Exploratory analysis: Determinants of body weight gain in New Zealand obese (NZO) mice: the role of initial body composition and time-dependent variables

General methods and statistics approach:

NZO/ /HlLtJ mice (n=23; all females, strain #:002105, JAX) were individually housed and fed High carbohydrate diet (HCD, D12450Ki, research diets) *ad libitum* under a 14 h light / 10 h dark schedule for ~12 weeks. We measured body composition longitudinally through the study and performed indirect calorimetry before and after 12 weeks with HCD.

Obesity is often attributed to a sustained increase in food intake (FI) and/or reduced total energy expenditure (TEE); but the relationship between additional dynamic variables including body weight (BW) and adiposity index (AI=fat/lean mass), that influence energy balance needs refinement to determine the best prediction model for BW gain. We aimed to determine which of these variables better predicted BW gain in mice. We hypothesized that changes in TEE is the best predictor of BW gain

We considered starting body composition values (starting BW, Fat mass, lean mass and AI) and FI values as well as the rate of change of these parameters to predict BW gain after 12 weeks with HCD. We fitted and compared four groups of models to identify the best predictors of BW gain (table 1) using: (1) all **S**tarting adiposity index and food intake **V**alues (**SV**), (2) the **R**ate **O**f **C**hange for all these **V**ariables (**ROCV**), (3) either **S**tarting or rate of change values for **S**ingle **V**ariables (**SSV**) and (4) **all** starting and rate of change values (**FULL**). To determine the model with the best predictive power, a repeated k-fold cross-validation (folds=5, repeats=100) method was used and the root mean square error (RMSE) was reported, while accounting for model complexity using the Akaike information criterion (AIC) and likelihood ratio test (LRT). We also use Mean Absolute Error (MAE) to represents the average magnitude of the errors made by each of our models when predicting BW change (Δbw).

Table 1. Models used to predict changes in BW over ~12 weeks with HCD in young female NZO/ /HlLtJ mice.

|  |  |  |
| --- | --- | --- |
| Model | group | # |
| Δbw ~ starting\_BW + starting\_FI + starting\_AI + starting\_fat + starting\_lean | SV | 1 |
| Δbw ~ ΔFI + Δ AI + Δ fat + Δ lean + Δ Total energy expenditure | ROCV | 2 |
| Δbw ~ starting\_BW | SSV | 3 |
| Δbw ~ starting\_FI | SSV | 4 |
| Δbw ~ starting\_AI | SSV | 5 |
| Δbw ~ starting\_fat | SSV | 6 |
| Δbw ~ starting\_lean | SSV | 7 |
| Δbw ~ ΔFI | SSV | 8 |
| Δbw ~ Δ AI | SSV | 9 |
| Δbw ~ Δ fat | SSV | 10 |
| Δbw ~ Δ lean | SSV | 11 |
| Δbw ~ Δ TEE | SSV | 12 |
| Δbw ~ starting\_BW + starting\_FI + starting\_AI+ starting\_fat + starting lean + ΔFI + Δ AI + Δ fat + Δ lean +Δ TEE | FULL | 13 |
| Δbw ~ null (means) | NULL | 14 |

Results:

Contrary to our hypothesis, the model including the ΔTEE (model #12) did not perform better than the null model (p=0.837, LRT, AICTEE=69.33, AICnull=68.24, data not shown). The model #2 (ROCV) showed the best fit (RMSE=0.42), followed by FULL (Model #13, RMSE=0.54), and performed better than the null model (p<.001, LRT, AICROCV=20.82) as showed figure 1. Also, starting AI (model #5) showed higher predictive power than model #12 (RMSE=0.58, AICAI=41.76) suggesting starting body composition is a better predictor than changes in TEE to predict Δbw in young female NZO mice.

The figure 1 showed the R squared, RMSE and MAE for each model. The R squared (also called the coefficient of determination) represents the proportion of the variance in Δbw that is predictable from the independent variables (our model predictors). The value can range from 0 to 1 in which 0 Indicates that the model explains none of the variability in Δbw and 1 Indicates that the model perfectly explains all the variability in the Δbw. Consequently, higher R squared suggests a better fit.  The model #2 has the highest R squared. This means that this model has the best fit, compared to the other models. The null model represents a baseline where we are predicting Δbw using only the mean. It's expected to have a very low R squared, as it doesn't consider any predictors. R squared should be interpreted in conjunction with other metrics, such as RMSE and MAE. Because #2 showed a low RMSE this indicates that, on average, the predictions from the model #2 are very close to the actual observed values of Δbw compared to the other models.  A low MAE indicates that, on average, the predictions from the model #2 are also very close to the actual observed values, regardless of whether the errors are model #2 reinforces the conclusion model #2 is the most accurate in predicting Δbw in our study. These results suggest that studies of obesity progression should apply an approach rooted in interindividual variation and dynamic change, rather than focusing solely on FI or TEE.

A graph with blue dots and white lines

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figure 1. R squared, RMSE and MAE for each model. The time course model (model #2 in table 1) showed the highest R squared and lowest RMSE and MAE suggesting this model is the most accurate in predicting Δbw after ~12 weeks with HCD in young female NZO mice.