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The effects of intentional weight loss as a latent variable problem

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SUMMARY

Although obesity is associated with increased mortality rate and short-term weight loss improves risk factors for mortality, it has not been convincingly shown that weight loss among obese people results in reduced mortality rate. When considering the human literature, it has been pointed out that weight loss is often a sign of illness and that investigators therefore need to separate intentional from unintentional weight loss. It has generally been assumed that among people who state that they do not intend to lose weight, weight change subsequently observed is unintentional. Among such people, weight loss has been consistently associated with increased mortality rate. Complementarily, it has generally been assumed that among people who state that they do intend to lose weight, weight change subsequently observed is intentional. In these people who are intending to lose weight, some studies show apparent benefits of weight loss, some are neutral, and some show deleterious effects. The overall conclusion that some reviewers have drawn from this literature is that intentional weight loss (IWL) is at best not beneficial and may even be harmful with respect to mortality rate.

We believe that this conclusion is drawn by inappropriately conflating weight loss (or more generally weight change) among people intending to lose weight with IWL (or change). Herein, under certain assumptions, we: (1) show that the association between mortality rate and weight loss among people intending to lose weight and between mortality rate and IWL are two different things; (2) show that the association between IWL and mortality rate is an inherently unobservable entity; (3) derive a method for estimating the plausible range of true effect of IWL on mortality rate if one is willing to make a

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number of restrictive, but perhaps reasonable assumptions; and (4) illustrate the method by application to a data set involving middle-age onset calorie restriction in mice.

KEY WORDS: mortality; obesity; death; unobserved variables

1. INTRODUCTION

Obesity is associated with increased mortality rate [1] and short-term weight loss improves risk factors for mortality [2]. However, it has not been convincingly shown that weight loss among obese people results in reduced mortality rate. On the contrary, most studies show that weight loss is associated with increased mortality rate [3]. This issue becomes ever more acute as the prevalence of obesity continues to rise [4, 5]. The finding that weight loss is associated with increased mortality rate could be taken to imply, somewhat counter-intuitively, that public health efforts focused on encouraging obese people to improve their health by losing weight could actually lead to decreased lifespan.

Similarly, although caloric restriction (CR) results in dramatically lower body weight and prolongs life in multiple species [6], research is equivocal on the effect of body weight *per se* on rodent longevity [7, 8]. Moreover, as in humans, under some circumstances, weight loss appears to be associated with increased mortality rate [9].

Despite the common observation that weight loss in humans is often associated with increased mortality rate, questions have been raised about the validity or meaning of this finding [10, 11]. In particular, since weight loss is often a sign of illness, it has been pointed out that investigators need to separate intentional weight loss (IWL) from unintentional weight loss (UWL [12–14]). Among people who express no intention to lose weight, it has generally been assumed that all weight loss subsequently observed is unintentional. Complementarily, among people who state that they do intend to lose weight, it has generally been assumed that *all* weight loss subsequently observed is intentional, that is, due solely to their intention.

Investigators have studied the association between weight change in these two groups separately (e.g. References [15–22]). Among people who are not intending to lose weight, weight loss has been consistently associated with increased mortality rate. Among people who are intending to lose weight, some studies show apparent benefits of weight loss (e.g. Reference [17]), some are neutral (e.g. Reference [15]), and some show deleterious effects (e.g. Reference [20]). The overall conclusion that some reviewers have drawn from this literature is that IWL is at best not beneficial and may even be harmful with respect to mortality rate (e.g. Reference [23]).

