calerie

Application of the Marginal Structural Model to Account for Suboptimal Adherence in a Randomized Controlled Trial

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Giving flight to research

Outline

1. Introduction
2. The CALERIE Study
3. Marginal Structural Model
4. Constructing the Weights
5. Results
6. Conclusions

1. Introduction

Peduzzi *et al*. *Stat Med* 1993;12:1185-95:

- **"Per-protocol" analysis**
- **Reassign to control group from Day 0**
- **Censor at point of non-adherence**
- **Reassign to control at point of non-adherence.**

Biases and interpretational problems with each of these methods.

Purpose:

- **Provide a case study on applying a causal model to account for suboptimal adherence in an RCT.**
- **Provide details on implementing the model for a continuous confounding measure (adherence) using the Gaussian distribution.**
- **Contrast causal results against ITT results.**

The overall purpose of CALERIE was to test the hypothesis that …

- **two years of sustained CR**
- **involving a 25% reduction of energy intake (i.e., 25% CR)**
- **in healthy human beings**

… results in the same adaptive changes as seen in laboratory animals subjected to CR.

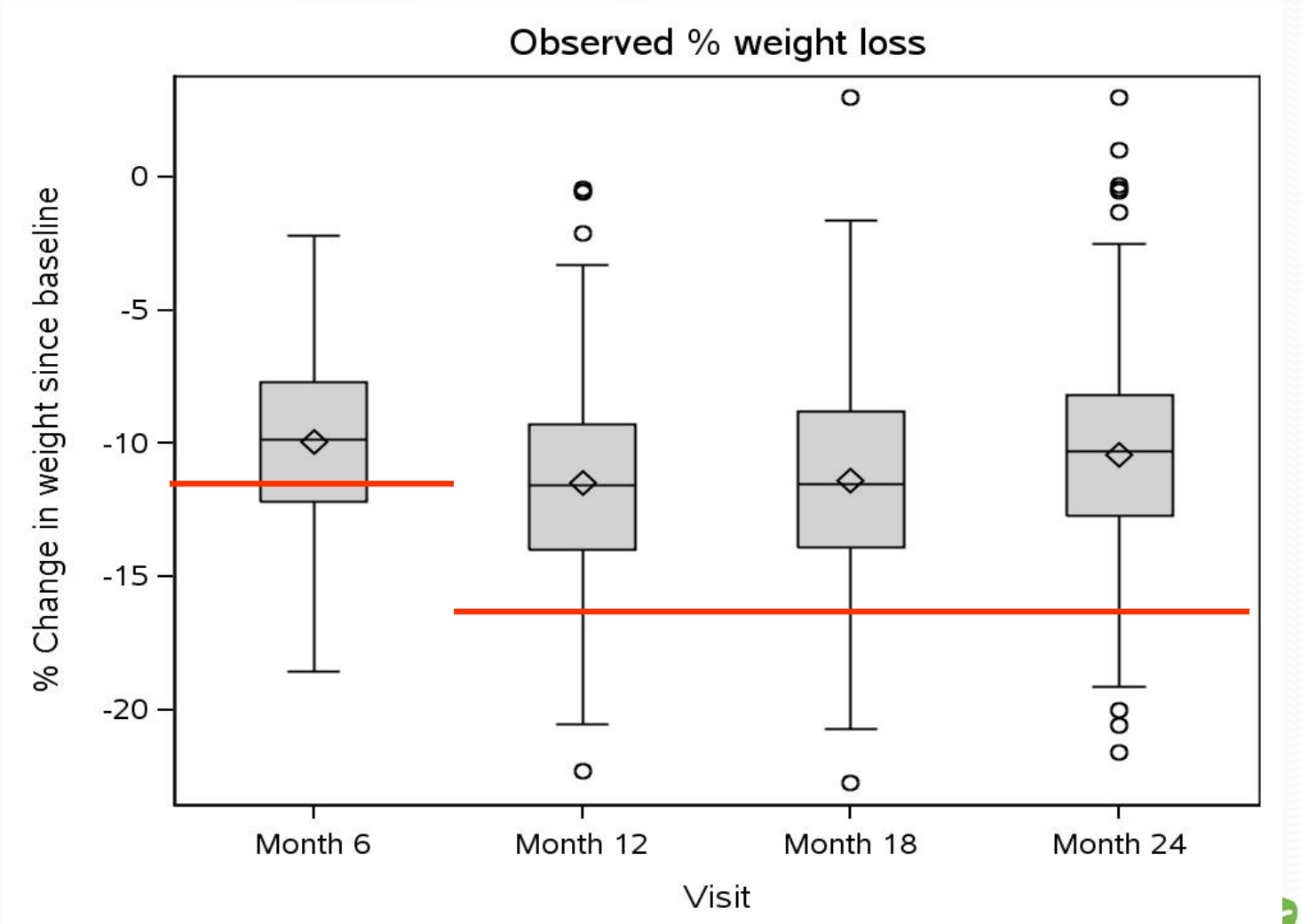
Primary Outcomes:

