance of treatment effect where V is a response to intention to lose weight and W is a response to no intention to lose weight, and $Z = V - W$. Thus the variance of Z depends on the same nonestimable correlation between W and V as before. When this variance is positive, then IWL varies across subjects or it might be said that there is subject-treatment interaction present, that is, the effect of treatment varies across subjects. Thus some of the material

on variance of individual treatment effects in a matched-pairs setting (Gadbury, 2001) can be adapted to the IWL problem where the objective is to estimate the variance of IWL which is a variable that is completely unobservable. The naïve estimate of this variance is the usual variance of observed paired differences. Gadbury (1998) compared matched pairs designs and two sample experimental designs. These two different designs provide different interpretations regarding the subject-treatment interaction term. Homogeneity within pairs is then the criteria that are needed to estimate the variance of *Z*. Homogeneity within pairs assumes that there is no subject by treatment interaction within pairs or, in the IWL problem, that both subjects within a pair have the same IWL value. The comparison for the bias and mean square errors naïve estimator of S_Z^2 between a two sample experimental design and a matched pairs design were simulated in Gadbury (1998) and it was suggested that a matched pairs design has advantages over a two sample experimental design when estimating nonestimable parameters with naïve estimators.

The next section adapts the matched pairs design to IWL problem using potential outcomes and within a pair, one subject is assumed to randomly be assigned to intention = yes, and the other to intention to lose weight = no, and it builds on some earlier work by Gadbury (1998, 2001). The results show that the variance of IWL, S_Z^2, is the summation of the within pair and between pairs sums of squares. It is shown that the naïve estimator is biased in general, and the conditions where it is unbiased are shown. Bounds for S_Z^2 are derived that depend on the matching parameters, in particular, on distributional parameters that are nonestimable. The issue of estimability relates to lack of homogeneity within pairs. Later, a matched pairs design where both subjects have the same intention within some pairs is considered in order to get more information about the quality of matching and, hence, refine estimates bounds for S_Z^2.

The last part will apply this to example data sets. The first illustration is applied to an eye experiment (the Krypton Argon Regression Neovascularization Study Research Group, 1993) which has two different treatments in each pair. Next, the mice data are considered but with specific matched pairs using the covariate, baseline weight, in order to get a mix of different treatments (i.e., intention) and the same treatments (i.e.,

intention) in each pair (Herein the term ‘treatment’ and ‘intention’ will be used interchangeably since the assignment of the treatment in usual matched pairs design terminology is assignment to intention in this application). Finally, the twins data (Sorensen et al., 2005) will be considered where some pairs are genetically homogeneous (monozygotic) and other pairs are dizygotic.

4.2. ESTIMATING BOUNDS FOR S_Z^2 WITH TWO DIFFERENT INTENTIONS WITHIN A PAIR

The potential outcomes framework of the finite population is written as in the matrix form

$$\begin{pmatrix} V_1-\varepsilon_1 & W_1-\eta_1 \\ V_1+\varepsilon_1 & W_1+\eta_1 \\ ---- & ---- \\ V_2-\varepsilon_2 & W_2-\eta_2 \\ V_2+\varepsilon_2 & W_2+\eta_2 \\ ---- & ---- \\ \vdots & \vdots \\ \vdots & \vdots \\ ---- & ---- \\ V_n-\varepsilon_n & W_n-\eta_n \\ V_n+\varepsilon_n & W_n+\eta_n \end{pmatrix},$$

where, within the i[th] pair, V_i and W_i are the average observed responses to the given treatment, and ε_i and η_i represent lack of homogeneity within the i[th] pair. The advantage of this parameterization is that certain characteristics of a point estimate of the true variance of treatment effects, S_Z^2, for example, bias, can be shown as a function of the parameters ε and η. Within the i[th] pair, one subject is randomly selected to one intention and the other subject to the other intention. With this notation, IWL for the two subjects within the i[th] pair could be written as

$$Z_{i1} = (V_i - \varepsilon_i) - (W_i - \eta_i) = (V_i - W_i) - (\varepsilon_i - \eta_i),$$
$$Z_{i2} = (V_i + \varepsilon_i) - (W_i + \eta_i) = (V_i - W_i) + (\varepsilon_i - \eta_i).$$

The mean of IWL for each pair is

$$\overline{Z}_i = V_i - W_i = \frac{Z_{i1} - Z_{i2}}{2}. \tag{22}$$

The average true IWL for the set of individuals is

$$\overline{Z} = \frac{1}{2n}\sum_{i=1}^{n}\sum_{j=1}^{2} Z_{i,j} = \overline{V} - \overline{W}\ , \tag{23}$$

which is the difference between the average of both weight loss variables. The total sum of squares of IWL is,

$$SSZ = \sum_{i=1}^{n}\sum_{j=1}^{2}\left(Z_{i,j} - \overline{Z}\right)^2 = \sum_{i=1}^{n}\sum_{j=1}^{2}\left(Z_{i,j} - \overline{Z}_i\right)^2 + 2\sum_{i=1}^{n}\left(\overline{Z}_i - \overline{Z}\right)^2\ , \tag{24}$$

which leads to the equation of the true variance of IWL, S_Z^2, by dividing equation (24) by the total sample sizes, *2n*, as

$$\begin{aligned} S_Z^2 &= \frac{SSZ}{2n} = \frac{SSW + SSB}{2n} \\ &= \frac{1}{2n}\sum_{i=1}^{n}\sum_{j=1}^{2}\left(Z_{i,j} - \overline{Z}_i\right)^2 + \frac{1}{n}\sum_{i=1}^{n}\left(\overline{Z}_i - \overline{Z}\right)^2 \end{aligned}\ , \tag{25}$$

where SSW and SSB are the within and between pairs sums of squares, respectively and written as,

$$SSW = \sum_{i=1}^{n} (\varepsilon_i - \eta_i)^2 \tag{26}$$

$$SSB = 2\sum_{i=1}^{n} \left[(V_i - W_i) - (\overline{V} - \overline{W}) \right]^2 . \tag{27}$$

It is stated earlier that, for the i[th] pair, one of two possible values are observed, each with probability one half, determined by the treatment assignment of the i[th] pair. That is, for the i[th] pair, the observed effect of intention to lose weight is,

$$z_i = \begin{cases} (V_i - \varepsilon_i) - (W_i + \eta_i) = (V_i - W_i) - (\varepsilon_i + \eta_i) & with\ probability\ 1/2 \\ (V_i + \varepsilon_i) - (W_i - \eta_i) = (V_i - W_i) + (\varepsilon_i + \eta_i) & with\ probability\ 1/2 \end{cases}.$$

Define

$$T_i = \begin{cases} 1 \quad if \quad \begin{pmatrix} T_{i1} \\ T_{i2} \end{pmatrix} = \begin{pmatrix} 1 \\ 0 \end{pmatrix} \\ 0 \quad if \quad \begin{pmatrix} T_{i1} \\ T_{i2} \end{pmatrix} = \begin{pmatrix} 0 \\ 1 \end{pmatrix} \end{cases}$$

as an indicator random variable which represent the treatment (intention) assignment for the i[th] pair where $P(T_i = 1) = 1/2$ for $i = 1,2,...,n$. The observed IWL for the i[th] pair can be written as

$$z_i = \left[X_i - Y_i - (\varepsilon_i + \eta_i) \right] T_i + \left[X_i - Y_i + (\varepsilon_i + \eta_i) \right] (1 - T_i).$$

Let the observed average IWL be

$$\bar{z} = \frac{1}{n} \sum_{i=1}^{n} z_i ,$$

and the observed variance of IWL be

$$S_z^2 = \frac{1}{n}\sum_{i=1}^{n}\left[\left(z_i - \bar{z}\right)^2\right] = \frac{1}{n}\left(\sum_{i=1}^{n} z_i^2 - n\bar{z}^2\right). \tag{28}$$

Note that, the randomizations have $k = 2^n$ possible outcomes. It is clear that $E(\bar{z}) = \bar{Z}$, that is, $\bar{z}$ is an unbiased for the true mean IWL $\bar{Z}$ where the expectation is taken with respect to the randomization. However, S_z^2 is not unbiased estimator for S_Z^2.

Proposition 2. Assume a random treatment is assigned for subjects in each pair using the potential outcomes framework with the notation stated before. The expectation of S_z^2 for all possible random treatment assignments is

$$E\left(S_z^2\right) = \frac{SSW}{2n} + \frac{SSB}{2n} + \frac{4}{n}\sum_{i=1}^{n}\varepsilon_i\eta_i - \frac{1}{n^2}\sum_{i=1}^{n}\left(\varepsilon_i + \eta_i\right)^2 \tag{29}$$

Proof. See Appendix F.

□

This proposition shows that the estimator S_z^2 is biased for S_Z^2 and the bias is,

$$bias = \frac{4}{n}\sum_{i=1}^{n}\varepsilon_i\eta_i - \frac{1}{n^2}\sum_{i=1}^{n}\left(\varepsilon_i + \eta_i\right)^2 . \tag{30}$$

The bias cannot be estimated because of the lack of homogeneity within the i[th] pairs, that is, ε_i and η_i are not estimable from observed data. Now, two conditions are considered. First, the strongest condition, if all of the subjects are perfectly matched, that is, $\varepsilon_i = \eta_i = 0$ for $i = 1,2,...,n$, then the bias will be zero and, also, the observed IWL for a pair is the true *Z* for each individual in the pair. Moreover, this implies the within sum of squares is zero. Hence, not only is S_z^2 unbiased for S_Z^2, but also, $S_z^2 = S_Z^2$. A second condition is when the subjects are matched only on the treatment effect, that is, $\varepsilon_i = \eta_i$ for $i = 1,2,...,n$, and is equivalent to the within sum of squares being zero.

Homogeneity within pairs, that is, $\varepsilon_i = \eta_i = 0$ for $i = 1,2,...,n$, could result S_z^2 to be unbiased for S_Z^2, and $S_z^2 = S_Z^2$. This strongest condition is not likely to hold, and ε_i and η_i are not estimable from observed data. If one has the information on how large ε and η could be, then that would help to estimate bounds for S_Z^2. One possible approach, that could get more information for ε and η, is using the matched pairs design using potential outcomes framework with the same treatment for both subjects in a pair which is considered later on.

Assume that (ε_i, η_i) are independent and identically distributed (*iid*) random variables for $i = 1,2,...,n$ from a superpopulation, without loss of generality with mean $(0,0)^T$ and covariance matrix $\sigma^2 \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$, where ρ is the correlation between ε and η. If the expectation operator over the bivariate distribution of ε and η is denoted by $\mathrm{E}_{\varepsilon,\eta}$, then the expectation of the bias of S_z^2 is give by (details in Appendix F),

$$\mathrm{E}_{\varepsilon,\eta}(bias) = \frac{\sigma^2}{n}[(4n-2)\rho - 2]. \tag{31}$$

By varying the values of ρ from -1 to 1, $\mathrm{E}_{\varepsilon,\eta}(bias)$ lies between $-4\sigma^2$ and $\frac{4(n-1)}{n}\sigma^2$.

Define the quantities $\hat{L}$ and $\hat{U}$,

$$\hat{L} = S_z^2 - \frac{4(n-1)}{n}\sigma^2, \tag{32}$$

$$\hat{U} = S_z^2 + 4\sigma^2. \tag{33}$$

Now, recall that the expectation operator over all possible randomization is denoted by *E*. Then $\mathrm{E}_{\varepsilon,\eta}\left[E(\hat{L}) - S_Z^2\right] \le 0$ and $\mathrm{E}_{\varepsilon,\eta}\left[E(\hat{U}) - S_Z^2\right] \ge 0$, this implies that $\hat{L}$ and $\hat{U}$ could be

bounds for S_Z^2 in the expectation sense, also, the bounds $(\hat{L},\hat{U})$ could give the idea how large or small S_Z^2 might be.

The bound for S_Z could be obtained by taking square roots of $\hat{L}$ and $\hat{U}$ and if $\hat{L}$ is negative, set the lower bound of S_Z to be zero. The bounds will be the most informative if the lower bound estimate is large and/or if the upper bound estimate is very small. They are also dependent on an assumption reference on how well the subjects in the population are paired.

Since (ε_i,η_i) is nonestimable, there is no estimate for σ^2. The bounds are sensitive to the value of σ^2; however, this parameter cannot be estimated without more information on the distribution of matching parameters. It is interesting to consider a matched pairs design using potential outcomes where the same intention to lose weight is "assigned" within a pair in order to get more information about ε and η. This is considered in the next section.

4.3. ESTIMATING BOUNDS FOR S_Z^2 WHERE SOME PAIRS HAD THE SAME INTENTION

Consider a modified matched pairs design using potential outcomes framework where some pairs had the same treatment (i.e., intention) within a pair assuming sample size is $N = 2n + n_1 + n_2$ where n is the number of pairs randomly assigned to two different intentions, and n_1, n_2 are the number of pairs with both subjects assigned to IWL or UWL, respectively. With two different intentions within a pair, the detail is already explained in Section 4.2. This section considers only the part that some pairs have the same intention. The observed potential outcomes framework is given as the matrix (34),

$$\begin{pmatrix} V_1-\varepsilon_1 & \\ V_1+\varepsilon_1 & \\ ---- & \\ & W_1-\eta_1 \\ & W_1+\eta_1 \\ & ---- \\ \vdots & \\ & \vdots \\ ---- & ---- \\ V_{n_1}-\varepsilon_{n_1} & \\ V_{n_1}+\varepsilon_{n_1} & \\ ---- & \\ & W_{n_2}-\varepsilon_{n_2} \\ & W_{n_2}+\varepsilon_{n_2} \end{pmatrix}, \tag{34}$$

where, within the i[th] pair both subjects are randomly assigned to the same treatment (i.e., intention), V_i and W_i are the average observed responses to the given intention, IWL and UWL. The variables ε_i and η_i, as before, represent lack of homogeneity within the i[th] pairs. With these pairs, differences within a pair are now $\pm 2\varepsilon_i$ or $\pm 2\eta_j$. This modified matched pairs design gives information for ε and η.