We believe that this conclusion is drawn by inappropriately conflating weight loss (or more generally weight change) among people intending to lose weight with IWL (or change). More specifically, we feel that it is unlikely that any study can truly measure IWL *per se*. Rather, the data that are collected represent the total weight loss among those intending to lose weight and may represent both IWL and UWL. Herein, under certain assumptions, we: (1) show that the association between mortality rate and weight loss among people intending to lose weight and between mortality rate and IWL are two different things; (2) show that the association between IWL and mortality rate is an inherently unobservable entity; (3) derive a method for

estimating the plausible range of true effect of IWL on mortality rate if one is willing to make a number of restrictive, but perhaps reasonable assumptions; and (4) illustrate the method by application to a data set involving middle-age onset CR in mice. The methods described in this paper are developed precisely for this situation and allow researchers to obtain a better understanding of the true relationship between mortality and IWL (which cannot be measured) based on the relationship between mortality rate and *observed* weight loss among those who do and do not intend to lose weight (which can be measured).

2. THE ASSOCIATION BETWEEN MORTALITY RATE AND IWL IS NOT THE SAME AS THE ASSOCIATION BETWEEN MORTALITY RATE AND WEIGHT LOSS AMONG THOSE INTENDING TO LOSE WEIGHT

Some people intend to lose weight. Some people do not. Similarly, in animal experiments, some animals are intentionally assigned to conditions that the experimenter expects will produce weight loss (e.g. CR) and others are not. In each situation we will refer to the cases assigned as 'subjects', those in the former conditions as in the intentional condition, and those in the latter condition as in the unintentional condition. We wish to estimate the effect of IWL, i.e. that part of weight loss that is attributable to being in the intentional condition, on an outcome such as lifespan or mortality rate.

Assume that N subjects are observed until the time of death. Denote the time until death (or some monotonic transformation thereof) as Y. 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 lost due to a subject's or experimenter's intention as Z ($Z=\text{IWL}$; by definition, $X=0$ implies $Z=0$) and the weight lost due to factors other than the intention as W ($W=\text{UWL}$).

Denote the model describing the influences on lifespan as

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

where W, X, Y, and Z are as described above, e is a random error term with mean zero and variance σ_e^2, W is distributed with mean μ_W and variance σ_W^2, Z is distributed with mean μ_Z and variance σ_Z^2 and $\beta_0, \beta_1, \beta_2$ and β_3 are constants. Finally, we adopt the usual assumption that $\text{Cov}(e,W)=\text{Cov}(e,Z)=0$.

The β_1 parameter captures the effect of UWL on Y. 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 the two groups and there is no X by W interaction). Of course, both of these assumptions can be questioned, but they are reasonable assumptions to begin with. The β_2 parameter captures the effect of IWL on Y. Note that the model assumes an interaction between Z and X due to the fact that, by definition, no IWL will occur in the group not intending to lose weight. The β_3 parameter allows for the fact that there may be some effect of intending to lose weight *per se* (or more likely the actions or conditions that follow from such intention) as some data suggest [16]. We will return to this point later.

This leads to two separate but intricately related models among those who do and do not intend to lose weight:

For those not intending to lose weight ($X=0$):

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

For those intending to lose weight ($X=1$):

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

However, in practice we are only able to observe total weight loss (V). Since we cannot assume that the simple intent to lose weight removes all factors contributing to UWL, the total observed weight loss consists of the sum of IWL and UWL, i.e. $V\equiv W+Z$. Hence, the model that we can actually fit in the two groups separately is given by

$$Y=\alpha_0+\alpha_1 V+e \tag{4}$$

Since no IWL is expected in the group not intending to lose weight (i.e. $X=0$ implies $Z=0$), it follows that $V=W$. Hence, W also represents the total weight loss in this subset and fitting the regression in equation (4) is equivalent to fitting the regression equation:

$$Y=\beta_0+\beta_1 W+e \tag{5}$$

Hence, it is easily seen that $E(\hat{\alpha}_1)=\beta_1$ and $E(\hat{\alpha}_0)=\beta_0$. However, when $X=1$, suppose we fit the regression equation:

$$Y=\lambda_0+\lambda_1 V+e \tag{6}$$

Denote the correlation of W and Z as $\rho_{W,Z}$ and note that

$$\sigma^2_{V|X=1}\equiv\sigma^2_{V|1}=\sigma^2_W+\sigma^2_Z+2\rho_{W,Z}\sigma_W\sigma_Z \tag{7}$$

$$\sigma_{V,Y|X=1}=\beta_1\sigma^2_W+\beta_2\sigma^2_Z+(\beta_1+\beta_2)\rho_{W,Z}\sigma_W\sigma_Z \tag{8}$$