- **Resting metabolic rate (RMR)**
- **Core body temperature**

Design:

- Multi-center, parallel-group, RCT.
- 218 subjects randomized 2:1 to CR or control.
- Intervention over 24 months
- Evaluations every 6 months
- Targeted percent weight loss (%WL) profile:
  - 11% at M6
  - 15.5% at M12, M18 and M24

%WL Achieved:


Observed % weight loss
% Change in weight since baseline
0
-5
-10
-15
-20
Month 6
Month 12
Month 18
Month 24
Visit

3. Marginal Structural Model

1. **Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; 11:550-60.**

2. **Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology* 2000; 11:561-70.**

3. **Faries DE, Kadziola ZA. Analysis of longitudinal data using marginal structural models. In: Faries DE, Leon AC, Haro JM, *et al*. (eds). *Analysis of Observational Heath Care Data using SAS*. Cary, NC: SAS Institute, 2010, pp 211-30.**

Causal Modeling:

- MSM is based upon the theory of "counterfactuals."
- Inference is drawn under the assumption that, possibly contrary to fact, all participants had adhered to the intervention.
- MSM is implemented using a weighted GEE model.
- Weights are inversely proportional to the probability of the adherence profile.

4. Constructing the Weights

- **Ancillary regression model among the CR participants with %WL as the *y*-variable.**
- **Key assumption is sequential ignorability, i.e., no unmeasured confounders conditional on past %WL and covariate history.**
- **Start with a broad list of potential independent variables as *x*-variables.**
- **Stepwise regression using PROC GLM.**

Category	Variables
1. Demographic	• Age • Sex • BMI stratum • Race • Height • Ethnicity • Marital Status • Housing Situation • Education • Family Income
2. Baseline Covariates	
Self-Reported Nutrition Variables	• kcal / day • %fat • %protein • %carbohydrate
Physical Activity	• Total minutes of physical activity
Safety Markers	• BDI (marker of depression) • MAEDS subscales (markers of eating disorders)
3. Time-Dependent Covariates	
Self-Reported Nutrition Variables	• kcal / day • %fat • %protein • %carbohydrate
Physical Activity	• Total minutes of physical activity
Safety Markers	• BDI (marker of depression • Hemoglobin (marker of anemia) • MAEDS subscales (markers of eating disorders)
Intervention Variables	• Percent attendance at individual intervention sessions • Percent attendance at group intervention sessions

Method:

1. Pool all available observations across the 4 follow-up visits.
2. Design variables – Time and clinical site were forced into the model.
3. Age, sex and BMI stratum were forced into the model.
4. The lagged %WL value was forced into the model.

5. **Lagged value of the outcome was forced into the model.**
6. **For time-dependent covariates, include contemporaneous and lagged values.**
7. **All interactions with age, sex, BMI stratum and site.**
8. **All predictors significant at $\alpha = 0.05$ plus those forced into the model advanced.**
9. **If an interaction term was significant, then the corresponding main effects also advanced.**

Variable	p-value
Lagged %WL*	< 0.001
Lagged adjusted RMR*	0.52
Study Visit*	< 0.001
Study Site*	0.97
Age*	< 0.001
Age × Lagged %WL	0.02
Sex*	0.03
BMI Stratum*	0.04
BMI stratum × study site	< 0.001
BMI stratum × lagged adjusted RMR	0.003
BMI stratum × self-reported kcal – lagged	0.04
Others:	
Marital status	< 0.001
Housing situation‡	0.006
Self-reported kcal – lagged	0.06†
Pct calories from carbohydrates – contemporaneous	0.04
MAEDS Binge eating subscale – contemporaneous	< 0.001
MAEDS Binge eating subscale – lagged	0.02
Pct attendance at group intervention sessions	< 0.001

