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Changes in Trunk, but Not Limb, Lean Body Mass Contribute to Variability in Metabolic Adaptation Following Weight Loss

C. Martins | B. A. Gower | G. R. Hunter

Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, Alabama, USA

Correspondence: C. Martins (catia197@uab.edu)

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ABSTRACT

Background: Metabolic adaptation (MA) in response to weight loss is highly variable. Several methodological issues are likely to contribute to the large inter-individual variability in MA, namely the lack of adjustment for changes in the composition of fat-free mass.

Objective: The aim of this analysis was to investigate the contribution of changes in trunk versus limb lean body mass (LBM) to the variability in MA, at the level of resting metabolic rate (RMR).

Methods: 116 premenopausal women with overweight (body mass index (BMI): 28.2 ± 1.2 kg/m^2; age: 34.4 ± 6.4 years) enrolled in a weight loss program. Body weight/composition (dual energy x-ray absorptiometry), RMR (indirect calorimetry) and insulin sensitivity (S_I) (intravenous glucose tolerance test) were measured after 4 weeks of weight stability at baseline and after weight loss. Multiple linear regression was used to determine the contribution of changes in trunk versus limb LBM to MA variability, after adjusting for relevant confounders.

Results: A large variation in MA (−206 to +233 kcal/day) was found after an average of 12.1 ± 2.4 kg weight loss. After adjusting for RMR at baseline and changes in S_I, changes in trunk (but not limb) LBM were a significant contributor to MA variability.

Conclusion: In premenopausal women with overweight and loss of trunk, but not limbs, LBM contributes to MA variability, suggesting that loss of organ mass might be more important than loss of skeletal mass in modulating the magnitude of MA.

Trial Registration: ClinicalTrial.gov Identifier (JULIET study): NCT00067873, URL: https://clinicaltrials.gov/ct2/show/NCT0006787

1 | Introduction

It has previously been shown that metabolic adaptation (MA), an exaggerated reduction in energy expenditure (EE) following weight loss, contributes to resistance to weight loss [1, 2], despite its role in weight regain remaining controversial [3, 4]. Even though the existence or not of MA at the group level, as well as its clinical relevance, remains one of the most disputed issues in obesity research [5–7], studies consistently show a very large interindividual variability in MA following weight loss. Several methodological issues are likely to contribute to this variability in MA, namely the energy balance (EB) status of the

participants when measurements of body composition and EE are taken [3, 4], as well as lack of adjustment for changes in the composition of fat-free mass (FFM) [7].

FFM is a heterogeneous compartment, representing the sum of all major molecular components including protein, glycogen, water, minerals, and electrolytes. It is made primarily of skeletal muscle (SM), organs, and bone mass, each of which has specific metabolic rates [8]. Compared with the metabolic rate of SM (13 kcal/kg/day), the metabolic rate of the liver is 15-fold higher, the brain 18-fold higher, and the heart and kidneys 33-fold higher [8]. SM comprises 40%–50% of total body weight, but accounts for only 20%–30% of resting metabolic rate (RMR) in adults. On the other hand, even though collectively the liver, brain, heart, and kidneys contribute to less than 6% of total body weight, they account for around 60%–70% of RMR [8]. Knowledge on the proportional loss of SM and organ mass during weight loss might therefore be paramount, in determining the existence and magnitude of MA, as shown in a recent study, where adjusting for changes in the anatomical and molecular composition of FFM, decreased the magnitude of MA to values considered clinically irrelevant [7].

Most of the studies on MA use two- or three-compartment models of body composition, which divide the body into FM and FFM or FM, lean body mass (LBM) and bone mineral content (BMC), respectively. These approaches assume that the changes in FFM, or LBM, observed with weight loss represent an equally proportional loss of its components, meaning SM, the mass of all organs, and tissues in the body. However, that is not necessarily true. Very few studies have investigated how weight loss impacts different FFM compartments, and the findings are inconsistent, with some reporting a greater relative loss of organ mass, compared with SM [9], and others not [10, 11]. Differences in the weight loss interventions and selected populations may account for some of the divergent findings observed among studies. Given the lack of knowledge regarding the proportional loss of different FFM components with weight loss, these need to be measured pre and post intervention, to allow for an accurate estimation of MA. That requires sophisticated methods of body composition, namely computer tomography (CT) or magnetic resonance imaging (MRI), which are expensive and not readily available.