Therefore,

$$\begin{aligned}E(\hat{\lambda}_1)=\lambda_1&=\frac{\sigma_{V,Y}|X=1}{\sigma^2_V|X=1}\\&=\frac{\beta_1\sigma^2_W+\beta_2\sigma^2_Z+(\beta_1+\beta_2)\rho_{W,Z}\sigma_W\sigma_Z}{\sigma^2_W+\sigma^2_Z+2\rho_{W,Z}\sigma_W\sigma_Z}\\&=\beta_2+\frac{(\beta_1-\beta_2)(\sigma^2_W+\rho_{W,Z}\sigma_W\sigma_Z)}{\sigma^2_W+\sigma^2_Z+2\rho_{W,Z}\sigma_W\sigma_Z}\end{aligned} \tag{9}$$

This shows that $E(\hat{\lambda}_1)=\beta_2$ (and hence estimates the true effect of IWL) only when $\sigma^2_W=0$ or $\beta_1=\beta_2$, both of which can be seen to be untrue on the basis of empirical observations. Specifically, assuming $\sigma^2_W=0$ among people who intend to lose weight is tantamount to assuming that the mere intention to lose weight eliminates all variation in UWL. And the fact that observed associations of weight loss with mortality rate are so different in subjects who

do and do not intent to lose weight [16] strongly implies that $\beta_1 \neq \beta_2$. Thus, estimating λ_1 by regressing the outcome on total weight change among subjects intending to lose weight is decidedly not equivalent to estimating β_2, the effect of IWL.

3. THE ASSOCIATION BETWEEN MORTALITY RATE AND IWL IS INHERENTLY UNOBSERVABLE

Solving equation (9) for the parameter of interest, β_2, yields:

$$\begin{aligned}\beta_2 &= \frac{\lambda_1(\sigma_W^2 + \sigma_Z^2 + 2\rho_{W,Z}\sigma_W\sigma_Z) - \beta_1(\sigma_W^2 + \rho_{W,Z}\sigma_W\sigma_Z)}{\sigma_Z^2 + \rho_{W,Z}\sigma_W\sigma_Z} \\ &= \frac{\lambda_1\sigma_{V|1}^2 - \beta_1(\sigma_W^2 + \rho_{W,Z}\sigma_W\sigma_Z)}{\sigma_Z^2 + \rho_{W,Z}\sigma_W\sigma_Z}\end{aligned} \tag{10}$$

In the previous section, we demonstrated that an unbiased estimate of β_2 cannot be obtained directly. However, if we had estimates of all of the terms on the right side of equation (10) we could substitute them into the equation and obtain an estimate of β_2. Note that estimates of λ_1 and β_1 may be obtained from the separate regression equations for those intending and not intending to lose weight as described above. Thus, we require estimates of $\sigma_{V|X=1}^2$, σ_W^2, σ_W^2, $\rho_{W,Z}$, and σ_Z^2 in order to estimate β_2.

3.1. Estimating $\sigma_{V|X=1}^2$ and σ_W^2

A reasonable estimate of $\sigma_{V|X=1}^2$ may be obtained by calculating the sample variance of observed weight change among those subjects intending to lose weight, i.e. with $X = 1$. Furthermore, under the assumption that the variance of unintentional weight change is the same regardless of intention, σ_W^2 may be estimated by the sample of observed weight change among subjects not intending to lose weight, i.e. with $X = 0$.

3.2. Estimating $\rho_{W,Z}$ and σ_Z^2

Finally, we can express $\rho_{W,Z}$ as

$$\rho_{W,Z} = \frac{\sigma_{V|X=1}^2 - \sigma_W^2 - \sigma_Z^2}{2\sigma_W\sigma_Z} \tag{11}$$

However, we are left with one equation and two unknowns ($\rho_{W,Z}$, σ_Z^2) and we are aware of no way to obtain another equation that is not linearly dependent and is a function of only these two unknowns. Thus, we are aware of no way to directly solve for $\rho_{W,Z}$ and σ_Z^2.