Constructing the Weights:

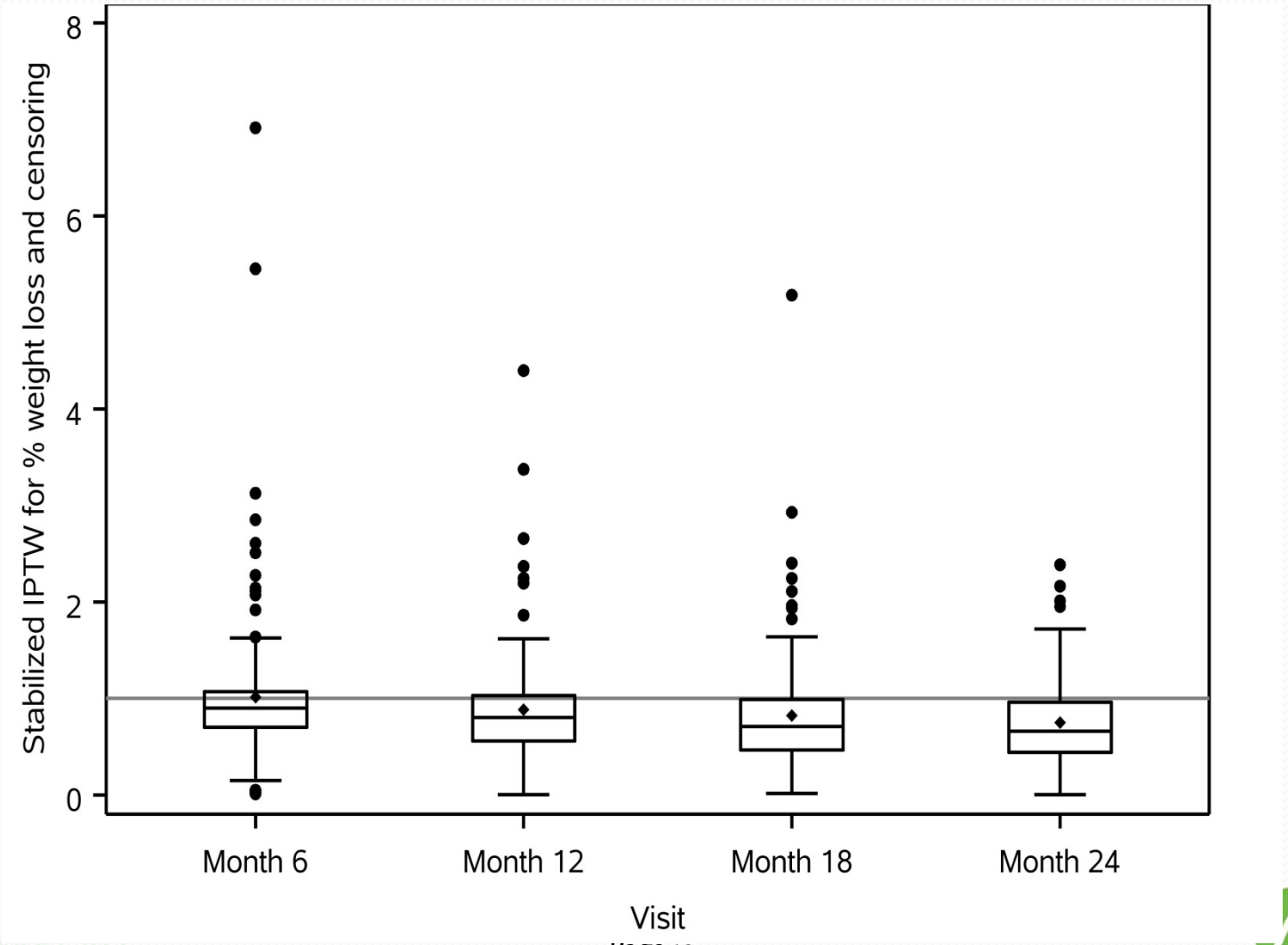
- **The probability of the observed %WL was derived from the Gaussian PDF.**
- **Mean was estimated by substituting the estimated regression parameters from the OLS regression.**
- **The residual variance was used as the estimate of σ^2.**