Assume that (ε_i, η_j) are independent and identically distributed (*iid*) random variables for $i = 1,2,...,n_1$ and $j = 1,2,...,n_2$ from a superpopulation with mean $(0,0)^T$ and covariance matrix $\sigma^2\begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$, where ρ is the correlation between ε and η. The point estimate of common variance of ε and η could be written as,

$$\hat{\sigma}^2 = \frac{1}{n_1+n_2}\left(\sum_{i=1}^{n_1}\varepsilon_1^2 + \sum_{j=1}^{n_2}\eta_j^2\right). \tag{35}$$

This point estimate of σ^2, $\hat{\sigma}^2$, comes from the information of the assumption that some pairs had the same intention. However, it is required that, in the experiment, S_z^2

comes from matched pairs design with one subject is randomly selected to one intention and the other subject to the other intention.

Therefore, by the result from Proposition 2 and the bounds of S_Z^2 in equations (32)-(33), the bounds for S_Z^2 are

$$\hat{L} = S_z^2 - \frac{4(n-1)}{n}\hat{\sigma}^2 \tag{36}$$

$$\hat{U} = S_z^2 + 4\hat{\sigma}^2, \tag{37}$$

where S_z^2 is the observed variance of IWL and $\hat{\sigma}^2$ is defined in equation (35).

Similarly, the bounds for S_Z is obtained by taking square roots to both $\hat{L}$ and $\hat{U}$ and in case that $\hat{L}$ is negative, this lower bound is set to be zero. Note that, the modified matched pairs design requires that some pairs got the same intention in order to get the estimate lower and upper bounds for the naïve estimator of the standard deviation of IWL effects, S_Z.

4.4. COMPARISON WITH TRI-VARIATE RANDOM VARIABLE

To relate the material on pairing to material from Section 3 that used σ_Z^2 rather than S_Z^2. If a random sample of potential outcomes is assumed, then $\frac{2n}{2n-1}E(S_Z^2) = \sigma_Z^2$. So when discussion a true variance of *Z* in the paired case, S_Z^2 will be used and in the two sample case from Section 3, σ_Z^2 will be used.

Under a two sample design, consider the tri-variate random variable (W,V,U). The two identities $\sigma_Z^2 = Var(V-W) = \sigma_V^2 + \sigma_W^2 - 2\sigma_{W,V}$ and $\sigma_{W,V} = \rho_{W,V}\sigma_V\sigma_W$ provide trivial bounds for standard deviation of IWL effect σ_Z, where no information of $\rho_{W,V}$ is obtained.

$$\sigma_Z \in [(\sigma_V - \sigma_W),(\sigma_V + \sigma_W)] \tag{38}$$

In fact, Section 3 gave bounds for $\rho_{W,V}$ where a covariate tightens the bounds for σ_Z^2. The bounds for σ_Z^2 using a covariate U, are giving by the following relation

$$\sigma_Z^2 = \sigma_V^2 + \sigma_W^2 - 2\rho_{W,V}\sigma_V\sigma_W . \tag{39}$$

Recall the correlation matrix of tri-variate correlation matrix (W,V,U) given by

$$\begin{pmatrix} 1 & \rho_{WV} & \rho_{WU} \\ \rho_{WV} & 1 & \rho_{VU} \\ \rho_{WU} & \rho_{VU} & 1 \end{pmatrix}.$$

Gadbury and Iyer (2000) used the positive definite requirement and get the result

$$\rho_{WU}\rho_{VU} - \sqrt{(1-\rho_{WU}^2)(1-\rho_{VU}^2)} \le \rho_{WV} \le \rho_{WU}\rho_{VU} + \sqrt{(1-\rho_{WU}^2)(1-\rho_{VU}^2)}.$$

This combined with equation (39) tighten bounds for σ_Z^2.

Also, with the identities $\rho_{WV} = \frac{\sigma_W}{\sigma_V} + \frac{\sigma_V}{\sigma_V}\rho_{WZ}$, the following equation is obtained,

$$\rho_{WZ} \in \left[\left(\rho_{WU}\rho_{VU} - \frac{\sigma_W}{\sigma_V}\right) \pm \sqrt{(1-\rho_{WU}^2)(1-\rho_{VU}^2)}\right]\frac{\sigma_V}{\sigma_Z}. \tag{40}$$

So ρ_{WZ} can be bounded for a given set of bounds for σ_Z. Data set illustrated can compare bounds obtained from pairing versus those using the formula given here.

4.5. ILLUSTRATION ON A DATASET

The illustration of this approach is applied to three examples. The eye data set is the experiment with one treatment randomly assigned to a subject within a pair and the other to another subject. This has two different treatments within a pair. Next, the mice

experiment which is the same as the previous but with specific matched pairs by considering a covariate, baseline weight, to pair the mice in order to get some pairs have the same treatment. The last, the twins data would be applied. The twins data is one of the interesting example since it was matched based on monozygotic and dizygotic twin pairs. The results are given in each section below.

4.5.1. Two Different Treatments Within a Pair. Consider the eye data experiment. Two laser treatments, Argon and Krypton, were being compared to see which produced a better outcome for an eye disease. Some patients had the disease in both eyes while others had the disease in only one eye. When patients had the disease in only one eye, that eye was randomly assigned to one of the two treatments. Here, consider 184 patients who had the disease in both eyes. One eye was randomly assigned to one treatment while the other is assigned to the other treatment. The baseline visual acuity is collected at the time before giving the laser treatment and also after 3 months of assigning treatment. This data are matched by the same person where each eye got a different laser treatment.

Only 157 patients are considered since there are some missing data. The observed variance of treatment effect, S_z^2, is 311.54. Apply matched pairs design with the potential outcomes in Section 4.2 to the eye experiment gives the results of the lower and upper bounds for the true variance of treatment effects as equations (32) and (33), however, the common variance of ε and η, σ^2, could not be obtained because ε and η are not estimable from observed data. The results of the bounds for naïve estimator of the variance of treatment effects, S_Z^2, is shown in Figure 4.1 where the x-axis represents the common variance σ^2 of ε and η and the y-axis represents the possible bounds for S_Z^2 in expectation sense. Since this common variance σ^2 could not be exactly estimated, this approach only gives the idea how large S_Z^2 might be.

Figure 4.1 shows that at the point $\sigma^2 = 0$, the expected value of the variance of treatment effects, $E\left(S_z^2\right)$ is exactly at the same as the observed variance of treatment effect, S_z^2. This case is, as stated earlier, the strongest condition of homogeneity within

pairs, that is, ε_i and η_i are all zero for all *i* which is not likely to hold. As the common variance σ^2 is increasing, the bounds for S_Z^2 are wider.

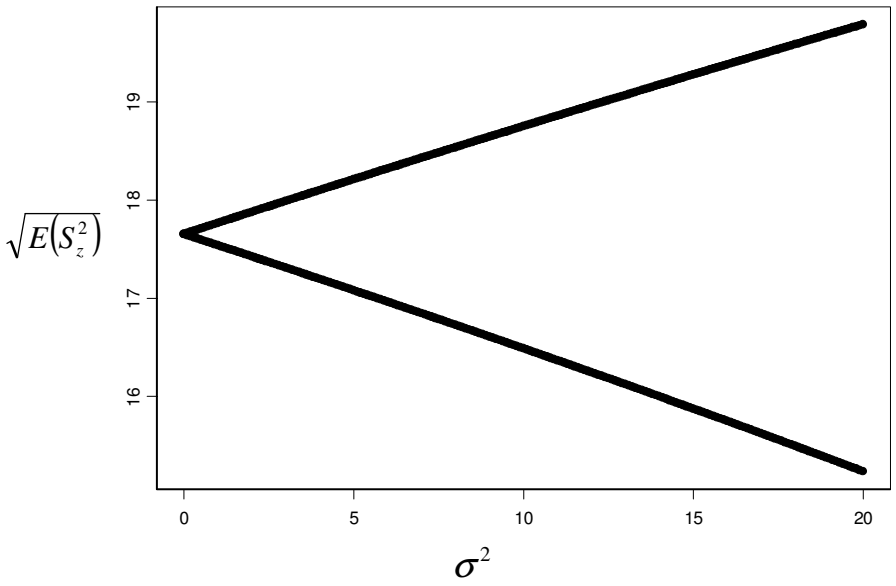

Figure 4.1. The Bounds for Naïve Estimator of the Standard Deviation of Treatment Effects, $\sqrt{E(S_z^2)}$, at which the Common Variance, σ^2, of ε and η Specified

4.5.2. Specific Matched Pairs Using Covariate where Some Pairs Had the Same Intention. Consider again the mice example in Section 3 with mice matched on the basis of the covariate, baseline weight at 12-months age. The mice were matched in pairs in order to get 32 pairs randomly assigned for two different treatments in a pair and the two sets of 16 pairs and 17 pairs were then designated to pairs when both mice were in the unintentional group or both in the intentional group, respectively. For these two sets, the assumption for the distribution of (ε_i, η_j) with mean $(0,0)^T$ and covariance matrix $\sigma^2 \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$ is made. Therefore, ε and η have mean zero with common estimated variance of ε and η is $\hat{\sigma}^2 = 1.011$. For those 32 pairs which, within a pair, one mice was

randomly assigned to one treatment and the other to another treatment, the observed variance of IWL effect is $S_z^2 = 26.859$, so $S_z = 5.18$. Applying the approach in Section 4.3, the bounds the true standard deviation of treatment effects, S_Z are [4.790,5.559] by equations (36) and (37).

Section 3.4 provided the bounds for ρ_{WV} as $(0.067,\ 0.89)$ where only the distribution of *W*, *V*, and *U* are considered. By using the tri-variate random variable (W,V,U) and the information of ρ_{WV}, the bounds for naïve estimator of the standard deviation of treatment effects, σ_Z, are $(2.379,6.834)$ using Section 3 material.

Furthermore, recall the correlation matrix of tri-variate correlation matrix (W,V,U) in Section 4.4 that give the result as in equation (40). This section, under the specific matched pairs, could provide the bounds for S_Z and this would help to get the bounds for ρ_{WZ} as in Figure 4.2.

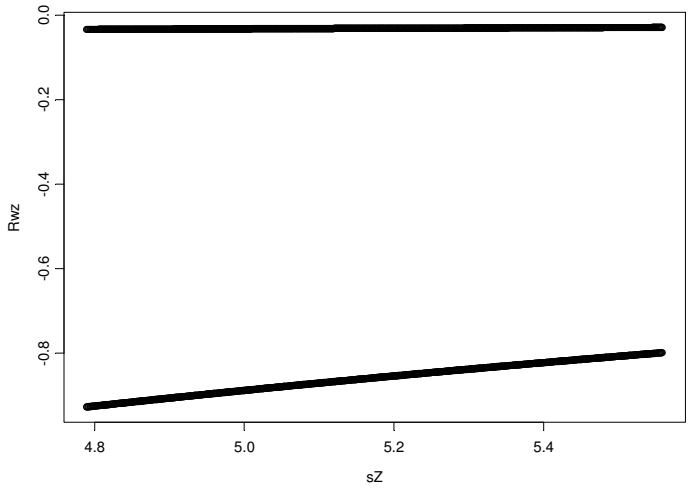

Figure 4.2. The Bounds for ρ_{WZ} given S_Z Using Positive Definite Requirement of the Correlation Matrix (W,V,U) under Specific Matched Pairs for the Mice Data

4.5.3 Twin Pairs with Some Pairs Had the Same Intention. The study was based on The Finnish Twin Cohort (Sorensen, 2005), which was composed of all same-sex twin pairs born in Finland before 1985 in which both twins were alive in 1967 (Kaprio, 2002) and are overweight with the body mass index, BMI $\geq$ 25 kg/m^2. In 1975, a cohort of individuals reported height, weight, and current attempts (i.e., "intention") to lose weight, and in 1981, they reported current weight. All the participants were followed from 1982 through 1999 without pre-existing or current diseases which is the confounding by diseases. They were asked whether they were currently trying to lose weight because of overweight, which was interpreted as "intention to lose weight". In addition, the lifestyle factors, such as smoking habits, alcohol drinking, physical activity, life satisfaction, work status, and income, were recorded and analyzed.

Monozygotic and dizygotic twins data are applied to this approach. There are total 445 pairs of twins data collected to see the BMI change and also other interesting factors such as gender, age, smoking habit, and etc. Two different groups are being considered which are 0 and 1, unintentional and intentional groups, respectively. The (0,0), (1,0) and (1,1) are from 208, 135, and 102 twins, respectively. The BMI mean differences are -0.27, -0.24, and 0.05, and the standard deviations are 2.3, 2.4 and 2,9 for those groups of twins, respectively. Matched pairs design from Sections 4.2 and 4.3 with this data, equations (36) and (37) provide the bounds for the standard deviation of IWL, S_Z in the range [0, 3.981].

Consider tri-variate random variable approach (W,V,U) from Section 3 to get the bounds for σ_Z. With covariate(s), the BMI before applying the treatment, the positive definiteness requirement helps tighten the bounds for $\rho_{W,V}$. Then, with this identity from two sample design would get the bound for σ_Z^2 as stated earlier. With the same 445 pairs of twins data using one covariate, the BMI recorded before assigning the treatment, the bounds for $\rho_{W,V}$ is (-0.9916, 0.9960) which give the bounds for σ_Z in (0.3911, 4.1226). Using many of the covariates, this helps a little bit on tightening the bounds for $\rho_{W,V}$ to be (-0.8739, 0.9374) and σ_Z in (0.8062, 3.9998). The covariates did not help in

tightening the bounds too much since the covariate probably is not a good linear predictor of *W* and *V*.