4. A METHOD FOR ESTIMATING THE PLAUSIBLE RANGE OF THE EFFECT OF IWL ON MORTALITY RATE

By combining equation (10) with the constraints that $|\rho_{W,Z}| \leqslant 1$ and $\sigma_Z^2 > 0$ (ignoring the trivial case when $\sigma_Z^2 = 0$), we can impose boundaries on possible values of $\rho_{W,Z}$ and σ_Z^2.[‡] Thus, we can describe the range of pairs of possible values for $\rho_{W,Z}$ and σ_Z^2 and examine the estimates of β_2 that would be obtained by plugging these pairs of values and the sample estimates of $\sigma_{v|X=1}^2$, σ_w^2, λ_1, and β_1 described above into equation (10):

$$\hat{\beta}_2 = \frac{\hat{\lambda}_1 \hat{\sigma}_{V|1}^2 - \hat{\beta}_1(\hat{\sigma}_W^2 + \rho_{w,z}\hat{\sigma}_W \sigma_Z)}{\sigma_Z^2 + \rho_{w,z}\hat{\sigma}_W \sigma_Z} \tag{12}$$

An additional mechanism for reducing the plausible range of estimates for β_2 is to consider the partial correlation of Y and Z, controlling for W:

$$\rho_{Y,Z|W} = \frac{\rho_{Y,Z} - \rho_{Y,W}\rho_{Z,W}}{\sqrt{(1 - \rho_{Y,W}^2)(1 - \rho_{Z,W}^2)}} \tag{13}$$

We have already considered a range of values for $\rho_{W,Z}$. Hence, in order to estimate the partial correlation coefficient, we need to come up with reasonable estimates of $\rho_{Y,Z}$ and $\rho_{Y,W}$. This can be done based on the following relationships:

$$\begin{aligned} \rho_{Y,Z} &= \frac{\sigma_{Y,Z}}{\sigma_Y \sigma_Z} = \frac{\beta_2 \sigma_Z + \beta_1 \rho_{WZ} \sigma_W}{\sigma_Y} \\ \rho_{Y,W} &= \frac{\sigma_{Y,W}}{\sigma_Y \sigma_W} = \frac{\beta_1 \sigma_W + \beta_2 \rho_{WZ} \sigma_Z}{\sigma_Y} \end{aligned} \tag{14}$$

From the raw data, we can compute $\hat{\sigma}_Y^2$. We have previously discussed how to estimate all of the other parameters involved in the above expressions.

Since $|\rho_{Y,Z|W}| \leqslant 1$, combinations of parameters that lead to values outside of this range are likely due to a non-Grammian covariance matrix and hence indicate impossible sets of values. In matrix terminology, a Grammian matrix is 'a symmetric square matrix whose eigenvalues are all greater than or equal to zero'.[§] To elaborate, covariance matrices should be positive definite. To understand why, consider the fact that there is a direct relationship between covariance matrices and correlation matrices. There are bounds on the elements of each. For instance, the diagonal elements of a covariance matrix represent the variance for each entry and hence must be positive. Similarly, the off-diagonal elements of a correlation matrix represent pairwise correlations and must lie between -1 and $+1$. Population covariance and/or correlation matrices which do not satisfy this property are impossible. Hence, this substantially reduces the plausible range for pairs of values of $\rho_{W,Z}$ and σ_Z^2, since pairs which do not lead to Grammian covariance matrices can be removed from further consideration.