Approximately half of the reduction in REE that follows weight loss can be accounted for by reductions in organ and tissue mass (liver, SM, adipose tissue, kidney, and brain). The remainder is what should be considered the true MA, resulting from a lowering of organ-tissue mass-specific metabolic rates (*KI*) values [12]. Muller and colleagues showed in non-obese men, that MA can be accounted for by slowing of heart rate, reduction in glomerular filtration rate, increased liver metabolic rate and, although not significant in that study, a decrease in core temperature, which all together lower whole-body total EE (TEE) [13]. Accurate estimation of MA requires the measurement of the different FFM compartments pre and post intervention, with either CT or MRI, which is challenging. Dual energy x-ray absorptiometry (DXA) can be used to measure limb and trunk LBM, proxies of SM and organ mass, respectively [14, 15], offering the opportunity to study the contribution of these FFM compartments to MA. Therefore, the aim of this secondary analysis was to determine the contribution of changes in trunk versus limb LBM to the variability in MA, at the level of RMR, in response to weight loss in overweight premenopausal women.

2 | Materials and Methods

2.1 | Participants

Participants in this analysis were overweight premenopausal women, both European American (EA) and African American (AA). They were 20–41 years of age, performing no more than one time per week of regular exercise, had normal glucose tolerance (2–h glucose $\leq$ 140 mg/dL following 75 g oral dose), a family history of overweight/obesity in at least one first-degree relative, and no use of medications that affect body composition or metabolism. All women were nonsmokers and reported a regular menstrual cycle. The study included in this retrospective analysis was approved by the Institutional Review Board for Human Use at the University of Alabama at Birmingham (UAB). All women provided informed consent before participating in the study.

2.2 | Study Design

Participants included in this retrospective analysis come from the JULIET study, performed at the Department of Nutritional Sciences at UAB, aiming to identify metabolic predictors of weight regain. The main outcomes have previously been published [16–21]. Participants were randomly assigned to one of three groups: (1) Weight loss with diet alone; (2) Weight loss with diet + aerobic exercise training 3 times/week; or (3) Weight loss with diet + resistance exercise training 3 times/week. Of note, no significant differences in metabolic adaptation were seen between the groups. During weight loss, all participants were provided an 800-kcal diet until reaching a BMI < 25 kg/m^2. Food was provided (20%–22% fat, 20%–22% protein, and 56%–58% carbohydrate) by the General Clinical Research Center (GCRC) Kitchen. For detailed information about the JULIET study, see Hunter et al, 2008 [19].

Testing was done, after a 4-week weight stabilization period (aiming to maintain body weight within a 1% range), at baseline, and after weight loss. During the 4-week weight stabilization period, participants were weighed 3 times/week the first 2 weeks while eating their own food and weighed 5 times/week with food provided by GCRC the last 2 weeks. All testing was conducted in the follicular phase of the menstrual cycle during a 4-day GCRC in-patient stay (to ensure that physical activity and diet was standardized). Testing was done in a fasted state in the morning after spending the night in the GCRC.

2.3 | Data Collection

The following measurements were conducted after a 4-week weight stabilization period, both at baseline and after weight loss.

2.3.1 | Body Weight and Composition

Body composition (FM, and FFM [LBM + bone mineral content (BMC)]) was determined by iDXA (DPX-L; Lunar Corp, Madison, WI) with the use of software version 1.5 g (Lunar Corp). Both total and regional (limbs and trunk) LBM were measured. iDXA takes into consideration inter-individual variations in bone density and the fact that AA women generally have a greater bone mineral content (BMC) than do white women [22].