Lagged %WL:

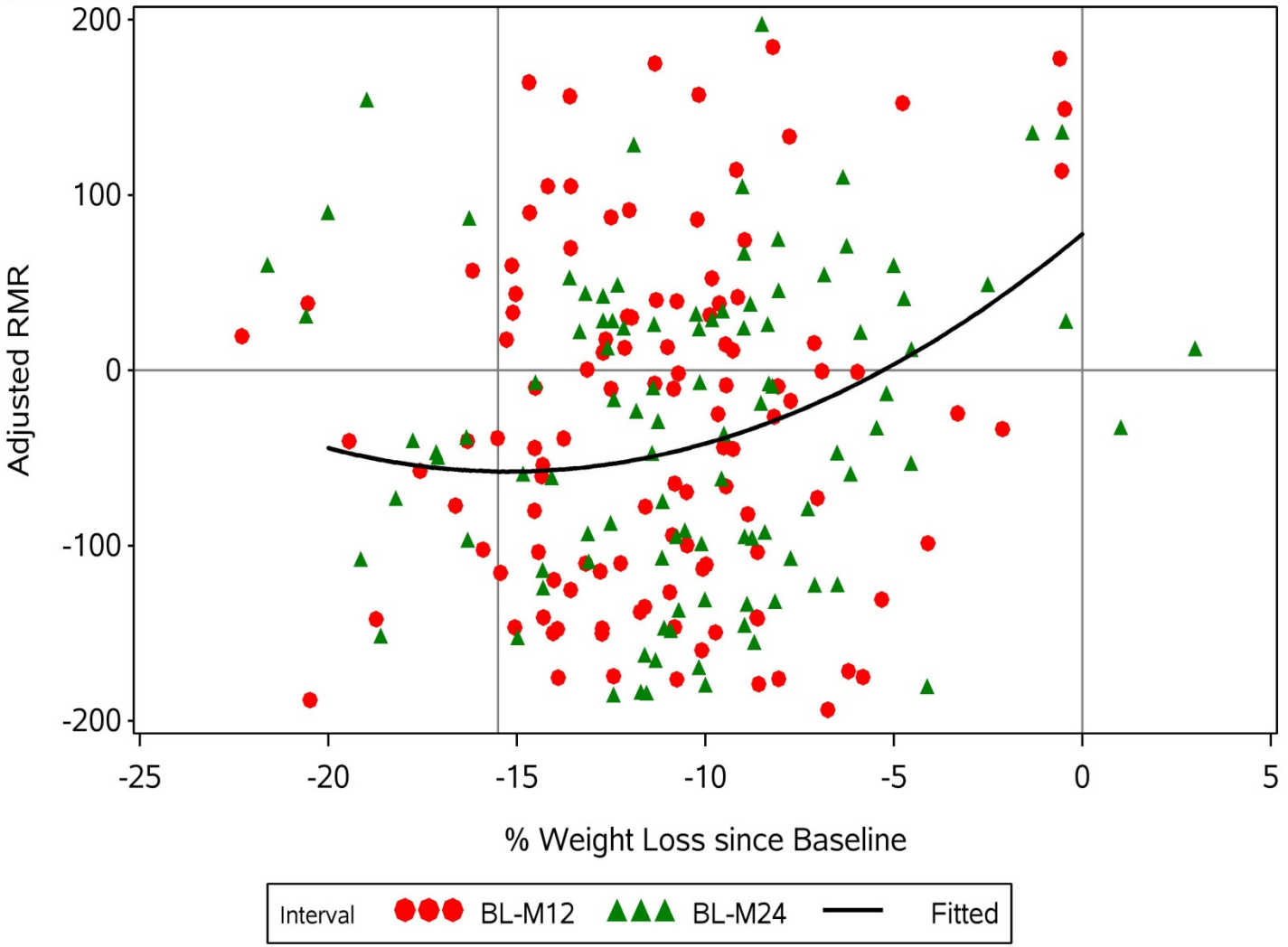
- **Because of the lagged %WL, probabilities are conditional given the previous %WL value.**
- **Cumulative product over a set of follow-up visits represents the joint probability of the %WL profile up to that visit.**
- **This is placed in the denominator for the participant- and time-specific weights.**