[‡]Note that if additional covariates are available especially in longitudinal designs, it may be possible to place tighter boundaries around the possible values of $\rho_{W,Z}$ by using methods elaborated by Gadbury and Iyer [24].
[§]http://www.siu.edu/~epse1/pohlmann/factglos/

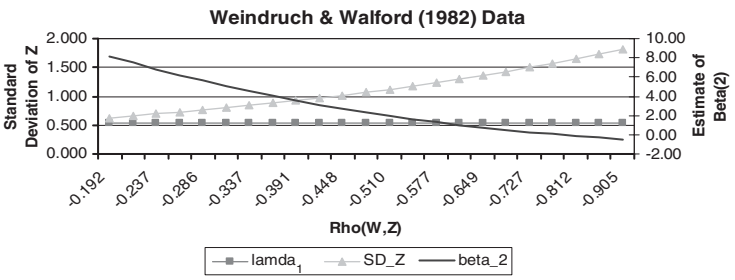

Figure 1. Estimates of the possible effects of IWL (β_2) on the lifespan (in months) of mice based on data from Reference [25].

5. AN EXAMPLE

We illustrate our approach with an example drawn from the field of rodent CR studies where animals are typically followed until all are dead and high quality control can be achieved [25]. This study involved two strains ($B10C3F_1$ and C57Bl/6J) of male mice studied to see the influence of CR started in early middle age on longevity and disease patterns. We herein consider the data obtained for the $B10C3F_1$ strain. In brief, 135 mice were fed *ad libitum* until 12 months of age at which point they were randomized, individually housed, and provided an intake of either an amount sufficient to maintain body weight (control—unintentional condition; $C = 160$ kcal/mouse/wk) or an intake of 90 kcal (restricted—intentional condition; R). To avoid malnutrition, the mice consumed a diet enriched in content of protein, vitamins and minerals so that the intakes of these dietary essentials were matched between groups. All animals were observed until death (i.e. there was no right censoring).

From the time of the last pre-randomization weight measurement (12 months of age) to 23 months of age, the R animals steadily lost weight, with a mean weight loss of 14.1 g (SD = 5.20). In contrast, C animals gained an average of 0.45 g (SD = 4.79). We regressed lifespan measured in months on weight change scaled in 5 g units (approximately 1 SD) and obtained estimates of λ_1 and β_1 equal to 0.546 and -2.144, respectively. Thus, as in humans, UWL was associated with reduced lifespan (i.e. each 5 g of UWL was estimated to decrease lifespan roughly 2.1 months) and IWL was associated with a small increase in lifespan (roughly 0.5 months/5 g). We tested models in which baseline weight (weight at month 12), the interaction of baseline weight with weight loss, and weight loss squared were included, but none were close to significant and were therefore dropped from the models. The sample variance of weight loss scaled in 5 g units for the two groups were

$$\hat{\sigma}^2_{V|1} = (5.20/5)^2 = 1.08 \quad \text{and} \quad \hat{\sigma}^2_{W} = (4.79/5)^2 = 0.92 \tag{15}$$

Using the four estimates obtained from these models and the estimation approach described above to examine pairs of values for $\rho_{W,Z}$ and σ^2_Z, we produced Figure 1.

As can be seen in Figure 1, the plausible effect of a 5 g IWL in these mice is -0.5–8 months. However, unless one posits that $\rho_{W,Z} < -0.60$, the estimate of β_2 remains larger than the estimate of λ_1. Using the partial correlation to check for non-Grammian covariance matrices eliminated many possible values. Specifically, this suggests that there almost has to be a negative correlation between the amounts of IWL versus UWL. Only four situations with

a positive correlation between IWL and UWL satisfied this check. However, these four values appear to be outliers since they suggest an implausible increase of 30 months in lifespan (a near doubling of lifespan) associated with IWL. To summarize, Figure 1 demonstrates that despite the modest increase in lifespan seen in CR animals in the intentional condition (i.e. approximately 0.5 months), the true effect of a 5 g IWL could be substantially larger and biologically quite meaningful. Moreover, although the range of estimates of β_2 is very large, as the value of $\rho_{W,Z}$ chosen decreases, the estimate of β_2 decreases, but the estimated variance of Z increases in a complementary fashion such that the overall impact of IWL may remain large when expressed in terms of a per cent variance metric.