These two bounds of standard deviation of IWL, S_Z and σ_Z, from two different methods are slightly different and cannot be directly compared. With the matched pairs, the covariate information was not used - just the twin pairs. For the tri-variate random variable (W,V,U), the covariate was used to tighten the bounds based on the information of the previous section, however, the twin pairs were ignored and the data were treated as two independent samples. It would be interesting to further incorporate these two approaches in order to get tightened bounds for a parameter of interest, that is, combine information in paring such as twin pairs, but adjust for observable differences within a pair, based on covariates, to increase homogeneity of responses within pairs, given the covariates.

5. CONCLUSION AND FUTURE WORK

The potential outcomes framework was applied to the IWL problem to estimate bounds for a nonestimable correlation and also a causal parameter in a linear model. The positive definiteness of the correlation matrix under certain assumptions is used to bound the unknown parameter. The valid bounds (bounds containing a continuous interval) were obtained in the mice data but the simulations suggest that the method will not always produce valid bounds when sample sizes are small because of the complicated relationship between $\rho_{Y^{(1)},W^{(1)}}$ and $\rho_{W,V}$. For example, in the mice data, using the relationship in equation (12) with the 3-variable correlation matrix, $\left(Y^{(1)},W^{(1)},V\right)$, the plausible range of $\rho_{W,V}$ is the union of the two intervals, (0.069, 0.676) and (0.792, 0.890). The upper range was nearly singular because of the complicated function of $\rho_{Y^{(1)},W^{(1)}}$ and $\rho_{W,V}$. The upper range was excluded by using a covariate and the intersection in section 3.2. However, in some simulations, this does not always happen and one is left with invalid bounds. More than one covariate could solve cases such as these (Gadbury et al., 2008).

Including additional covariates in the causal model modifies the definition of causal parameter. A covariate using in the mice data is the baseline weight which helps tightening the bounds for $\rho_{W,V}$ since it was a good linear predictor of *W* and *V*. This presents the problem of colinearity when it was used in the causal model. Questions arise as to whether high baseline weight is associated with higher weight loss tending to decrease mortality, or whether high baseline weight itself is associated with mortality. The potential outcomes framework for a two treatment comparison would essentially assume that a potential outcome response variable corresponds to each treatment. When treatment assignment is random, one can obtain an unbiased estimate of an average causal effect of one treatment with respect to the other. The assignment to intention was assumed to be random and that there is no interference between subjects (Rubin, 1980), but there are two different potential outcome variables to this assignment, the pairs $\left(W,V\right)$ and $\left(Y^{(0)},Y^{(1)}\right)$. The effect of intention on the variables $\left(Y^{(0)},Y^{(1)}\right)$ is difficult to

interpret. Future challenges are dealing with the more practical scenario, for example, human studies with nonrandom assignment.

Some results from other applications have been reported by others that might be helpful in addressing some issues encountered in this application. One possibility is to borrow from the concepts related to partial compliance in clinical trials (Jin and Rubin, 2007). That is, the weight loss might be considered as "dosage received" after the assignment of treatment (i.e. intention). If such a connection between these two applications can be made, then material on principal stratification (Frangakis and Rubin, 2002) might help to more clearly define the relationship between "intention to lose weight" and some subsequent measure of health or mortality.

The casual models considered here are simple and do not include many of the potential confounders and nonlinearities in the relationship between weight loss and mortality that have been seen or suspected in other studies (Allison et al., 1997; Fontaine and Allison, 2001; Brock et al., 2006). Bayesian MCMC techniques could be used for more complicated models since these techniques can accommodate censoring, nonlinear effects and do not necessary require the assumption that the slope parameter on UWL, β_1, has to be the same in both groups. The choices of a prior for nonestimable parameters are still the issue to consider. This work is in progress (Yi et al., 2008).

Herein, a subject's intention was assumed to remain the same for the study. A longitudinal design might be useful for assessing the effect of IWL on mortality or some other subsequent measure of health. That is, the subject's intention may change over time periods and still allow one to compare the weight loss and intention within subjects. A likely issue would be the effect of carry-over of intention from one period to the next. Gadbury (2001) presented the potential outcomes framework for a matched pairs design and for a two time period design. These other types of designs may provide a more flexible way to separate the effects of IWL and UWL on mortality, using assumptions that are perhaps more plausible in practical situations.

A difficulty in human data is to find some variables that are predictive of subsequent weight loss (Allison and Engel, 1995). Unfortunately "intention to lose" has been shown to be a weak predictor of subsequent weight loss, particularly among older people who have the highest death rates (Lee et al., 2004). Subsequent weight loss

appears to be confounded by many other possible variables (Hardy and Kuh, 2006). Other study designs might prove useful in adjusting for potential confounders which could clarify more on the effect of intention on subsequent weight loss.

Our treatment of this topic can be seen as an exemplar of a broader class of approaches all aimed at reducing the influence of obesity and mortality rate. Such putative biases include the so-called 'late-life bias', 'reverse-causation bias', and 'regression-dilution bias' (c.f., Greenberg, 2001; 2002). Future research should address those additional hypothesized biases and see if our method could be combined with methods aimed at reducing those hypothesized biases.

In many human studies, weights are self-reported and this could conceivably introduce additional bias. Such conceivable biases also merit further investigation. Also, note that, any conclusions from a sample from one population must be generalized to other populations with caution. Thus, it will be useful to conduct such analyses across multiple species and multiple human populations to assess the consistency of result. For additional discussion of these issues see Campbell and Kenny (1997).

Finally, in matched pairs design, the bounds for human were not that useful. This might be because, for twin pairs, the covariate was not use and the weight loss for humans is confounded with too many factors. Future research could further combine information in pairing but adjust for observable differences with a pair (two independent samples), based on covariates, to increase homogeneity of responses within pairs, given the covariates, in order to tighten the bounds for a parameter of interest.

APPENDIX A.

DERIVATION FOR PARAMETERS OF INTEREST FROM THE CASUAL MODEL WITHOUT COVARIATE

Coffey et al. (2005) proposed equation (5) for the parameter of interest, β_2, as $\beta_2 = \frac{\lambda_1\sigma_V^2 - \beta_1\left[\sigma_W^2 + \sigma_W\left(\sigma_V\rho_{W,V} - \sigma_W\right)\right]}{\sigma_Z^2 + \sigma_W\left(\sigma_V\rho_{W,V} - \sigma_W\right)}$. Applying these two identities, $\rho_{W^{(1)},Z}\sigma_Z = \sigma_V\rho_{W,V} - \sigma_W$ and $\sigma_Z^2 = \sigma_V^2 + \sigma_W^2 - 2\sigma_V\sigma_W\rho_{W,V}$ leads equation (5) to be equation (11),

$$\begin{aligned}\beta_2 &= \frac{\lambda_1\sigma_V^2 - \beta_1\left[\sigma_W^2 + \sigma_W\left(\sigma_V\rho_{W,V} - \sigma_W\right)\right]}{\sigma_Z^2 + \sigma_W\left(\sigma_V\rho_{W,V} - \sigma_W\right)} \\ &= \frac{\lambda_1\sigma_V^2 - \beta_1\sigma_W\sigma_V\rho_{W,V}}{\sigma_V^2 - 2\sigma_W\sigma_V\rho_{W,V} + \sigma_W\sigma_V\rho_{W,V}} \\ &= \frac{\sigma_{Y^{(1)},V} - \frac{\sigma_{Y^{(0)},W}}{\sigma_W^2}\sigma_W\sigma_V\rho_{W,V}}{\sigma_V\left(\sigma_V - \sigma_W\rho_{W,V}\right)} \\ &= \frac{\sigma_{Y^{(1)}}\rho_{Y^{(1)},V} - \sigma_{Y^{(0)}}\rho_{Y^{(0)},W}\rho_{W,V}}{\sigma_V - \sigma_W\rho_{W,V}}.\end{aligned}$$

Recall the regression model (6) and the causal model (10) without covariate,

$$Y^{(0)} = \beta_0 + \beta_1 W^{(0)} + \varepsilon^{(0)}, \tag{A1}$$

$$Y^{(1)} = (\beta_0 + \beta_3) + (\beta_1 - \beta_2)W^{(1)} + \beta_2 V + \varepsilon^{(1)}. \tag{A2}$$

Equation (A1) gives $\beta_1 = \frac{Cov\left(Y^{(0)}, W^{(0)}\right)}{Var\left(W^{(0)}\right)}$. Since the covaince between $Y^{(0)}$ and $W^{(0)}$ can be written as $Cov\left(Y^{(0)}, W^{(0)}\right) = \sigma_{Y^{(0)},W^{(0)}} = \sigma_{Y^{(0)}}\sigma_{W^{(0)}}\rho_{Y^{(0)},W^{(0)}}$, then β_1 becomes

$$\beta_1 = \frac{\sigma_{Y^{(0)}}\sigma_{W^{(0)}}\rho_{Y^{(0)},W^{(0)}}}{\sigma_{W^{(0)}}^2} = \frac{\sigma_{Y^{(0)}}\rho_{Y^{(0)},W^{(0)}}}{\sigma_{W^{(0)}}} \tag{A3}$$

Equation (A2) gives two forms of β_2 which are

$$\beta_2^{(1)} = \frac{Cov\left(Y^{(1)}, V \mid W^{(1)}\right)}{Var\left(V \mid W^{(1)}\right)}, \tag{A4}$$

$$\beta_1 - \beta_2^{(2)} = \frac{Cov\left(Y^{(1)}, W^{(1)} \mid V\right)}{Var\left(W^{(1)} \mid V\right)} \text{ or } \beta_2^{(2)} = \beta_1 - \frac{Cov\left(Y^{(1)}, W^{(1)} \mid V\right)}{Var\left(W^{(1)} \mid V\right)}. \tag{A5}$$

It would be easier to simplify each of necessarily conditional variance-covariance terms in equation (A4) and (A5). Note that, the two variable $W^{(0)}$ and $W^{(1)}$ are assumed to have the same variance σ_W^2. Consider 3-variable framework $\left(Y^{(1)}, V, W^{(1)}\right)$,

	$Y^{(1)}$	V	$W^{(1)}$
$Y^{(1)}$	$\sigma^2_{Y^{(1)}}$	$\sigma_{Y^{(1)},V}$	$\sigma_{Y^{(1)},W^{(1)}}$
V	$\sigma_{Y^{(1)},V}$	σ_V^2	$\sigma_{W,V}$
$W^{(1)}$	$\sigma_{Y^{(1)},W^{(1)}}$	$\sigma_{W,V}$	σ_W^2

.

It is now straightforward to get

$$Var\left(Y^{(1)}, V \mid W^{(1)}\right) = \begin{bmatrix} \sigma^2_{Y^{(1)}} & \sigma_{Y^{(1)},V} \\ \sigma_{Y^{(1)},V} & \sigma_V^2 \end{bmatrix} - \begin{bmatrix} \sigma_{Y^{(1)},W^{(1)}} \\ \sigma_{W,V} \end{bmatrix} \frac{1}{\sigma_W^2} \begin{bmatrix} \sigma_{Y^{(1)},W^{(1)}} & \sigma_{W,V} \end{bmatrix}$$

$$= \begin{bmatrix} \sigma^2_{Y^{(1)}} & \sigma_{Y^{(1)},V} \\ \sigma_{Y^{(1)},V} & \sigma_V^2 \end{bmatrix} - \frac{1}{\sigma_W^2} \begin{bmatrix} \sigma^2_{Y^{(1)},W^{(1)}} & \sigma_{Y^{(1)},W^{(1)}}\sigma_{W,V} \\ \sigma_{Y^{(1)},W^{(1)}}\sigma_{W,V} & \sigma^2_{W,V} \end{bmatrix},$$

and, therefore, $Cov\left(Y^{(1)}, V \mid W^{(1)}\right) = \sigma_{Y^{(1)},V} - \frac{1}{\sigma_W^2}\sigma_{Y^{(1)},W^{(1)}}\sigma_{W,V}$

$$= \sigma_{Y^{(1)}}\sigma_V\rho_{Y^{(1)},V} - \sigma_{Y^{(1)}}\rho_{Y^{(1)},W^{(1)}}\sigma_V\rho_{W,V}$$

$$= \sigma_{Y^{(1)}}\sigma_V\left[\rho_{Y^{(1)},V} - \rho_{Y^{(1)},W^{(1)}}\rho_{W,V}\right],$$

and $Var\left(V \mid W^{(1)}\right) = \sigma_V^2 - \frac{\sigma^2_{W,V}}{\sigma_W^2} = \sigma_V^2 - \frac{\sigma_W^2\sigma_V^2\rho^2_{W,V}}{\sigma_W^2} = \sigma_V^2 - \sigma_V^2\rho^2_{W,V} = \sigma_V^2\left(1-\rho^2_{W,V}\right).$

These turns $\beta_2^{(1)}$ into the form

$$\beta_2^{(1)} = \frac{Cov\left(Y^{(1)}, V \mid W^{(1)}\right)}{Var\left(V \mid W^{(1)}\right)} = \frac{\sigma_{Y^{(1)}}\left[\rho_{Y^{(1)},V} - \rho_{Y^{(1)},W^{(1)}}\rho_{W,V}\right]}{\sigma_V\left(1-\rho^2_{W,V}\right)} \tag{A6}$$