5. Results

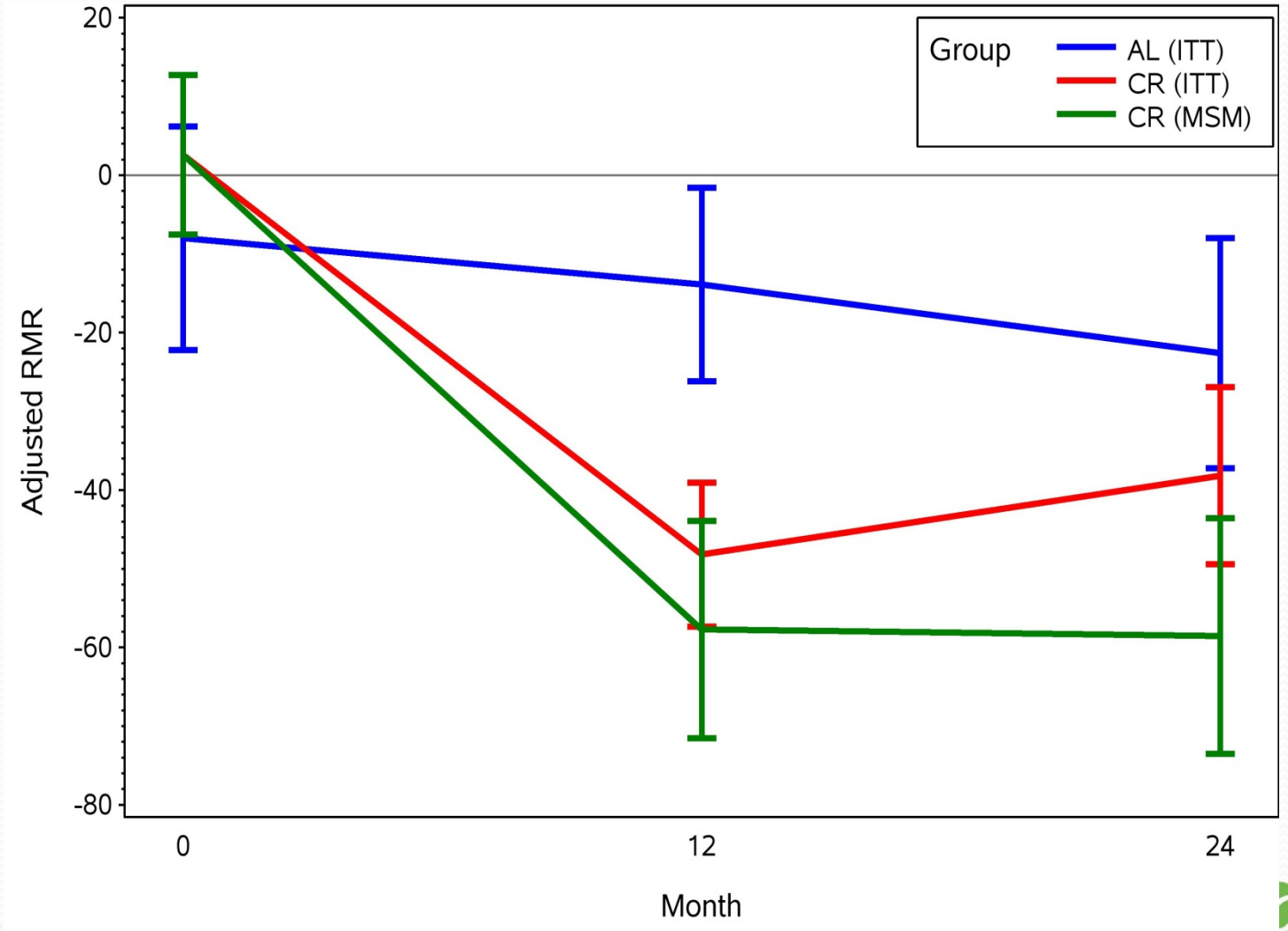
B&W Plots of the Stabilized Weights:



Relationship Between RMR and %WL:



Mean ± s.e. Adjusted RMR



6. Conclusions

- **MSM requires careful attention to detail and there are a number of extra steps.**
  - **Which variables to force into the model**
  - **How to construct interaction terms**
  - **How to address time-dependent covariates**
- **Despite this, the exercise is well worth the additional effort.**
- **Gave additional support to the metabolic adaptation theory of calorie restriction.**