6. POSSIBLE FUTURE EXTENSIONS

6.1. Utilizing the information in the intercepts

Given the assumptions and equations above, it can be shown that $\alpha_0 = \beta_0$, which implies:

$$\lambda_0 = \beta_0 + (\beta_1 - \lambda_1)\mu_W + (\beta_2 - \lambda_1)\mu_Z + \beta_3 \tag{16}$$

Thus, if we fit the regression equation

$$Y = \gamma_0 + \gamma_1 V + \gamma_2 X + \gamma_3 XV + e \tag{17}$$

it can be shown that

$$\begin{aligned}
\gamma_2 &= \lambda_0 - \alpha_0 \\
&= \beta_3 + (\beta_1 - \lambda_1)\mu_W + (\beta_2 - \lambda_1)\mu_Z \\
&= \beta_3 + \left(\beta_1 - \beta_2 - \frac{(\beta_1 - \beta_2)(\sigma_W^2 + \rho_{W,Z}\sigma_W\sigma_Z)}{\sigma_W^2 + \sigma_Z^2 + 2\rho_{W,Z}\sigma_W\sigma_Z}\right)\mu_W - \frac{(\beta_1 - \beta_2)(\sigma_W^2 + \rho_{W,Z}\sigma_W\sigma_Z)}{\sigma_W^2 + \sigma_Z^2 + 2\rho_{W,Z}\sigma_W\sigma_Z}\mu_Z \\
&= \beta_3 + (\beta_1 - \beta_2)\left[\mu_W - \left(\frac{\sigma_W^2 + \rho_{W,Z}\sigma_W\sigma_Z}{\sigma_W^2 + \sigma_Z^2 + 2\rho_{W,Z}\sigma_W\sigma_Z}\right)(\mu_W + \mu_Z)\right]
\end{aligned} \tag{18}$$

Hence, the coefficient γ_2 estimated for the effect of the intention to lose weight (either directly or through the behaviours subsequently enacted) *per se* (that is, after controlling for the effect of weight loss) when fitting the model $Y = \gamma_0 + \gamma_1 V + \gamma_2 X + \gamma_3 XV + e$ is not equivalent to the true effect of the intention to lose weight, β_3, but rather is β_3 plus a bias term that is, in part, a function of the mean and variance of UWL. This implies that the apparently beneficial effect of the mere intention to lose weight identified by Gregg *et al.* [16] may be due not so much to the intention to lose weight, but rather to differential effects of IWL and UWL and the presence of both among people who intend to lose weight.

6.2. Categorical and time-to-event data

Most studies of weight loss and mortality in human subjects do not follow all subjects until the time of death. Thus, data are typically analysed using either logistic regression, Cox

proportional hazards regression, or some other form of survival analysis. Therefore, in the future, it will be useful to extend this approach from ordinary least squares (OLS) regression to logistic or Cox regression. However, doing so may require assumptions about the distribution of the predictor variables involved whereas the OLS approach used herein involved only the first and second moments of the distributions and required no other assumptions for estimation, although OLS testing and confidence interval construction may require distribution assumptions or reliance on asymptotic properties.

Nevertheless, the formulae derived here may still be applicable to many cases. Although it is true that most human mortality studies do not follow all subjects until the time of death, as the 'age' of many large epidemiologic studies increases, there are beginning to be substantial data sets that have body weight and related variables and include a large proportion of subjects that are dead at present or will be so in the very near future. An illustrative listing of such studies is included in Table 1.

As these and similar studies with long histories progress, it may become appropriate to revert from Cox regression to OLS regression when studying effects on mortality in humans.

6.3. Including covariates

The formulae presented herein involved no covariates beyond those specified in equation (1). In most real studies of humans, multiple covariates such as age, sex, and smoking status are included. Thus, extending these models to allow for additional covariates would be useful. This could likely be achieved by utilizing R^2 values obtained from nested models. The parameters of interest would then be the effects of IWL and UWL after adjustment for all other covariates. This should be an important area of future research for extending these results.