Similarly, $Var\left(Y^{(1)}, V \mid W^{(1)}\right) = \begin{bmatrix} \sigma^2_{Y^{(1)}} & \sigma_{Y^{(1)},V} \\ \sigma_{Y^{(1)},V} & \sigma_V^2 \end{bmatrix} - \begin{bmatrix} \sigma_{Y^{(1)},W^{(1)}} \\ \sigma_{W,V} \end{bmatrix} \frac{1}{\sigma_W^2} \begin{bmatrix} \sigma_{Y^{(1)},W^{(1)}} & \sigma_{W,V} \end{bmatrix}$

$$= \begin{bmatrix} \sigma^2_{Y^{(1)}} & \sigma_{Y^{(1)},V} \\ \sigma_{Y^{(1)},V} & \sigma_V^2 \end{bmatrix} - \frac{1}{\sigma_W^2} \begin{bmatrix} \sigma^2_{Y^{(1)},W^{(1)}} & \sigma_{Y^{(1)},W^{(1)}}\sigma_{W,V} \\ \sigma_{Y^{(1)},W^{(1)}}\sigma_{W,V} & \sigma^2_{W,V} \end{bmatrix},$$

and, $Cov\left(Y^{(1)}, W^{(1)} \mid V\right) = \sigma_{Y^{(1)},W^{(1)}} - \frac{1}{\sigma_V^2}\sigma_{Y^{(1)},V}\sigma_{W,V}$

$$= \sigma_{Y^{(1)}}\sigma_W\left[\rho_{Y^{(1)},W^{(1)}} - \rho_{Y^{(1)},V}\rho_{W,V}\right],$$

also, $Var\left(W^{(1)} \mid V\right) = \sigma_W^2 - \frac{\sigma_{W,V}^2}{\sigma_V^2} = \sigma_W^2 - \frac{\sigma_W^2 \sigma_V^2 \rho_{W,V}^2}{\sigma_V^2} = \sigma_W^2 - \sigma_W^2 \rho_{W,V}^2 = \sigma_W^2 \left(1 - \rho_{W,V}^2\right)$

Finally, these make $\beta_2^{(2)} = \frac{\sigma_{Y^{(0)}} \rho_{Y^{(0)},W^{(0)}}}{\sigma_W} - \frac{\sigma_{Y^{(1)}} \sigma_W \left[\rho_{Y^{(1)},W^{(1)}} - \rho_{Y^{(1)},V} \rho_{W,V}\right]}{\sigma_W^2 \left(1 - \rho_{W,V}^2\right)}$

$$= \frac{1}{\sigma_W} \left[\sigma_{Y^{(0)}} \rho_{Y^{(0)},W^{(0)}} - \frac{\sigma_{Y^{(1)}} \left[\rho_{Y^{(1)},W^{(1)}} - \rho_{Y^{(1)},V} \rho_{W,V}\right]}{\left(1 - \rho_{W,V}^2\right)} \right]. \qquad \text{(A7)}$$

Equating both equation (A6) and (A7) to get $\rho_{Y^{(1)},W^{(1)}}$ as a function of the nonestimable $\rho_{W,V}$, the same as equation (12) as,

$$\rho_{Y^{(1)},W^{(1)}} = \frac{\sigma_{Y^{(0)}} \sigma_V \rho_{Y^{(0)},W} \left(1 - \rho_{W,V}^2\right) + \sigma_{Y^{(1)}} \rho_{Y^{(1)},V} \left(\sigma_V \rho_{W,V} - \sigma_W\right)}{\sigma_{Y^{(1)}} \left(\sigma_V - \sigma_W \rho_{W,V}\right)}.$$

APPENDIX B.

DERIVATION FOR PARAMETERS OF INTEREST FROM THE CASUAL MODEL WITH COVARIATE

Recall the regression model (17) and the causal model (18) with a covariate,

$$Y^{(0)} = \beta_0 + \beta_1 W^{(0)} + \beta_3 U + \varepsilon^{(0)}, \tag{B1}$$

$$Y^{(1)} = (\beta_0 + \beta_4) + (\beta_1 - \beta_2) W^{(1)} + \beta_2 V + (\beta_3 + \beta_5) U + \varepsilon^{(1)}. \tag{B2}$$

Equation (B1) gives $\beta_1 = \dfrac{Cov(Y^{(0)}, W^{(0)} \mid U)}{Var(W^{(0)} \mid U)}$. Consider the 3-variable framework $(Y^{(0)}, W^{(0)}, U)$,

	$Y^{(0)}$	$W^{(0)}$	U
$Y^{(0)}$	$\sigma^2_{Y^{(0)}}$	$\sigma_{Y^{(0)},W^{(0)}}$	$\sigma_{Y^{(0)},U}$
$W^{(0)}$	$\sigma_{Y^{(0)},W^{(0)}}$	σ^2_W	$\sigma_{W,U}$
U	$\sigma_{Y^{(0)},U}$	$\sigma_{W,U}$	σ^2_U

This gives $Var(Y^{(0)}, W^{(0)} \mid U) = \begin{bmatrix} \sigma^2_{Y^{(0)}} & \sigma_{Y^{(0)},W^{(0)}} \\ \sigma_{Y^{(0)},W^{(0)}} & \sigma^2_U \end{bmatrix} - \begin{bmatrix} \sigma_{Y^{(0)},U} \\ \sigma_{W,U} \end{bmatrix} \frac{1}{\sigma^2_U} \begin{bmatrix} \sigma_{Y^{(0)},U} & \sigma_{W,U} \end{bmatrix}$

$$= \begin{bmatrix} \sigma^2_{Y^{(0)}} & \sigma_{Y^{(0)},W^{(0)}} \\ \sigma_{Y^{(0)},W^{(0)}} & \sigma^2_U \end{bmatrix} - \frac{1}{\sigma^2_U} \begin{bmatrix} \sigma^2_{Y^{(0)},U} & \sigma_{Y^{(0)},U}\sigma_{W,U} \\ \sigma_{Y^{(0)},U}\sigma_{W,U} & \sigma^2_{W,U} \end{bmatrix},$$

and $Cov(Y^{(0)}, W^{(0)} \mid U) = \sigma_{Y^{(0)},W^{(0)}} - \dfrac{1}{\sigma^2_U}\sigma_{Y^{(0)},U}\sigma_{W,U}$

$$= \sigma_{Y^{(0)}}\sigma_W \rho_{Y^{(0)},W^{(0)}} - \frac{1}{\sigma^2_U}\sigma_{Y^{(0)}}\sigma_U \rho_{Y^{(0)},U}\sigma_W\sigma_U\rho_{W,U}$$

$$= \sigma_{Y^{(0)}}\sigma_W \left[\rho_{Y^{(0)},W^{(0)}} - \rho_{Y^{(0)},U}\rho_{W,U}\right],$$

and $Var(W \mid U) = \sigma^2_W - \dfrac{\sigma^2_{W,U}}{\sigma^2_U} = \sigma^2_W - \dfrac{\sigma^2_W\sigma^2_U\rho^2_{W,U}}{\sigma^2_U} = \sigma^2_W - \sigma^2_W\rho^2_{W,U} = \sigma^2_W(1-\rho^2_{W,U})$. Then β_1 becomes

$$\beta_1 = \frac{\sigma_{Y^{(0)}}\sigma_W\left[\rho_{Y^{(0)},W^{(0)}} - \rho_{Y^{(0)},U}\rho_{W,U}\right]}{\sigma^2_W(1-\rho^2_{W,U})} = \frac{\sigma_{Y^{(0)}}}{\sigma_W}\frac{\left[\rho_{Y^{(0)},W^{(0)}} - \rho_{Y^{(0)},U}\rho_{W,U}\right]}{(1-\rho^2_{W,U})} \tag{B3}$$

Equation (B2) gives two forms of β_2 which are

$$\beta_2^{(1)} = \frac{Cov(Y^{(1)}, V \mid W^{(1)}, U)}{Var(V \mid W^{(1)}, U)}, \tag{B4}$$

$$\beta_1 - \beta_2^{(2)} = \frac{Cov(Y^{(1)}, W^{(1)} \mid V)}{Var(W \mid V)} \text{ or } \beta_2^{(2)} = \beta_1 - \frac{Cov(Y^{(1)}, W^{(1)} \mid V)}{Var(W \mid V)}. \tag{B5}$$

Similarly, simplify each of necessarily conditional variance-covariance terms in equation (B4) and (B5). Consider 4-variable framework $\left(Y^{(1)},V,W^{(1)},U\right)$,

	$Y^{(1)}$	V	$W^{(1)}$	U
$Y^{(1)}$	$\sigma^2_{Y^{(1)}}$	$\sigma_{Y^{(1)},V}$	$\sigma_{Y^{(1)},W^{(1)}}$	$\sigma_{Y^{(1)},U}$
V	$\sigma_{Y^{(1)},V}$	σ^2_V	$\sigma_{W,V}$	$\sigma_{V,U}$
$W^{(1)}$	$\sigma_{Y^{(1)},W^{(1)}}$	$\sigma_{W,V}$	σ^2_W	$\sigma_{W,U}$
U	$\sigma_{Y^{(1)},U}$	$\sigma_{V,U}$	$\sigma_{W,U}$	σ^2_U

.

It is now straightforward to get

$$Var\left(Y^{(1)},V\mid W^{(1)},U\right)$$

$$=\begin{bmatrix}\sigma^2_{Y^{(1)}} & \sigma_{Y^{(1)},V}\\ \sigma_{Y^{(1)},V} & \sigma^2_V\end{bmatrix}-\begin{bmatrix}\sigma_{Y^{(1)},W^{(1)}} & \sigma_{Y^{(1)},U}\\ \sigma_{W,V} & \sigma_{V,U}\end{bmatrix}\begin{bmatrix}\sigma^2_W & \sigma_{W,U}\\ \sigma_{W,U} & \sigma^2_U\end{bmatrix}^{-1}\begin{bmatrix}\sigma_{Y^{(1)},W^{(1)}} & \sigma_{W,V}\\ \sigma_{Y^{(1)},U} & \sigma_{V,U}\end{bmatrix}$$

$$=\begin{bmatrix}\sigma^2_{Y^{(1)}} & \sigma_{Y^{(1)},V}\\ \sigma_{Y^{(1)},V} & \sigma^2_V\end{bmatrix}-\begin{bmatrix}\sigma_{Y^{(1)},W^{(1)}} & \sigma_{Y^{(1)},U}\\ \sigma_{W,V} & \sigma_{V,U}\end{bmatrix}\frac{1}{\sigma^2_W\sigma^2_U-\sigma^2_{W,U}}\begin{bmatrix}\sigma^2_U & -\sigma_{W,U}\\ -\sigma_{W,U} & \sigma^2_W\end{bmatrix}\begin{bmatrix}\sigma_{Y^{(1)},W^{(1)}} & \sigma_{W,V}\\ \sigma_{Y^{(1)},U} & \sigma_{V,U}\end{bmatrix}$$

$$=\begin{bmatrix}\sigma^2_{Y^{(1)}} & \sigma_{Y^{(1)},V}\\ \sigma_{Y^{(1)},V} & \sigma^2_V\end{bmatrix}-\frac{1}{\sigma^2_W\sigma^2_U-\sigma^2_{W,U}}\begin{bmatrix}V(1,1) & V(1,2)\\ V(2,1) & V(2,2)\end{bmatrix},$$

where $V(1,1)=\sigma_{Y^{(1)},W^{(1)}}\left(\sigma^2_U\sigma_{Y^{(1)},W^{(1)}}-\sigma_{W,U}\sigma_{Y^{(1)},U}\right)+\sigma_{Y^{(1)},U}\left(-\sigma_{W,U}\sigma_{Y^{(1)},W^{(1)}}+\sigma^2_W\sigma_{Y^{(1)},U}\right)$

$V(2,1)=\sigma_{W,V}\left(\sigma^2_U\sigma_{Y^{(1)},W^{(1)}}-\sigma_{W,U}\sigma_{Y^{(1)},U}\right)+\sigma_{V,U}\left(-\sigma_{W,U}\sigma_{Y^{(V)},W}+\sigma^2_W\sigma_{Y^{(1)},U}\right)$

$V(1,2)=\sigma_{Y^{(1)},W^{(1)}}\left(\sigma^2_U\sigma_{W,V}-\sigma_{W,U}\sigma_{V,U}\right)+\sigma_{Y^{(1)},U}\left(-\sigma_{W,U}\sigma_{W,V}+\sigma^2_W\sigma_{V,U}\right)$

$V(2,2)=\sigma_{W,V}\left(\sigma^2_U\sigma_{W,V}-\sigma_{W,U}\sigma_{V,U}\right)+\sigma_{V,U}\left(-\sigma_{W,U}\sigma_{W,V}+\sigma^2_W\sigma_{V,U}\right).$

The term $Cov\left(Y^{(1)},V\mid W^{(1)},U\right)$

$$=\sigma_{Y^{(1)},V}-\frac{\sigma_{W,V}\left(\sigma^2_U\sigma_{Y^{(1)},W^{(1)}}-\sigma_{W,U}\sigma_{Y^{(1)},U}\right)+\sigma_{V,U}\left(-\sigma_{W,U}\sigma_{Y^{(1)},W^{(1)}}+\sigma^2_W\sigma_{Y^{(1)},U}\right)}{\sigma^2_W\sigma^2_U-\sigma^2_{W,U}}$$

$$=\sigma_{Y^{(1)}}\sigma_V\rho_{Y^{(1)},V}-\frac{\sigma_W\sigma_V\rho_{W,V}\left(\sigma^2_U\sigma_{Y^{(1)}}\sigma_W\rho_{Y^{(1)},W^{(1)}}-\sigma_W\sigma_U\rho_{W,U}\sigma_{Y^{(1)}}\sigma_U\rho_{Y^{(1)},U}\right)}{\sigma^2_W\sigma^2_U-\sigma^2_W\sigma^2_U\rho^2_{W,U}}$$

$$-\frac{\sigma_V\sigma_U\rho_{V,U}\left(-\sigma_W\sigma_U\rho_{W,U}\sigma_{Y^{(1)}}\sigma_W\rho_{Y^{(1)},W^{(1)}}+\sigma^2_W\sigma_{Y^{(1)}}\sigma_U\rho_{Y^{(1)},U}\right)}{\sigma^2_W\sigma^2_U-\sigma^2_W\sigma^2_U\rho^2_{W,U}}$$

$$=\frac{\sigma_{Y^{(1)}}\sigma_V}{1-\rho^2_{W,U}}\left[\rho_{Y^{(1)},V}\left(1-\rho^2_{W,U}\right)-\rho_{W,V}\left(\rho_{Y^{(1)},W^{(1)}}-\rho_{W,U}\rho_{Y^{(1)},U}\right)-\rho_{V,U}\left(\rho_{Y^{(1)},U}-\rho_{W,U}\rho_{Y^{(1)},W^{(1)}}\right)\right].$$