2.3.2 | Resting Energy Expenditure

Three consecutive mornings after an overnight stay in the GCRC and 12-h fast, RMR was measured immediately after awakening between 6 and 7 a.m. Subjects were not allowed to sleep and measurements were made in a quiet, softly lit, well-ventilated room. The temperature was maintained between 22°C and 24°C. Subjects were allowed to use a cover if desired. Measurements were made supine on a comfortable bed, with the head enclosed in a plexiglass canopy. After resting for 15 min, RMR was measured for 30 min with a computerized, open-circuit, indirect calorimetry system with a ventilated canopy (Delta Trac II; Sensor Medics, Yorba Linda, CA). The last 20 min of measurement was used for analysis. Oxygen uptake (VO_2) and carbon dioxide production (CO_2) were measured continuously, and values were averaged at 1-min intervals. The coefficient of variation for the repeat RMR was < 4%. The average of the 3 days of measured RMR are reported in this study.

2.3.3 | Insulin Sensitivity

Insulin sensitivity (S_I) was assessed with an intravenous glucose tolerance test and minimal modeling, as previously described [23]. Acute insulin response to glucose (AIRg) was calculated as the incremental insulin area-under-the-curve from minutes 0–10 following glucose injection using the trapezoidal method.

2.4 | Statistical Analysis

Statistical analysis was performed using SPSS version 22 (SPSS Inc., Chicago, IL), data presented as mean ± SD and statistical significance set at $p < 0.05$. Changes in body weight/composition and RMR overtime were assessed with a paired sample *t*-test. The presence of MA was tested by paired t-tests, comparing measured RMR (RMRm) and predicted RMR (RMRp) at the same time points. RMR was predicted from baseline data of 223 participants that started the study and had measurements of RMR, FM and FFM at baseline (114 EA), aged 34.3 ± 6. years and BMI 28.3 ± 1.4 kg/m^2.

$$\begin{aligned}\text{RMRp (kcal/day)} = {} & 591.297 - (1.940 \text{ x Age (years)}) \\ & - (96.903 * \text{ Race (0 AA, 1 EA)} \\ & + (3.302 \text{ x FM (kg)}) + (17.786 \text{ x FFM (kg)}).\end{aligned}$$

$$R^2 = 0.497;\ p < 0.001.$$

This small R^2 is due to the very narrow range of BMI and age of the participants, and the fact that all were women.

Regression analysis was performed to test if changes in trunk and limb LBM could explain the variability in MA after adjusting for group, baseline RMR, and changes in fasting insulin plasma concentration, AIRg, as well as S_I. Insulin dynamics were added to the model as both insulin secretion [13] and S_I [24] have previously been reported to modulate MA. However, as group, and changes in fasting insulin and AIRg were not associated with MA and the model got weaker, they were not included in the final models. The structure of the regression models was as follows:

A. MA (kcal/day) = Δ limb LBM + Δ trunk LBM
B. MA (kcal/day) = Baseline RMR + Δ limb LBM + Δ trunk LBM
C. MA (kcal/day) = Baseline RMR + Δ limb LBM + Δ trunk LBM + Δ S_I

There was no multicollinearity among the independent variables included in the models (variance inflation factor < 1.3).

3 | Results

Baseline characteristics of the study participants can be seen in Table 1. One hundred and sixteen women (62 EA) with an average BMI of 28.2 ± 1.2 kg/m^2 and an age of 34.4 ± 6.4 years were included in the present analysis. Average weight loss was −12.1 ± 2.4 kg (−15.6 ± 2.7%) and despite changes in limb and trunk LBM not being significant, there was a very large inter-individual variability (see Figure 1A and B).

RMRm was significantly lower than RMRp after weight loss (1297 ± 139 vs. 1327 ± 91 kcal/day, respectively, $p < 0.001$) resulting in a metabolic adaptation of −30.8 ± 95.8 kcal/day, ranging from −206 to 233 kcal/day (see Figure 1C). Metabolic adaptation was significantly associated with changes in S_I and

TABLE 1 | Anthropometrics and resting metabolic rate over time ($n = 116$).