6.4. Narrowing and defining the plausible range of β_2

As can be seen in Figure 1, the *possible* range of β_2 can be very large. The *plausible* range may be quite smaller. One way to narrow the range of plausible values is to narrow the plausible range $\rho_{W,Z}$. It may be possible to use the methods described by Gadbury and Iyer [24] to accomplish this, but that is a topic for future research. If the uncertainty of $\rho_{W,Z}$ can be reduced sufficiently, it would then be important to quantify the uncertainty in β_2 due to random sampling variability by deriving a standard error estimator for the estimate of β_2.

6.5. Relaxing the assumption of homogenous slopes and variances for effect of UWL

We acknowledge that our assumption that the slope and variance of the effect of UWL is the same for subjects who do and do not intend to lose weight may be unlikely. However, the assumption allows us to describe a method that attempts to examine the 'true' relationship between IWL and mortality. Moreover, it seems far more likely than the current alternative which is to assume that all weight change among people who profess an intention to lose weight is indeed intentional. Future research is needed to examine this relationship when the distribution of UWL differs according to intent.

Table I. Selected human studies of mortality and body weight.

Study name	Reference	Number of subjects born in or before 1913	Repeated measures of weight	Was intentionality measured?	Comments
Framingham Heart Study	[26]	>3000	Yes	No	Adults aged 28–62 at entry in 1948–1952. Biannual examinations. As of 1999, there were 993 surviving participants
Honolulu Heart Program Study	[27]	8006 men	Yes	No	American men of Japanese ancestry born in 1900–1919 and living on Oahu in 1965. Examined on 5 occasions through 1996
Seven Countries Study	[28]	~7000 men	Yes	No	Initiated in 1958, a cohort of 12 467 healthy men aged 40–59 from 7 countries (Finland, Italy, Greece, Japan, The Netherlands, United States, Yugoslavia) periodically followed
The Gothenburg Study	[29]	~3000	Yes	No	Four birth cohorts of 70 year olds born in 1901–1922 in Gothenburg, Sweden followed periodically from 1971–1992
Minnesota Heart Study (Twin Cities Prospective Study)	[30]	217 men	Yes	No	Men aged 45–55 at entry in 1948 were re-examined yearly to 1975 and followed up through 1983
Cancer Prevention Study I	[31]	>500 000	Self-reported	Yes, only at baseline	Approximately 1 million adults enrolled in 1959 and 1960. Eight follow-up questionnaires through 1972
Bangor Longitudinal Study of Ageing	[32]	597	Yes	No	Adults in rural Wales aged 65–99 in 1978. Re-examined 6 times and followed through 1999
Amherst College Study	[33]	~2500	No	No	Amherst College students in years 1861–1900. Height and weight at age 20 linked to mortality that covered a follow-up period extending to 1949
Terman's Lifecycle Study of children with high ability	[34]	1428	Yes	No	'Bright' children (IQ ~135) aged 10–12 residing in California at entry in 1921. Restudied at 5–10 year intervals for 70 years (through 1991)

7. DISCUSSION

The method developed herein has broad applicability. First, in humans, observational epidemiology studies are frequently used to assess associations between risk factors and outcomes. In the long run, consideration of changes in body composition, including body fat, may be more important than consideration of changes in body weight [3, 11, 35–39]. Perhaps most directly relevant is Reference [36] which provided evidence that the loss of body fat conditional on change in body weight was associated with reduced mortality rate, whereas loss of body weight conditional on change in body fat was associated with increased mortality rate. Following this, we have opined extensively that body composition rather than merely body weight should be examined in future studies and data collection that will allow such analyses are underway in several ongoing studies. However, at the present time, very few (if any) longitudinal studies have high-quality body composition measurements at multiple points in time on sufficiently large numbers of subjects to produce meaningful results with respect to mortality rate. For this reason, weight change will likely remain 'the coin of the realm' in this area of inquiry for the near future and, hence, we have chosen to focus on weight in this paper.