The conditional variance of V given $W^{(1)}$ and U is

$$Var\left(V \mid W^{(1)},U\right)=\sigma_V^2-\begin{bmatrix}\sigma_{W,V} & \sigma_{V,U}\end{bmatrix}\begin{bmatrix}\sigma_W^2 & \sigma_{W,U}\\ \sigma_{W,U} & \sigma_U^2\end{bmatrix}^{-1}\begin{bmatrix}\sigma_{W,V}\\ \sigma_{V,U}\end{bmatrix}$$

$$=\sigma_V^2-\begin{bmatrix}\sigma_{W,V} & \sigma_{V,U}\end{bmatrix}\frac{1}{\sigma_W^2\sigma_U^2-\sigma_{W,U}^2}\begin{bmatrix}\sigma_U^2 & -\sigma_{W,U}\\ -\sigma_{W,U} & \sigma_W^2\end{bmatrix}\begin{bmatrix}\sigma_{W,V}\\ \sigma_{V,U}\end{bmatrix}$$

$$=\sigma_V^2-\frac{\sigma_W\sigma_V\rho_{W,V}\left(\sigma_U^2\sigma_W\sigma_V\rho_{W,V}-\sigma_W\sigma_U\rho_{W,U}\sigma_V\sigma_U\rho_{V,U}\right)}{\sigma_W^2\sigma_U^2-\sigma_W^2\sigma_U^2\rho_{W,U}^2}$$

$$-\frac{\sigma_V\sigma_U\rho_{V,U}\left(-\sigma_W\sigma_U\rho_{W,U}\sigma_W\sigma_V\rho_{W,V}+\sigma_W^2\sigma_V\sigma_U\rho_{V,U}\right)}{\sigma_W^2\sigma_U^2-\sigma_W^2\sigma_U^2\rho_{W,U}^2}$$

$$=\frac{\sigma_V^2}{1-\rho_{W,U}^2}\left[\left(1-\rho_{W,U}^2\right)-\rho_{W,V}\left(\rho_{W,V}-\rho_{W,U}\rho_{V,U}\right)-\rho_{V,U}\left(\rho_{V,U}-\rho_{W,U}\rho_{W,V}\right)\right]$$

These turns $\beta_2^{(1)}$ into the form

$$\beta_2^{(1)}=\frac{Cov\left(Y^{(1)},V \mid W^{(1)},U\right)}{Var\left(V \mid W^{(1)},U\right)}$$

$$=\frac{\frac{\sigma_{Y^{(1)}}\sigma_V}{1-\rho_{W,U}^2}\left[\rho_{Y^{(v)},V}\left(1-\rho_{W,U}^2\right)-\rho_{W,V}\left(\rho_{Y^{(v)},W}-\rho_{W,U}\rho_{Y^{(v)},U}\right)-\rho_{V,U}\left(\rho_{Y^{(v)},U}-\rho_{W,U}\rho_{Y^{(v)},W}\right)\right]}{\frac{\sigma_V^2}{1-\rho_{W,U}^2}\left[\left(1-\rho_{W,U}^2\right)-\rho_{W,V}^2+\rho_{W,V}\rho_{W,U}\rho_{V,U}-\rho_{V,U}^2+\rho_{W,V}\rho_{W,U}\rho_{V,U}\right]}$$

$$=\frac{\sigma_{Y^{(1)}}}{\sigma_V}\left[\frac{\rho_{Y^{(1)},W^{(1)}}\left(\rho_{W,U}\rho_{V,U}-\rho_{W,V}\right)+\rho_{Y^{(1)},V}\left(1-\rho_{W,U}^2\right)+\rho_{Y^{(1)},U}\left(\rho_{W,V}\rho_{W,U}-\rho_{V,U}\right)}{1-\rho_{W,U}^2-\rho_{V,U}^2-\rho_{W,V}^2+2\rho_{W,V}\rho_{W,U}\rho_{V,U}}\right]. \qquad \text{(B6)}$$

With the same approach, $Cov\left(Y^{(1)},W^{(1)} \mid V,U\right)$

$$=\frac{\sigma_{Y^{(1)}}\sigma_W}{1-\rho_{V,U}^2}\left[\rho_{Y^{(1)},W^{(1)}}\left(1-\rho_{V,U}^2\right)-\rho_{W,V}\left(\rho_{Y^{(1)},V}-\rho_{V,U}\rho_{Y^{(1)},U}\right)-\rho_{W,U}\left(\rho_{Y^{(1)},U}-\rho_{V,U}\rho_{Y^{(1)},V}\right)\right]$$

and

$$Var\left(W \mid V,U\right)=\frac{\sigma_W^2}{1-\rho_{V,U}^2}\left[\left(1-\rho_{V,U}^2\right)-\rho_{W,V}\left(\rho_{W,V}-\rho_{V,U}\rho_{W,U}\right)-\rho_{W,U}\left(\rho_{W,U}-\rho_{V,U}\rho_{W,V}\right)\right].$$

Finally, these make $\beta_2^{(2)}=\beta_1-\frac{Cov\left(Y^{(1)},W^{(1)} \mid V,U\right)}{Var\left(W \mid V,U\right)}$

$$= \frac{\sigma_{Y^{(0)}}}{\sigma_W} \frac{\left[\rho_{Y^{(0)},W^{(0)}} - \rho_{Y^{(0)},U}\rho_{W,U}\right]}{\left(1-\rho_{W,U}^2\right)}$$

$$- \frac{\frac{\sigma_{Y^{(1)}}\sigma_W}{1-\rho_{V,U}^2}\left[\rho_{Y^{(1)},W^{(1)}}\left(1-\rho_{V,U}^2\right) - \rho_{W,V}\left(\rho_{Y^{(1)},V} - \rho_{V,U}\rho_{Y^{(1)},U}\right) - \rho_{W,U}\left(\rho_{Y^{(1)},U} - \rho_{V,U}\rho_{Y^{(1)},V}\right)\right]}{\frac{\sigma_W^2}{1-\rho_{V,U}^2}\left[\left(1-\rho_{V,U}^2\right) - \rho_{W,V}\left(\rho_{W,V} - \rho_{V,U}\rho_{W,U}\right) - \rho_{W,U}\left(\rho_{W,U} - \rho_{V,U}\rho_{W,V}\right)\right]}$$

$$= \frac{\sigma_{Y^{(0)}}\left[\rho_{Y^{(0)},W^{(0)}} - \rho_{Y^{(0)},U}\rho_{W,U}\right]}{\sigma_W\left(1-\rho_{W,U}^2\right)}$$

$$- \frac{\sigma_{Y^{(1)}}}{\sigma_W}\left[\frac{\rho_{Y^{(1)},W^{(1)}}\left(1-\rho_{V,U}^2\right) + \rho_{Y^{(1)},V}\left(\rho_{W,U}\rho_{V,U} - \rho_{W,V}\right) + \rho_{Y^{(1)},U}\left(\rho_{W,V}\rho_{V,U} - \rho_{W,U}\right)}{1-\rho_{W,U}^2 - \rho_{V,U}^2 - \rho_{W,V}^2 + 2\rho_{W,U}\rho_{V,U}\rho_{W,V}}\right] \qquad \text{(B7)}$$

Now, define these three new variables,

$$E_1 = \rho_{Y^{(1)},V}\left(1-\rho_{W,U}^2\right) + \rho_{Y^{(1)},U}\left(\rho_{W,V}\rho_{W,U} - \rho_{V,U}\right),$$

$$D = 1 - \rho_{W,U}^2 - \rho_{V,U}^2 - \rho_{W,V}^2 + 2\rho_{W,V}\rho_{W,U}\rho_{V,U},$$

$$E_2 = \rho_{Y^{(1)},V}\left(\rho_{W,U}\rho_{V,U} - \rho_{W,V}\right) + \rho_{Y^{(1)},U}\left(\rho_{W,V}\rho_{V,U} - \rho_{W,U}\right),$$

and substitute them back to the two equations of the β_2. Equating both equation (B6) and (B7) to get $\rho_{Y^{(1)},W^{(1)}}$ as a function of the nonestimable $\rho_{W,V}$ as

$$\frac{\sigma_{Y^{(1)}}}{\sigma_V}\left[\frac{\rho_{Y^{(1)},W^{(1)}}\left(\rho_{W,U}\rho_{V,U} - \rho_{W,V}\right) + E_1}{D}\right] = \beta_1 - \frac{\sigma_{Y^{(1)}}}{\sigma_W}\left[\frac{\rho_{Y^{(1)},W^{(1)}}\left(1-\rho_{V,U}^2\right) + E_2}{D}\right]$$

$$\frac{\sigma_{Y^{(1)}}E_1}{\sigma_V D} + \frac{\sigma_{Y^{(1)}}}{\sigma_V}\left[\frac{\rho_{Y^{(1)},W^{(1)}}\left(\rho_{W,U}\rho_{V,U} - \rho_{W,V}\right) +}{D}\right] = \beta_1 - \frac{\sigma_{Y^{(1)}}E_2}{\sigma_W D} - \frac{\sigma_{Y^{(1)}}}{\sigma_W}\left[\frac{\rho_{Y^{(1)},W^{(1)}}\left(1-\rho_{V,U}^2\right)}{D}\right]$$

$$\frac{\sigma_{Y^{(1)}}}{\sigma_V}\left[\frac{\rho_{Y^{(1)},W^{(1)}}\left(\rho_{W,U}\rho_{V,U} - \rho_{W,V}\right)}{D}\right] + \frac{\sigma_{Y^{(1)}}}{\sigma_W}\left[\frac{\rho_{Y^{(1)},W^{(1)}}\left(1-\rho_{V,U}^2\right)}{D}\right] = \beta_1 - \frac{\sigma_{Y^{(1)}}E_2}{\sigma_W D} - \frac{\sigma_{Y^{(1)}}E_1}{\sigma_V D}$$

$$\rho_{Y^{(1)},W^{(1)}}\left[\frac{\sigma_{Y^{(1)}}\left(\rho_{W,U}\rho_{V,U} - \rho_{W,V}\right)}{\sigma_V D} + \frac{\sigma_{Y^{(1)}}\left(1-\rho_{V,U}^2\right)}{\sigma_W D}\right] = \beta_1 - \frac{\sigma_{Y^{(1)}}E_2}{\sigma_W D} - \frac{\sigma_{Y^{(1)}}E_1}{\sigma_V D}$$

$$\rho_{Y^{(1)},W^{(1)}} = \left[\frac{\sigma_{Y^{(1)}}\left(\rho_{W,U}\rho_{V,U} - \rho_{W,V}\right)}{\sigma_V D} + \frac{\sigma_{Y^{(1)}}\left(1-\rho_{V,U}^2\right)}{\sigma_W D}\right]^{-1}\left[\beta_1 - \frac{\sigma_{Y^{(1)}}E_2}{\sigma_W D} - \frac{\sigma_{Y^{(1)}}E_1}{\sigma_V D}\right] \qquad \text{(B8)}$$

APPENDIX C.

S-PLUS CODE FOR THE MICE EXAMPLE DATA WITHOUT COVARIATE

Using the approach explained in Section 3.2 with the mice data without covariate and this S-plus code below provide the results in Section 3.4.1.

```
#Below are commands to compute estimable correlations from the mice data set
# and to bound the nonestimable ones. We have 4 potential outcome variables,
# lifespan(IWL) = yv
# lifespan(UWL) = yw
# Total weight loss = v
# UWL     = w
#-----------------------------------------

#These lines extract the variables from the mice data
#They also omit mice that died before wt5 was recorded

vars_c("Diet","wt12mo","wt5","Lifespan")
data_IWLmouse[,vars]

data_na.omit(data)
x1_data[data[,"Diet"]==1,]
x0_data[data[,"Diet"]==0,]

v_x1[,"wt12mo"] - x1[,"wt5"]

w_x0[,"wt12mo"] - x0[,"wt5"]

y.v_x1[,"Lifespan"]
y.w_x0[,"Lifespan"]


#Here we estimate the correlations that can be estimated from observed data,
   there are 2
ryw.w_cor(y.w,w); ryv.v_cor(y.v,v)

it_1000
rwv_seq(-1,1,length=it)

beta1_sqrt(var(y.w)) / sqrt(var(w)) * ryw.w
# beta1 = -0.4287891
# beta1*5 = -2.143945

lamda1_sqrt(var(y.v))*ryv.v/sqrt(var(v))
# lamda1 = 0.1092931
# lamda1*5 = 0.5464653

num_( sqrt(var(y.v))*ryv.v ) - ( sqrt(var(w))*ryw.w*rwv )
denum_sqrt(var(v)) - (sqrt(var(w))*rwv)
beta2_num/denum

beta.result_cbind(rwv,beta2)

bounds_rbind(apply(beta.result,2,min),apply(beta.result,2,max))
dimnames(bounds)[2]_list(c("Cor(W,V)","Beta2"))
dimnames(bounds)[1]_list(c("min","max"))

it
bounds

##
## applying 3*3 correlation matrix of y(1), W(1) and v
##
```

```
sy.v_sqrt(var(y.v)); sy.w_sqrt(var(y.w)); sv_sqrt(var(v)); sw_sqrt(var(w))

it_100
rwv_seq(-1,1, length=it)      # i
ryv.w_( (sy.w*sv*ryw.w*(1-rwv^2)) + ( sy.v*ryv.v*(sv*rwv-sw) ) ) / (sy.v*(sv-
    (sw*rwv)) )

x_matrix(0,3,3)
result_c(0,0,0)

it_length(rwv)

for(i in 1:it) {

x_cbind(  c(1,          ryv.w[i],     ryv.v),
          c(ryv.w[i],   1,            rwv[i]),
          c(ryv.v,      rwv[i],       1) )

e_eigen(x)$values
r_c(rwv[i],ryv.w[i],min(e))
result_rbind(result,r)
}

result_result[-1,]
cor.result_result[result[,3]>0,]
plot(cor.result[,1],cor.result[,3])

num_( sy.v*ryv.v ) - ( sw*ryw.w*cor.result[,1] )
denum_sv - (sw*cor.result[,1])
beta2_num/denum
```

APPENDIX D.

