Accounting for Regression to the Mean and Natural Growth in Uncontrolled Weight Loss Studies

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Consider a study that enrolls children and adolescents ages 6 to 19 years in a study to investigate an intervention to reduce mean body mass index in $kg/m^2$ (BMI) during an observation period of, for example, 2 years.

The focus of this presentation is on the analysis and interpretation of uncontrolled weight loss studies where a condition for enrollment is weight elevated to a level of being overweight or obese.

In adults being overweight or obese is often defined as having BMI $\geq 30$ regardless of age or gender; however, in children and adolescents overweight or obese is often defined as having BMI that exceeds the 85th percentile for individuals in the U.S. with age and gender identical to the subject.

Let $Y_1$ and $Y_2$ respectively denote BMI for a subject at the beginning (BOS) and end of study (EOS). The intervention administered during the study is assessed by comparing the mean BMI at EOS against the mean BMI at BOS.

Even if there is no intervention effect, the mean BMI at EOS would be less than the mean BMI at BOS due to Regression to the Mean.

Ideally participants would be randomized to the intervention or a comparative control but a surprising number of studies are uncontrolled.
Regression to the Mean

1. Let $Y_1$ and $Y_2$ be bivariate normal random variables where
   
   $E(Y_1) = \mu_1$ and $E(Y_2) = \mu_2$
   
   $\text{Var}(Y_1) = \text{Var}(Y_2) = \sigma^2$ and $\text{Cov}(Y_1, Y_2) = \rho \sigma^2$

2. Consider the hypothesis
   
   $H_0: \mu_1 - \mu_2 = 0$

3. The paired $t$-test would be the test statistic of choice.
Regression to the Mean

To derive analytic data that are absent variations attributable to age and gender, we use CDC Growth Charts to find each subject’s gender and age-specific BMI percentile at BOS and at EOS (after their age increased at EOS).

All percentiles are then converted to z-scores using the standard normal distribution \(N(0,1)\) to determine the z-scores for each specific subject’s percentiles at BOS and EOS, respectively.

Note that the BOS and EOS z-scores are two subsets of z-scores that would be distributed as \(N(0,1)\) only if the corresponding subsets of percentiles are representative samples of gender and age-specific percentiles for the U.S. population.

Let \(X_1\) and \(X_2\) denote the resulting z-scores at BOS and EOS, respectively, and then standardize them to distributions with standard deviations =1 by the transformation 
\[Z_1 = \frac{X_1}{\delta}\] and \[Z_2 = \frac{X_2}{\delta}\] where \(\delta\) is the common standard deviation for \(X_1\) and \(X_2\).
Suppose subjects are enrolled in the study only if their $Z_1 \geq z_c$ where $z_c \geq 0$ is called the BMI $z$-score cut-point for determining study eligibility.

For example, suppose a requirement for enrollment in a study is $Z_1 \geq z_{85}$ where the cut-point $z_{85} = 1.036$ is the 85th percentile in the U.S. for a subject’s gender and age.

Thus, if the subject’s BMI exceeds the 85th percentile he/she is defined to be overweight or obese and eligible for study provided other conditions are also satisfied.
Regression to the Mean

Let $\theta$ denote the mean z-score at BOS, $\tau \leq 0$ the treatment effect and $\theta + \tau = \text{the mean z-score at EOS}$. Further, let $\rho_z$ denote the correlation of z-scores between BOS and EOS. Thus,

- $E(Z_1) = \theta$, $E(Z_2) = \theta + \tau$,
- $\text{Var}(Z_1) = \text{Var}(Z_2) = 1$ and $\text{Cov}(Z_1, Z_2) = \rho_z$

- $E(Z_1|Z_1 \geq z_c) = \theta + \frac{q(z_c)}{Q(z_c)}$ and $E(Z_2|Z_1 \geq z_c) = \theta + \tau + \rho_z \frac{q(z_c)}{Q(z_c)}$

- $q(z_c) = \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{z_c^2}{2}\right)$ and $Q(z_c) = \int_{z_c}^{\infty} q(u)du$
Regression to the Mean

\[ E(Z_2 - Z_1 | Z_1 \geq z_c) = \tau - (1 - \rho_z) \frac{q(z_c)}{Q(z_c)} \]

\[ RTM = - (1 - \rho_z) \frac{q(z_c)}{Q(z_c)} = \text{regression to the mean} \]

Let \( z_c = z_{0.85} = 1.036, q(1.036) = 0.2332, Q(1.036) = 0.15 \), then for \( \rho_z = 1, 0.8, 0.5, 0.2, 0 \): \[ RTM = 0, 0.311, 0.777, 1.244, 1.555 \]
Regression to the Mean

Proportion of Estimated Treatment Effect Due to Regression Toward the Mean

- $\tau=1, P_{80}$
- $\tau=1, P_{90}$
- $\tau=2, P_{80}$
- $\tau=2, P_{90}$

Correlation

Proportion
Concluding Remarks

- Regression to the mean is an important consideration in the interpretation of intervention in weight loss studies where subjects are selected from the upper end of weight distribution.
- Ideally the study design would be randomized control trial.
- If good estimates of the parameters of the underlying un-truncated distribution of pre-intervention weights (BMI) are available, good estimates of the effect weight loss intervention can be obtained even if a condition for study eligibility requires oe-intervention weight to be elevated.
- Normal growth during childhood can be accounted for by transforming weight (BMI) to gender and age-specific percentiles.
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