	Baseline	After weight loss	*p* value
Weight (kg)	77.7 ± 7.4	65.6 ± 6.6	< 0.001
BMI (kg/m^2)	28.2 ± 1.2	23.9 ± 1.1	< 0.001
FM (kg)	33.8 ± 5.3	22.0 ± 4.6	< 0.001
FFM (kg)	43.9 ± 4.1	43.6 ± 4.1	0.031
Limb LBM (kg)	18.9 ± 2.1	18.8 ± 2.3	0.107
Trunk LBM (kg)	18.7 ± 2.2	18.8 ± 2.0	0.132
S_I (x10^{-4} min^{-1}/[μlU/mL])	2.83 ± 1.33	4.32 ± 1.87	< 0.001
RMRm (kcal/day)	1370 ± 129	1297 ± 139	< 0.001
RMRp (kcal/day)	1373 ± 95	1327 ± 91	< 0.001
RMRm-p (kcal/day)		*−31 ± 96****	

Note: Data shown as mean ± SD.
Abbreviations: FFM, fat-fRMR mass; FM, fat mass; LBM, lean body mass; RMR, resting metabolic rate; RMRm, RMR measured; RMRp, RMR predicted.
***$p < 0.001$ for the comparison between RMRm-p.

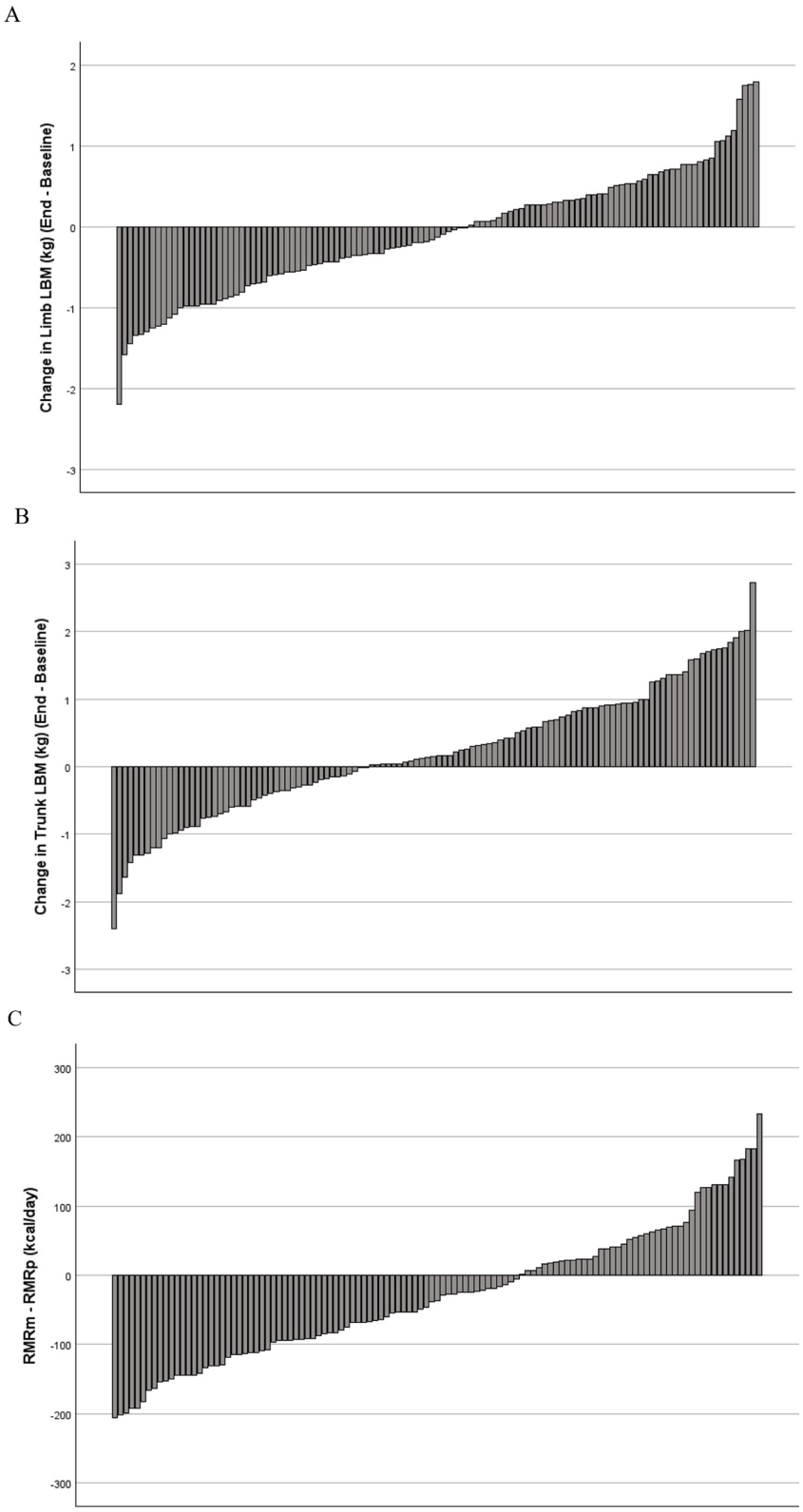

FIGURE 1 | Individual changes in limb (A) and trunk (B) lean body mass (LBM) over time, as well as differences between measured and predicted RMR (C). RMR, resting metabolic rate.

baseline RMR, but not with changes in trunk or limb LBM (see Table 2).

When only changes in trunk and limb LBM were included in a regression model, none was a predictor of MA and the model was not significant (Table 2, model A). Adding baseline RMR significantly improved the model and there was a trend for changes in trunk LBM to predict variability in MA (Table 2, model B). Adding changes in S_I further improved the model and changes in trunk, but not limb LBM, were significantly

associated with MA (see Table 3, model C). The lower the RMR at baseline, and the greater the improvement in S_I and the loss of trunk LBM with the weight loss intervention, the greater the MA at the level of RMR (see Figure 2).

4 | Discussion

The present secondary analysis aimed to investigate the contribution of changes in trunk versus limb LBM to variability in MA following weight loss. A very large interindividual variability in MA (defined as measured minus predicted RMR) was found in response to an average 12.1 ± 2.4 kg (15.6 ± 2.7%) weight loss in premenopausal women with overweight. Some women experienced a greater than predicted reduction in RMR of up to −206 kcal/day, while others experienced a smaller than expected reduction in RMR of up to +233 kcal. This represents a range of 441 kcal/day. Changes in trunk (but not limb) LBM were found to significantly contribute to MA variability, after