S-PLUS CODE FOR THE MICE EXAMPLE DATA WITH COVARIATE

Using the approach explained in Section 3.3 with the mice data without covariate and this S-plus code below provide the results in Section 3.4.2.

```
#Below are commands to compute estimable correlations from the mice data set
# and to bound the nonestimable ones. We have 5 potential outcome variables,
# lifespan(IWL) = yv
# lifespan(UWL) = yw
# Total weight loss = v
# UWL     = w
# covariate = baseline weight = u
#-----------------------------------------

#These lines extract the variables from the mice data
#They also omit mice that died before wt5 was recorded

vars_c("Diet","wt12mo","wt5","Lifespan")
data_IWLmouse[,vars]

data_na.omit(data)
x1_data[data[,"Diet"]==1,]
x0_data[data[,"Diet"]==0,]

v_x1[,"wt12mo"] - x1[,"wt5"]
w_x0[,"wt12mo"] - x0[,"wt5"]

y.v_x1[,"Lifespan"]
y.w_x0[,"Lifespan"]


#now consider baseline covariate = initial weight
covar_"wt12mo"

u.no_data[data[,"Diet"]==0,covar]
u.yes_data[data[,"Diet"]==1,covar]
u_data[,covar]    # u is now the set of covariates observable for all
   individuals.

#Here we estimate the correlations that can be estimated from observed data,
   there are 6
ryw.w_cor(y.w,w); ryw.u_cor(y.w,u.no); ryv.v_cor(y.v,v)
ryv.u_cor(y.v,u.yes); rwu_cor(w,u.no); rvu_cor(v,u.yes)

#The following produces bounds for the correlation beteen w and v
s0_rwu
s1_rvu
s_cbind(s0,s1)

h_t(s)%*%solve(cor(u))%*%s

low_h[1,2] - sqrt((1-h[1,1])*(1-h[2,2]))
up_h[1,2] + sqrt((1-h[1,1])*(1-h[2,2]))
b1_c(low,up)   #here are the estimated bounds for the simple correlation
   between w and v
rwv.L_b1[1]         # 0.06731668
rwv.U_b1[2]         # 0.8899493

cbind(b1[1],b1[2])  # From 3*3 correlation matrix of [w(1),V,U]
##  [1,] 0.06731668 0.8899493
```

```
### 4*4 matrix and using the relationship between rwv & ryv.w (NO COVARIATE)

it_1000

rwv_seq(rwv.L+.0000000001,rwv.U-.0000000001,length=it)
ryv.w_( (sy.w*sv*ryw.w*(1-rwv^2)) + ( sy.v*ryv.v*(sv*rwv-sw) ) ) / (sy.v*(sv-
    (sw*rwv)) )
ee_0
for(i in 1:length(rwv)){ testmat_cbind(c(1,ryv.v,ryv.w[i],ryv.u),
          c(ryv.v,1,rwv[i],rvu),
          c(ryv.w[i],rwv[i], 1, rwu),
          c(ryv.u,rvu,rwu,1) )

ee[i]_min(eigen(testmat)$values)
}

rwv_rwv[ee>0]
ryv.w_ryv.w[ee>0]

E1_( ryv.v * (1-(rwu^2)) ) + ( ryv.u * ( (rwv*rwu)- rvu ) )

D_1 - (rwu^2) - (rvu^2) - (rwv^2)  + ( 2*rwv * rwu * rvu )

E2_( ryv.v*( (rwu*rvu)-rwv ) ) + ( ryv.u*( (rwv*rvu)-rwu ) )


# version1
Beta2_sy.v / sv * ( (ryv.w*((rvu*rwu)-rwv) ) + E1 ) / D


# version2
Beta2v2_beta1-( sy.v / sw * ( (ryv.w*(1-(rvu^2)))  + E2 ) / D )



beta.result_cbind(rwv,ryv.w,Beta2,Beta2v2)

bounds_rbind(apply(beta.result,2,min),apply(beta.result,2,max))
dimnames(bounds)[2]_list(c("Cor(W,V)","Cor(yv.w)","Beta2","Beta2v2"))
dimnames(bounds)[1]_list(c("min","max"))

it
bounds
 #     Cor(W,V)  Cor(yv.w)     Beta2   Beta2v2
# min 0.2031869 -0.6180382 -1.908373 0.6879764
# max 0.7203174 -0.5398768  1.502665 1.4012451



### 4*4 matrix and using the relationship between rwv & ryv.w (w COVARIATE)

it_1000

rwv_seq(rwv.L,rwv.U,length=it)
beta1_sy.w / sw * ( ryw.w - (ryw.u*rwu) ) / ( 1 - (rwu^2) )
# beta1 = -0.4041165
# beta1*5 = -2.020582

E1_( ryv.v * (1-(rwu^2)) ) + ( ryv.u * ( (rwv*rwu)- rvu ) )
D_1 - (rwu^2) - (rvu^2) - (rwv^2)  + ( 2*rwv * rwu * rvu )
E2_( ryv.v*( (rwu*rvu)-rwv ) ) + ( ryv.u*( (rwv*rvu)-rwu ) )

A_( (sy.v*((rwu*rvu)-rwv)) / (sv*D) ) + ( (sy.v*(1-(rvu^2))) / (sw*D) )
```

```
E12_-sy.v/D*( (E2/sw) + (E1/sv) )

ryv.w_(beta1+E12)/A

ee_0
for(i in 1:length(rwv)){ testmat_cbind(c(1,ryv.v,ryv.w[i],ryv.u),
          c(ryv.v,1,rwv[i],rvu),
          c(ryv.w[i],rwv[i], 1, rwu),
          c(ryv.u,rvu,rwu,1) )

ee[i]_min(eigen(testmat)$values)
}

rwv_rwv[ee>0]
ryv.w_ryv.w[ee>0]

E1_( ryv.v * (1-(rwu^2)) ) + ( ryv.u * ( (rwv*rwu)- rvu ) )

D_1 - (rwu^2) - (rvu^2) - (rwv^2)  + ( 2*rwv * rwu * rvu )

E2_( ryv.v*( (rwu*rvu)-rwv ) ) + ( ryv.u*( (rwv*rvu)-rwu ) )


# version1
Beta2_sy.v / sv * ( (ryv.w*((rvu*rwu)-rwv) ) + E1 ) / D


# version2
Beta2v2_beta1-( sy.v / sw * ( (ryv.w*(1-(rvu^2)))  + E2 ) / D )



beta.result_cbind(rwv,ryv.w,Beta2,Beta2v2)

bounds_rbind(apply(beta.result,2,min),apply(beta.result,2,max))
dimnames(bounds)[2]_list(c("Cor(W,V)","Cor(yv.w)","Beta2","Beta2v2"))
dimnames(bounds)[1]_list(c("min","max"))

it
bounds

##### This gives discontinuous range of rwv.
```

APPENDIX E.