However, studies have been conducted that could examine the differential effects of intentional and unintentional body composition changes on other outcomes of interest (e.g. [40, 41]). Therefore, it is noteworthy that the method we have developed can be applied to examine the differential effects of intentional change in any variable (Z) versus unintentional change in that variable (W) on any other variable (Y), where only the combined change ($Z+W$) is actually observed. In fact, because our method is currently fully developed for situations in which Y is observed without censoring, it is well suited to situations as in Reference [40] or [41] in which body composition changes are examined for their putative effects on changes on other continuous variables that are measurable in the short-term such as cardiorespiratory fitness.

It might be tempting to think that this does not apply to randomized clinical trials (RCTs) and that, in fact, rather than modelling IWL as a latent variable, we should just conduct RCTs. It is, in part, because of the obvious need to clarify the knowledge regarding the relationship between IWL and mortality rate underlying these recommendations that the NIH invested in the LOOK AHEAD trial, an RCT of the effects of weight loss on hard endpoints [42]. It is well established that the ideal way to definitively eliminate confounders is to randomize subjects to levels of the independent variable under study. However, in practice, it is not possible to randomize people to different degrees of weight loss [11]. As Yanovski *et al.* [43] stated in a report of a working group that paved the way for the ongoing national LOOK AHEAD Trial, 'Subjects in an RCT could not be randomly assigned to lose or not lose weight; they could only be randomly assigned to receive or not receive interventions that might result in weight loss. These interventions, however, might well produce changes in health status that are not due to weight loss. Promotion and maintenance of weight loss through increased physical activity, reduced saturated fat intake, and consumption of large amounts of fruit and vegetables are examples of such interventions. It may appear that one could never infer that weight loss itself caused the changes in health status. However, if participants in an RCT were randomly assigned to several interventions that produce weight loss through different mechanisms and these interventions yielded similar improvements in health status, then the conclusion that weight loss was responsible for the improvements in health outcomes may be justified.'

The point of this quotation is clear. Although randomization is generally considered the *sin qua non* of the true experiment and potentially offers the strongest causal inferences of any available study design, the inferential validity of the RCT refers to the effects of the independent variable to which subjects are assigned [44]. Subjects can be assigned to treatments that produce, *on average*, particular degrees of weight loss but because: (a) the treatments themselves may have effects beyond the weight loss *per se* and; (b) within any one treatment condition, there will be uncontrolled variability in weight change, some of which may be due to unintentional factors, RCTs cannot be counted upon to yield unbiased estimates of the effect of IWL. This is not to be dismissive of the enormous value of RCTs in this area. Definitively testing whether treatments that produce weight loss have beneficial effects is important in and of itself. The point is that such RCTs will not fully address questions about the effects of IWL. Therefore, even in RCTs, the amounts of IWL are still unobservable and may be confounded to some extent. Appropriate statistical methods are needed for RCT's in which the effects of post-randomization weight change are estimated and the approach offered herein can be considered a first generation of such methods.

Finally, the method we propose can also, as we have shown, be applied to animal CR experiments. Animal experiments are usually randomized and are essentially just RCTs in model organisms. Thus, our comments about the applicability of our method to RCTs apply equally to animal studies.

As mentioned by Yang *et al*. [11], a more critical variable than whether weight loss is intentional or unintentional may be what more proximal factors produced the weight loss following an intention or lack thereof. People try to lose weight through a wide variety of methods [45], some of which, such as increasing cigarette smoking [46], may have profound deleterious effects on mortality rate. On the other hand, people may lose weight by adopting a more healthy lifestyle without having any intention of losing weight. These proximal causes of weight change may have independent effects on mortality rate and may also moderate the effects of the weight change they produce. Therefore, in addition to trying to separate the effects of IWL from UWL, future studies might benefit from modelling the putative main effects of the proximal causes of weight loss on mortality rate and the interactions of these proximal causes with subsequent weight change with respect to influencing mortality rate.

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