adjusting for RMR at baseline and changes in S_I, suggesting that loss of organ mass might be more important than loss of SM in modulating the magnitude of MA. Interestingly, these results were seen independently of the method used to induce weight loss: diet alone, diet plus aerobic training, or diet plus resistance training, which increases the generalizability of the findings. However, it needs to be pointed out that despite being significant, the contribution of changes in trunk LBM to MA variability was relatively small, explaining only 3% of MA, a value similar to the contribution of changes in S_I. The main determinant of MA in the present model was baseline RMR, which alone explained 28% of the variability in MA.

Studies able to capture changes in body composition at the tissue and organ level with DXA show that RMR can be accurately predicted based on a 5-compartemnt model, which includes body weight, total FM, BMC, appendicular LBM, and head area [25, 26]. However, studies that have measured changes in organs and SM, concurrently with EE, during weight loss have produced inconsistent results regarding their contribution to RMR variability [27]. A study by Pourhassan and colleagues used a 4-compartment model and whole-body MRI to acquire detailed body composition data with weight loss and reported that changes in SM and kidney mass explained 35% and 5%, respectively, of the variability in RMR with weight loss [11]. Similarly, Martin et al. showed in a retrospective analysis of the CALERIE trial that a 11% weight loss achieved with calorie restriction resulted in a reduction in RMR of approximately 100 kcal/day, with 60% being accounted for by loss of FM, SM and organs and only 40% being attributed to MA [28]. On the other hand, and in line with the present findings, a previous study in postmenopausal women with overweight showed that RMR correlated better with trunk LBM, than with total-body or peripheral LBM, suggesting that changes in the visceral component of LBM might be more important than changes in SM mass in explaining inter-individual variation in RMR [29]. In another study in individuals with a BMI ranging from normal-weight to obesity, DXA trunk LBM was shown to be a

TABLE 2 | Correlations between metabolic adaptation and several variables of interest.