S-PLUS CODE FOR SIMULATIONS USING PARAMETRIC BOOTSTRAP

The parametric bootstrap is using to assess the sampling variability of the variables of interest, $\rho_{W,V}$, β_2^{No}, and β_2^{Yes}. As in Section 3.4.3, consider two models (17) and (18) and applied a multivariate normal distribution corresponding to a random vector $\left(Y^{(0)},W^{(0)},U\right)'$ and $\left(Y^{(1)},W^{(1)},V,U\right)'$, respectively. All estimable parameters were set as the sample estimates from the mice experiment. Moreover, nonestimable $\rho_{W,V}$ was set to particular values, 0.3, 0.4, 0.5, and 0.6, within the interval specified by the estimated bounds. The code below provides the results as in Tables 3.2-3.4.

```
#Below are commands to compute estimable correlations from the mice data set
# and to bound the nonestimable ones. We have 5 potential outcome variables,
# lifespan(IWL) = yv
# lifespan(UWL) = yw
# Total weight loss = v
# UWL     = w
# covariate = baseline weight = u
#-----------------------------------------

#These lines extract the variables from the mice data
#They also omit mice that died before wt5 was recorded

#The function sim.data will take an input data set and simulate data from it.
sim.data<-function(data.in=DATA.in,n=N,rwv.in=RWV.in){

#the input data set must have variables defined by vars below

vars_c("Diet","wt12mo","wt5","Lifespan")

data_data.in[,vars]
data_na.omit(data)
x1_data[data[,"Diet"]==1,]
x0_data[data[,"Diet"]==0,]

v_x1[,"wt12mo"] - x1[,"wt5"]; w_x0[,"wt12mo"] - x0[,"wt5"]

y.v_x1[,"Lifespan"];          y.w_x0[,"Lifespan"]


#now consider baseline covariate = initial weight

covar_vars[2]

u.no_data[data[,"Diet"]==0,covar]
u.yes_data[data[,"Diet"]==1,covar]
u_data[,covar]    # u is now the set of covariates observable for all
   individuals.


#Here we estimate the correlations that can be estimated from observed data,
   there are 6
ryw.w_cor(y.w,w); ryw.u_cor(y.w,u.no); ryv.v_cor(y.v,v)
ryv.u_cor(y.v,u.yes); rwu_cor(w,u.no); rvu_cor(v,u.yes)
check1<<-c(ryw.w,ryw.u,ryv.v,ryv.u,rwu,rvu)
```

```
sw_sqrt(var(w)); sv_sqrt(var(v))
sy.v_sqrt(var(y.v)); sy.w_sqrt(var(y.w))
su_sqrt(var(u))
#values defined up to hear ------------------------------------------------

# Simulate data with covariate

rwv<-rwv.in
beta1_sy.w / sw * ( ryw.w - (ryw.u*rwu) ) / ( 1 - (rwu^2) )
E1_( ryv.v * (1-(rwu^2)) ) + ( ryv.u * ( (rwv*rwu)- rvu ) )
D_1 - (rwu^2) - (rvu^2) - (rwv^2)  + ( 2*rwv * rwu * rvu )
E2_( ryv.v*( (rwu*rvu)-rwv ) ) + ( ryv.u*( (rwv*rvu)-rwu ) )
A_( (sy.v*((rwu*rvu)-rwv)) / (sv*D) ) + ( (sy.v*(1-(rvu^2))) / (sw*D) )
E12_-sy.v/D*( (E2/sw) + (E1/sv) )
ryv.w_(beta1+E12)/A

mat_cbind(          c(1,      ryv.w,    ryv.v,    ryv.u),
             c(ryv.w,  1,     rwv,      rwu),
             c(ryv.v,  rwv,      1,     rvu),
             c(ryv.u,  rwu,      rvu,      1) )

#print(min(eigen(mat)$values))

sd_c(sy.v,sw,sv,su)
mu_c(mean(y.v),mean(w),mean(v),mean(u))

data_rmvnorm(n,mean=mu,cov=mat,sd=sd)
testdat<<-data
fit.yw_lm(y.w~w+u.no)

#Now produce estimates from the simulated data set
m_(n/2)+1

y.v.s_data[1:(m-1),1]
w.s_data[m:n,2]
v.s_data[1:(m-1),3]
u.s_data[,4]
u.yes.s_u.s[1:(m-1)]
u.no.s_u.s[m:n]

cor.wmat_c(1,ryw.w,ryw.u,ryw.w,1,rwu,ryw.u,rwu,1)
cor.wmat_matrix(cor.wmat,ncol=3)

covmat_diag(c(sy.w,sw,su))%*%cor.wmat%*%diag(c(sy.w,sw,su))
var.yw_sy.w^2 - covmat[1,2:3]%*%solve(covmat[2:3,2:3])%*%covmat[2:3,1]

pred.yw_fit.yw$coeff[1] + fit.yw$coeff[2]*w.s + fit.yw$coeff[3]*u.no.s

y.w.s_pred.yw + rnorm(length(pred.yw),0,sqrt(var.yw))
Lifespan_c(y.v.s,y.w.s)

Diet_c(rep(1,length(y.v.s)),rep(0,length(y.w.s)))
wt5_u.s-c(v.s,w.s)
wt12mo_u.s
data.sim_data.frame(Diet,wt12mo,wt5,Lifespan)
return(data.sim)
}


#----------------------------------------
#now the analysis code for a data set
#This function analyzes data from an input data set
```

```
analyze.data_function(simdata.in,it=IT){
vars_c("Diet","wt12mo","wt5","Lifespan")
data_simdata.in[,vars]
data_na.omit(data)
x1_data[data[,"Diet"]==1,]
x0_data[data[,"Diet"]==0,]

v_x1[,"wt12mo"] - x1[,"wt5"];     w_x0[,"wt12mo"] - x0[,"wt5"]
y.v_x1[,"Lifespan"];              y.w_x0[,"Lifespan"]

#now consider baseline covariate = initial weight

covar_"wt12mo"
u.no_data[data[,"Diet"]==0,covar]
u.yes_data[data[,"Diet"]==1,covar]
u_data[,covar]    # u is now the set of covariates observable for all
   individuals.

#Here we estimate the correlations that can be estimated from observed data
ryw.w_cor(y.w,w); ryw.u_cor(y.w,u.no); ryv.v_cor(y.v,v)
ryv.u_cor(y.v,u.yes); rwu_cor(w,u.no); rvu_cor(v,u.yes)
check2<<-c(ryw.w,ryw.u,ryv.v,ryv.u,rwu,rvu)

sw_sqrt(var(w)); sv_sqrt(var(v))
sy.v_sqrt(var(y.v)); sy.w_sqrt(var(y.w))
rwv_seq(-1,1,length=it)

#-----------------------no covariate investigating positive definiteness
tt_sy.w*sv*ryw.w*(1-rwv^2) + (sy.v*ryv.v *( (sv*rwv) - sw ) )
dd_sy.v*sv - sy.v*sw*rwv
ryv.w1_tt/dd
ee1a_0

for(i in 1:length(rwv)){
testmat_cbind(c(1,ryv.v,ryv.w1[i]),
              c(ryv.v,1,rwv[i]),
              c(ryv.w1[i],rwv[i],1) )
ee1a[i]_min(eigen(testmat)$values)
}

beta1_sy.w / sw * ( ryw.w - (ryw.u*rwu) ) / ( 1 - (rwu^2) )
E1_( ryv.v * (1-(rwu^2)) ) + ( ryv.u * ( (rwv*rwu)- rvu ) )
D_1 - (rwu^2) - (rvu^2) - (rwv^2)  + ( 2*rwv * rwu * rvu )
E2_( ryv.v*( (rwu*rvu)-rwv ) ) + ( ryv.u*( (rwv*rvu)-rwu ) )
A_( (sy.v*((rwu*rvu)-rwv)) / (sv*D) ) + ( (sy.v*(1-(rvu^2))) / (sw*D) )
E12_-sy.v/D*( (E2/sw) + (E1/sv) )
ryv.w2_(beta1+E12)/A

ee1b_0
for(i in 1:length(rwv)){ testmat_cbind(c(1,ryv.v,ryv.w1[i],ryv.u),
          c(ryv.v,1,rwv[i],rvu),
          c(ryv.w1[i],rwv[i], 1, rwu),
          c(ryv.u,rvu,rwu,1) )
ee1b[i]_min(eigen(testmat)$values)
}

ee2_0
for(i in 1:length(rwv)){ testmat_cbind(c(1,ryv.v,ryv.w2[i],ryv.u),
          c(ryv.v,1,rwv[i],rvu),
          c(ryv.w2[i],rwv[i], 1, rwu),
          c(ryv.u,rvu,rwu,1) )

ee2[i]_min(eigen(testmat)$values)
```

```
}

mm<-cbind(rwv,ee1a,ee1b,ee2)

mma<-apply(mm[,2:4],1,min)
r1_(1:(dim(mm)[1]))[mma>0]
flag_rep(0,dim(mm)[1])
flag[r1]_1

m1a_min(r1)
m2a_max(r1)

flag.sum_0
for (i in 1:length(flag))
{   flag.sum_flag.sum+flag[i]
}

print (flag.sum)

if ( flag.sum >0)
{
print(c(m1a,m2a))
tta_m1a:m2a
test.cont_prod(flag[tta])
mm<-mm[mm[,2]>0&mm[,3]>0&mm[,4]>0,]
#now compute the beta2 bounds
rwv1<-mm[,1]
beta1_sy.w / sw * ( ryw.w - (ryw.u*rwu) ) / ( 1 - (rwu^2) )
E1_( ryv.v * (1-(rwu^2)) ) + ( ryv.u * ( (rwv1*rwu)- rvu ) )
D_1 - (rwu^2) - (rvu^2) - (rwv1^2)  + ( 2*rwv1 * rwu * rvu )
E2_( ryv.v*( (rwu*rvu)-rwv1 ) ) + ( ryv.u*( (rwv1*rvu)-rwu ) )
A_( (sy.v*((rwu*rvu)-rwv1)) / (sv*D) ) + ( (sy.v*(1-(rvu^2))) / (sw*D) )
E12_-sy.v/D*( (E2/sw) + (E1/sv) )

B2.no_(sy.v*ryv.v - sy.w*ryw.w*rwv1)/(sv-sw*rwv1)
B2.yes_(sy.v / (sv*D)) * (((beta1+E12)/A)*(rwu*rvu - rwv1) + E1)

Beta2.no.min<-min(B2.no)
Beta2.no.max<-max(B2.no)
Beta2.yes.min<-min(B2.yes)
Beta2.yes.max<-max(B2.yes)
rwv.min<-min(rwv1)
rwv.max<-max(rwv1)
}

else
{
m1a<-0
m2a<-0
print(c(m1a,m2a))
test.cont<-0

rwv.min<-0
rwv.max<-0
Beta2.no.min<-0
Beta2.no.max<-0
Beta2.yes.min<-0
Beta2.yes.max<-0
}

# ----------- CALCULATE BETA2 at RWV.in ------------------

rwvsetup_RWV.in
```

```
beta1_sy.w / sw * ( ryw.w - (ryw.u*rwu) ) / ( 1 - (rwu^2) )

E1_( ryv.v * (1-(rwu^2)) ) + ( ryv.u * ( (rwvsetup*rwu)- rvu ) )
D_1 - (rwu^2) - (rvu^2) - (rwvsetup^2)  + ( 2*rwvsetup * rwu * rvu )
E2_( ryv.v*( (rwu*rvu)-rwvsetup ) ) + ( ryv.u*( (rwvsetup*rvu)-rwu ) )
A_( (sy.v*((rwu*rvu)-rwvsetup)) / (sv*D) ) + ( (sy.v*(1-(rvu^2))) / (sw*D) )
E12_-sy.v/D*( (E2/sw) + (E1/sv) )

Beta2.no_(sy.v*ryv.v - sy.w*ryw.w*rwvsetup)/(sv-sw*rwvsetup)
Beta2.yes_(sy.v / (sv*D)) * (((beta1+E12)/A)*(rwu*rvu - rwvsetup) + E1)

result_data.frame(Beta2.no,Beta2.yes,rwv.min,rwv.max,Beta2.no.min,Beta2.no.max,
   Beta2.yes.min,Beta2.yes.max,test.cont)
return(result)
}

#----------Here is the Master simulation function
Master.mouse<-function(DATA.in,N=1000,RWV.in=.5,IT=200,sim.nos=10,seed=222){
#DATA.in = input template data set
#N = total sample size to be divided into two groups
#RWV.in = true value of RWV
#IT = number of divisions of the vector RWV in the simulations
#sim.nos = number of simulations
#seed = seed for entire simulation run
DATA.in<<-DATA.in
N<<-N
RWV.in<<-RWV.in
IT<<-IT
RESULT<-
   data.frame(Beta2.no=0,Beta2.yes=0,rwv.min=0,rwv.max=0,Beta2.no.min=0,Beta2.n
   o.max=0,Beta2.yes.min=0,Beta2.yes.max=0,test.cont=0)
for(i in 1:sim.nos){
SDATA.in<-sim.data()
res.sim<-analyze.data(simdata.in=SDATA.in,it=IT)
RESULT<-rbind(RESULT,res.sim)
}
RESULT<-RESULT[-1,]
return(RESULT)
}


## Save above program as the name simcode.txt with the specific folder and run
   those function first and these commands later.

source("c:\\research\\papercode\\simcode.txt")

test11_Master.mouse(DATA.in,N=1000,RWV.in=.5,IT=200,sim.nos=5,seed=233)
```

APPENDIX F.
DERIVATION IN SECTION 4.2

1. The sums of squares

Recall IWL for the two subjects within the i[th] pair,

$$Z_{i1} = (V_i - \varepsilon_i) - (W_i - \eta_i) = (V_i - W_i) - (\varepsilon_i - \eta_i), \quad \text{(F1)}$$

$$Z_{i2} = (V_i + \varepsilon_i) - (W_i + \eta_i) = (V_i - W_i) + (\varepsilon_i - \eta_i), \quad \text{(F2)}$$

and the observed effect of intention to lose weight is either one of the following

$$z_i = \begin{cases} (V_i - \varepsilon_i) - (W_i + \eta_i) = (V_i - W_i) - (\varepsilon_i + \eta_i) & \textit{with probability } 1/2 \\ (V_i + \varepsilon_i) - (W_i - \eta_i) = (V_i - W_i) + (\varepsilon_i + \eta_i) & \textit{with probability } 1/2 \end{cases}.$$

The total sum of squares of the treatment effect in equation (24) is

$$SSZ = \sum_{i=1}^{n}\sum_{j=1}^{2}(Z_{i,j} - \overline{Z})^2 = \sum_{i=1}^{n}\sum_{j=1}^{2}\left[(Z_{i,j} - \overline{Z}_i) + (\overline{Z}_i - \overline{Z})\right]^2$$

$$= \sum_{i=1}^{n}\sum_{j=1}^{2}(Z_{i,j} - \overline{Z}_i)^2 + 2\sum_{i=1}^{n}(\overline{Z}_i - \overline{Z})^2 .$$

The average of the true IWL effect in equation (23) could be written as

$$\overline{Z} = \frac{1}{n}\sum_{i=1}^{n}\overline{Z}_i = \overline{V} - \overline{W} ,$$

where $\overline{Z}_i = (V_i - W_i) = \frac{1}{2}(Z_{i1} + Z_{i2})$, and this could use to rewrite the equations (F1) and (F2) as

$$Z_{i1} = \overline{Z}_i - (\varepsilon_i - \eta_i),$$

$$Z_{i2} = \overline{Z}_i + (\varepsilon_i - \eta_i).$$

The within pairs sum of squares is

$$SSW = \sum_{i=1}^{n}\sum_{j=1}^{2}(Z_{i,j} - \overline{Z}_i)^2 = \sum_{i=1}^{n}\left[(Z_{i1} - \overline{Z}_i)^2 + (Z_{i2} - \overline{Z}_i)^2\right]$$

$$= 2\sum_{i=1}^{n}(\varepsilon_i - \eta_i)^2 .$$

The between pairs sum of squares is

$$SSB = 2\sum_{i=1}^{n}(\overline{Z}_i - \overline{Z})^2 = 2\sum_{i=1}^{n}\left[(V_i - W_i) - (\overline{V} - \overline{W})\right]^2 .$$

2. Proof of Proposition 2

Recall equation (28), the observed variance of IWL be

$$S_z^2 = \frac{1}{n}\sum_{i=1}^{n}\left[\left(z_i - \bar{z}\right)^2\right] = \frac{1}{n}\left(\sum_{i=1}^{n} z_i^2 - n\bar{z}^2\right).$$

The expectation, denoted by *E*, of S_z^2 for all possible random treatment assignments is

$$E\left(S_z^2\right) = \frac{1}{n}\left[\sum_{i=1}^{n} E\left(z_i^2\right) - \frac{1}{n}E\left(\sum_{i=1}^{n} z_i\right)^2\right].$$

Consider the first term on the right hand side, $E\left(z_i^2\right)$, by using another form of equations $z_{i1} = Z_{i1} - 2\eta_i$ and $z_{i2} = Z_{i2} + 2\eta_i$,

$$\begin{aligned} E\left(z_i^2\right) &= E\left[\left(Z_{i1} - 2\eta_i\right)^2 T_i + \left(Z_{i2} + 2\eta_i\right)^2 \left(1 - T_i\right)\right] \\ &= \frac{Z_{i1}^2 + Z_{i1}^2}{2} + 4\eta_i^2 + 2\eta_i\left(Z_{i1} + Z_{i1}\right) \\ &= \frac{Z_{i1}^2 + Z_{i1}^2}{2} + 4\varepsilon_i\eta_i \ . \end{aligned} \tag{F3}$$

The last term, $E\left(\sum_{i=1}^{n} z_i\right)^2$, is

$$\begin{aligned} E\left(\sum_{i=1}^{n} z_i\right)^2 = \sum_{i=1}^{n}\sum_{i'=1}^{n}\Bigg[&\left(Z_{i1} - 2\eta_i\right)\left(Z_{i'1} - 2\eta_{i'}\right)\frac{1 + \delta_{ii'}}{4} + \left(Z_{i2} + 2\eta_i\right)\left(Z_{i'2} + 2\eta_{i'}\right)\frac{1 + \delta_{ii'}}{4} \\ &+ 2\left(Z_{i2} + 2\eta_i\right)\left(Z_{i'1} - 2\eta_{i'}\right)\frac{1 - \delta_{ii'}}{4}\Bigg], \end{aligned}$$

where $\delta_{ii'} = 1$ if $i = i'$ and 0 otherwise. Algebraically simplify above equation and get

$$E\left(\sum_{i=1}^{n} z_i\right)^2 = \frac{1}{4}\left[\sum_{i=1}^{n}\sum_{j=1}^{2}\left(Z_{ij}\right)\right]^2 + \sum_{i=1}^{n}\left(\varepsilon_i + \eta_i\right)^2 . \tag{F4}$$

Equations (F3) and (F4) give the result of the expectation of S_z^2, $E\left(S_z^2\right)$, as in equation (29),

$$E\left(S_z^2\right) = S_Z^2 + \frac{4}{n}\sum_{i=1}^{n}\varepsilon_i\eta_i - \frac{1}{n^2}\sum_{i=1}^{n}\left(\varepsilon_i + \eta_i\right)^2 ,$$

where $SSZ = \sum_{i=1}^{n}\sum_{j=1}^{2}\left(Z_{i,j} - \bar{Z}\right)^2 = \sum_{i=1}^{n}\sum_{j=1}^{2} {Z_{i,j}}^2 - 2n\bar{Z}^2 = \sum_{i=1}^{n}\sum_{j=1}^{2} {Z_{i,j}}^2 - \frac{1}{2n}\left(\sum_{i=1}^{n}\sum_{j=1}^{2} Z_{i,j}\right)^2$.