	Correlation coefficient (r)	*p* value
Baseline RMR (kcal/day)	0.525	< 0.001
Δ limb LBM (kg)	0.085	0.360
Δ trunk LBM (kg)	0.136	0.148
Δ S_I (x10^{-4} min^{-1}/[μlU/mL])	−0.189	0.041

Abbreviations: LBM, lean body mass; RMR, resting energy expenditure; SI, insulin sensitivity; *Δ*, calculated as post-intervention minus baseline.

TABLE 3 | Regression models for predicting metabolic adaptation after weight loss.

	Unstandardized *ß*	Standardized *ß*	R^2 adjusted	*p*
Model A			0.010	0.191
Intercept	−32.744			
Δ limb LBM (kg)	0.645	0.005		0.957
Δ trunk LBM (kg)	15.747	0.157		0.099
Model B			0.308	< 0.001
Intercept	−602.570			
Baseline RMR (kcal/day)	0.417	0.556		< 0.001
Δ limb LBM (kg)	2.394	0.019		0.826
Δ trunk LBM (kg)	16.375	0.160		0.061
Model C			0.340	< 0.001
Intercept	−574.953			
Baseline RMR (kcal/day)	0.408	0.548		< 0.001
Δ limb LBM (kg)	1.275	0.010		0.903
Δ trunk LBM (kg)	−21.291	−0.233		0.008
Δ S_I (x10^{-4} min^{-1}/[μlU/mL])	−11.275	−0.207		0.008

Abbreviations: LBM, lean body mass; RMR, resting energy expenditure; S_I, insulin sensitivity; *Δ*, calculated as post-intervention minus baseline.