3. The expectation of the bias of S_z^2.

Proposition 2 shows that the estimator S_z^2 is biased for S_Z^2 and the bias is defined by equation (30). The expectation of the bias of S_z^2 is

$$\begin{aligned}
\mathrm{E}_{\varepsilon,\eta}(bias) &= \frac{4}{n}\sum_{i=1}^{n}\mathrm{E}_{\varepsilon,\eta}(\varepsilon_i\eta_i) - \frac{1}{n^2}\sum_{i=1}^{n}\mathrm{E}_{\varepsilon,\eta}\left[(\varepsilon_i+\eta_i)^2\right] \\
&= \frac{1}{n}\left[4n\sigma^2\rho - 2\sigma^2\rho - 2\sigma^2\right], \text{ using } \rho_{XY} = \frac{E(XY)-E(X)E(Y)}{\sigma_X\sigma_Y} \\
&= \frac{\sigma^2}{n}\left[(4n-2)\rho - 2\right].
\end{aligned}$$

4. The bounds for S_Z^2

The quantities $\hat{L}$ and $\hat{U}$ in equations (32) and (33) give the bounds for S_Z^2, if the expectation operator over the bivariate distribution is denoted by $\mathrm{E}_{\varepsilon,\eta}$ and the expectation operator over possible random treatment is denoted by *E*,

$$\begin{aligned}
\mathrm{E}_{\varepsilon,\eta}\left[E(\hat{L}) - S_Z^2\right] &= \frac{\sigma^2}{n}\left[4n\rho - 2\rho - 2 - 4(n-1)\right] = \frac{\sigma^2}{n}\left[(\rho-1)(2n-1)\right] \\
&\le 0 \text{ for all } n. \\
\mathrm{E}_{\varepsilon,\eta}\left[E(\hat{U}) - S_Z^2\right] &= \frac{\sigma^2}{n}\left[4n\rho - 2\rho - 2\right] + 4\sigma^2 = \frac{2\sigma^2}{n}\left[(\rho+1)(2n-1)\right] \\
&\ge 0 \text{ for all } n.
\end{aligned}$$

This implies that the bounds $(\hat{L},\hat{U})$ could give the idea how large or small S_Z^2 might be as in Section 4.2.

APPENDIX G.
S-PLUS CODE FOR SECTION 4.5

1. Eye data

```
attach(EyeData)

data_EyeData
data_na.omit(data)

x1_0; x2_0
x1_data[data[,2]==1,]
x2_data[data[,2]==2,]
## cbind(x1,x2)


id_0; trt.x_0; va.x_0; va3.x_0; trt.y_0; va.y_0; va3.y_0; x_0; y_0
id_c(x1[,1],x2[,1]); trt.x_c(x1[,2],x2[,5]); va.x_c(x1[,3],x2[,6]);
   va3.x_c(x1[,4],x2[,7])
x_va3.x-va.x
trt.y_c(x1[,5],x2[,2]); va.y_c(x1[,6],x2[,3]); va3.y_c(x1[,7],x2[,4])
y_va3.y-va.y

cbind(x,y)

z_0
z_x-y

n_length(z)
var.z_var(z)*(n-1)/n          # var(z) = 313.5365
# [1] 311.5395


s2_5

varZ.L_var.z - (4*(n-1)/n*s2)
varZ.U_var.z + (4*s2)

cbind(varZ.L, varZ.U)
# [1,] 291.6668 331.5395
cbind(sqrt(varZ.L), sqrt(varZ.U))
# [1,] 17.07826 18.20822

s2_seq(0,20,.1)
varZ.L_var.z - (4*(n-1)/n*s2)
varZ.U_var.z + (4*s2)

plot(s2,sqrt(varZ.L), type="n",xlab="var(eps) or var(eeta)",
   ylab="var(Z)",ylim=c( min(sqrt(varZ.L)), max(sqrt(varZ.U)) ))

points(s2,sqrt(varZ.L))
points(s2,sqrt(varZ.U))
```

2. Mice data with specific matched pairs using baseline weight at 12 months

```
attach(IWLmouseSS)  # this data is matched based on the baseline weight

vars_c("Diet","wt12mo","wt22mo","wt5","Lifespan")
data_0;
data_IWLmouseSS[,vars]

data_na.omit(data)
x1_0; x0_0
x1_data[data[,"Diet"]==1,]
x0_data[data[,"Diet"]==0,]

v_0; w_0
v_x1[,"wt12mo"] - x1[,"wt5"]
w_x0[,"wt12mo"] - x0[,"wt5"]

y1_0; y0_0; y_0
y1_x1[,"Lifespan"]
y0_x0[,"Lifespan"]
y_data[,"Lifespan"]

u.no_0; u.yes_0; u_0
u.no_data[data[,"Diet"]==0,"wt12mo"]     # 64
u.yes_data[data[,"Diet"]==1,"wt12mo"]    # 67
u_data[,"wt12mo"]

eps_0; i_1
for (i in 1:16)
{
   eps[i]_( w[32+(2*i)]-w[32+(2*i)-1] )/2
}

eeta_0
for (i in 1:17)
{
   eeta[i]_( v[32+(2*i)]-v[32+(2*i)-1] )/2
}

## CHECK     sum(eps); sum(eeta)
mean(eps); var(eps)        # 0  1.191667
mean(eeta); var(eeta)      # 0  0.96875

n.eeta<-length(eeta)
n.eps<-length(eps)
s22_(sum(eps^2)+sum(eeta^2)) / (n.eeta+n.eps)     # 1.011364 ## this is sigma^2

z_0
z_v[1:32]-w[1:32]
n.z<-length(z)
var.z_var(z)*(n.z-1)/n.z         # var(z) = 27.72581
# [1] 26.85938                   This is S(z)^2

varZ.L_var.z - (4*(n.z-1)/n.z*s22)
varZ.U_var.z + (4*s22)
cbind(varZ.L, varZ.U)            # [1,] 22.94034 30.90483
cbind(sqrt(varZ.L), sqrt(varZ.U)) # [1,] 4.789608 5.559211


rwv.L_( var(w) + var(v) - varZ.L ) / (2*sw*sv)
rwv.U_( var(w) + var(v) - varZ.U ) / (2*sw*sv)
```

```
cbind(rwv.L,rwv.U)
##  [1,] 0.5436294 0.3840173

sZ_seq( sqrt(varZ.L),sqrt(varZ.U),.001)
rwz1_sv/sZ*( (rwu*rvu) - (sw/sv) - sqrt((1-rwu^2)*(1-rvu^2)) )
rwz2_sv/sZ*( (rwu*rvu) - (sw/sv) + sqrt((1-rwu^2)*(1-rvu^2)) )

plot(sZ,rwz1, type="n",xlab="sZ", ylab="Rwz",ylim=c( min(rwz1,rwz2),
   max(rwz1,rwz2) ))

lines(sZ,rwz1,type="b", lty=1)
lines(sZ,rwz2,type="b", lty=1)


#### TRi-VARIATE

vars_c("Diet","wt12mo","wt5","Lifespan")
data_0
data_IWLmouse[,vars]

data_na.omit(data)
x1_data[data[,"Diet"]==1,]
x0_data[data[,"Diet"]==0,]

v_x1[,"wt12mo"] - x1[,"wt5"]
w_x0[,"wt12mo"] - x0[,"wt5"]

y.v_x1[,"Lifespan"]
y.w_x0[,"Lifespan"]


#now consider baseline covariate = initial weight

covar_"wt12mo"
u.no_data[data[,"Diet"]==0,covar]
u.yes_data[data[,"Diet"]==1,covar]
u_data[,covar]    # u is now the set of covariates observable for all
   individuals.

#Here we estimate the correlations that can be estimated from observed data,
   there are 6
ryw.w_cor(y.w,w); ryw.u_cor(y.w,u.no); ryv.v_cor(y.v,v)
ryv.u_cor(y.v,u.yes); rwu_cor(w,u.no); rvu_cor(v,u.yes)

sw_sqrt(var(w)); sv_sqrt(var(v))
sy.v_sqrt(var(y.v)); sy.w_sqrt(var(y.w))

rwv.WVU_cbind( (rwu*rvu) - sqrt((1-rwu^2)*(1-rvu^2)), (rwu*rvu) + sqrt((1-
   rwu^2)*(1-rvu^2)))
### [1,] 0.06731668 0.8899493

sz.wvu_sqrt(var(w)+var(v)-(2*sw*sv*rwv.WVU))
## [1,] 6.834317 2.378932
```

3. Twins data

```
attach(finnishdata1)
i<-2:(length(fam.id))

m<-fam.id[i]-fam.id[i-1]
m0<-(1:(length(m)))[m==0]
m1<-m0+1

###### ignoring matched pairs and use the 2 sample design
vars<-
   c("fam.id","zyg","Sex","age81","death","ftime","bmi75","bmidiff","wtloss","d
   iet","act","medic","smokstat",
"sm81.st","smokch1","smokch2","smokch3","heavych1","heavych2","heavych3","lsch1
   ","lsch2","lsch3",
"vigch1","vigch2","vigch3","work","income75","hyper","dysp")

mat<-finnishdata1[,vars]

mat[,"wtloss"]<-mat[,"wtloss"]-1
mat[,"diet"]<-mat[,"diet"]-1
mat[,"act"]<-mat[,"act"]-1
mat[,"medic"]<-mat[,"medic"]-1
mat[,"hyper"]<-mat[,"hyper"]-1
mat[,"bmi75"]<-mat[,"bmi75"]-1

twin1<-mat[m0,]
twin2<-mat[m1,]
dim(twin1); dim(twin2)

mat<-rbind(twin1,twin2)
dim(mat)         # [1] 890  30

mat[,"wtloss"]<-mat[,"wtloss"]-1
mat[,"diet"]<-mat[,"diet"]-1
mat[,"act"]<-mat[,"act"]-1
mat[,"medic"]<-mat[,"medic"]-1
mat[,"hyper"]<-mat[,"hyper"]-1

mat0<-mat[mat[,"wtloss"]==0,] #0 = wtloss = no
mat1<-mat[mat[,"wtloss"]==-1,] #1 = wtloss = yes

w<-mat0[,"bmidiff"]
v<-mat1[,"bmidiff"]

## covar<-
   c("Sex","age81","bmi75","smokch1","smokch2","smokch3","heavych1","heavych2",
   "heavych3","lsch1","lsch2","lsch3",
   "vigch1","vigch2","vigch3","income75","hyper")

covar<-c("bmi75")

u<-mat[,covar]
u.no<-mat0[,covar]
u.yes<-mat1[,covar]

s0_cor(w,u.no)
s1_cor(v,u.yes)
s_cbind(s0,s1)

h_t(s)%*%solve(cor(u))%*%s
```

```
low_h[1,2] - sqrt((1-h[1,1])*(1-h[2,2]))
up_h[1,2] + sqrt((1-h[1,1])*(1-h[2,2]))
b1_c(low,up)   #here are the estimated bounds for the simple correlation
   between w and v
##  -0.9915891  0.9960139    1 covariate ##
##  -0.8739296  0.9373542  all covariate ##
rwv.L_b1[1]
rwv.U_b1[2]
## cbind(rwv.L,rwv.U)  == b1

rwv.u_seq(rwv.L,rwv.U,.0001)
max(rwv.u); min(rwv.u)
sv_sqrt(var(v))
sw_sqrt(var(w))
sz.u_sqrt(var(v)+var(w)-(2*rwv.u*sv*sw))
sz.um_sqrt(var(v)+var(w)-(2*rwv.U*sv*sw))
cbind(min(sz.u,sz.um),max(sz.u,sz.um))

## This are the bounds for S(Z)
## [1,] 0.3910776 4.122554    1 covariate
## [1,] 0.8062324 3.999804  all covariates



###### START using matched pairs for 445 pairs

zy<-twin1[,"zyg"]
wt1<-twin1[,"wtloss"]
wt2<-twin2[,"wtloss"]
u1<-twin1[,"bmi75"]
u2<-twin2[,"bmi75"]
d1<-twin1[,"death"]
d2<-twin2[,"death"]
ftime1<-twin1[,"ftime"]
ftime2<-twin2[,"ftime"]
bmidiff1<-twin1[,"bmidiff"]
bmidiff2<-twin2[,"bmidiff"]

twindata<-cbind(zy,wt1,wt2,d1,d2,ftime1,ftime2,u1,u2,bmidiff1,bmidiff2)
dim(twindata)

######################################################## MATCH

mat0<-0; mat1<-0; w<-0; v<-0; u<-0; u.no<-0; u.yes<-0

mat0<-twindata[twindata[,"wt1"]==0 & twindata[,"wt2"]==0,] #0 = wtloss = no
   BOTH 00

mat1<-twindata[twindata[,"wt1"]==1 & twindata[,"wt2"]==1,] #1 = wtloss = yes
   BOTH 11

eeta<-(mat1[,"bmidiff1"]-mat1[,"bmidiff2"])/2        # 1 IWL
cbind(mean(eeta),var(eeta))                        #  0.02257535 2.070687
eps<-(mat0[,"bmidiff1"]-mat0[,"bmidiff2"])/2      # 0 UWL
cbind(mean(eps),var(eps))                       # -0.1340113 1.32709

n.eeta<-length(eeta)                     #  102
n.eps<-length(eps)                   #  208

s22_( ( sum(eps)^2)+  ( sum(eeta)^2)) / (n.eeta+n.eps)            # 2.523488
## THIS IS Sigma^2
######################### TC - CT #############
```

```
mat10<-twindata[twindata[,"wt1"]==1 & twindata[,"wt2"]==0,]      # 58
z10<-mat10[,"bmidiff2"]-mat10[,"bmidiff1"]
mat01<-twindata[twindata[,"wt1"]==0 & twindata[,"wt2"]==1,]        # 77
z01<-mat01[,"bmidiff1"]-mat01[,"bmidiff2"]
z<-c(z10,z01)

n.z<-length(z)
var.z_var(z)*(n.z-1)/n.z                #  5.751557      This is S(z)^2


varZ.l_var.z - (4*(n.z-1)/n.z*s22)
varZ.u_var.z + (4*s22)
cbind(varZ.l, varZ.u)                   # -4.267626 15.84551


if (varZ.l<0 )
{
   varZ.l<-0
}

cbind(sqrt(varZ.l), sqrt(varZ.u))       #  0 3.980642
                                        #  This is bounds for S(Z)


############################
############################################################
############################
```

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VITA

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