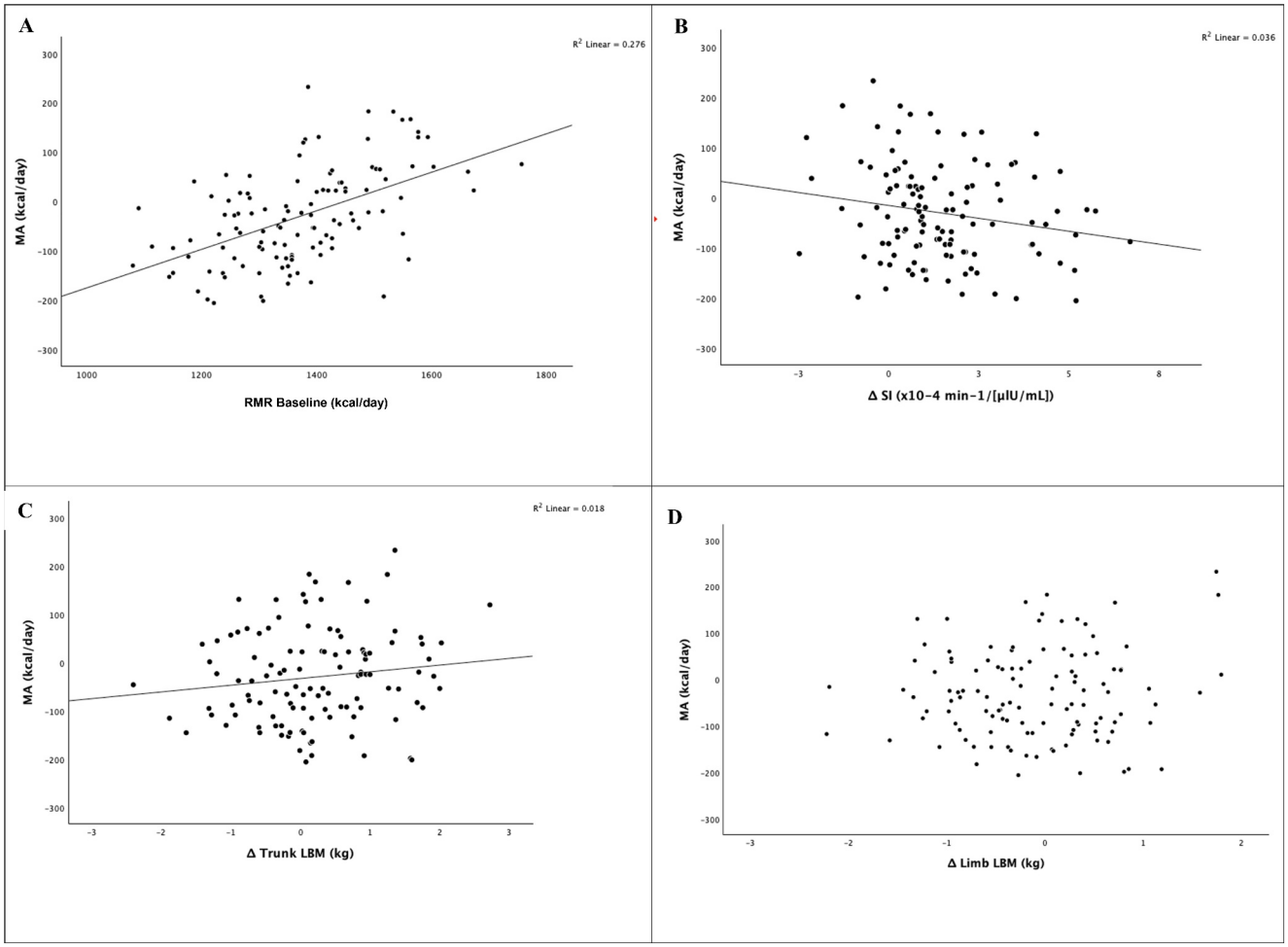

FIGURE 2 | Scatterplots for the association between metabolic adaptation (MA) after weight loss and baseline RMR (A), changes in S_I (B), trunk (C) and limb lean body mass (LBM) (D). RMR, resting metabolic rate; S_I, insulin sensitivity.

superior predictor of RMR compared to peripheral LBM [30]. Differences in the population (race, BMI, sex distribution), intervention (diet alone, diet + aerobic and diet + resistance training vs. diet alone), method used to measure body composition (DXA vs. MRI), and EB status of the participants when measurements of RMR and body composition were taken (after a 4-week weight stabilization period vs. uncontrolled) are likely to have contributed to the divergent findings. A significant reduction in organ mass with weight loss has been reported in females, but not in males [31], suggesting sex differences in the loss of organ mass versus SM. This might have contributed to the discordant findings between the present paper (with only women) and Pourhassan and colleagues, as well as the CALORIE trial (with men and women) [11, 28].

MA has been previously shown to be related to decreases in insulin secretion [13]. Additionally, S_I, measured both as HOMA, or hepatic S_I, has been reported to be associated with changes in RMR, independent of changes in body composition [24], suggesting that insulin dynamics might play a role in MA. In line with this, animal studies show that a reduction in insulin is associated with an increase in EE [32], suggesting a role for insulin in energy metabolism, even though evidence in humans is lacking. Improved S_I may also reduce EE, and increase MA, via decreased hepatic gluconeogenesis [33]. In the present study, changes in S_I, but not AIRg, or fasting insulin concentrations, contributed to the variability in MA seen with weight loss, with a greater improvement in S_I being associated with a greater degree of MA. Obesity is associated with an expansion of beta-cell mass, and an accompanying increase in insulin secretion [34]. Beta-cell mass remains expanded following short-term weight loss, resulting in a disproportionate amount of insulin secretion for the amount of body fat. This residual elevation of insulin could contribute to both weight regain and MA. In the current study, a greater increase in S_I was associated with a greater increase in MA. It is possible that the increase in S_I exacerbated the effect of the already high insulin secretion on EE in these post-obese women, explaining the independent effect of the change in S_I in predicting MA. Further research is needed to more closely examine the independent and interactive effects of insulin secretion and S_I on MA.

This study has several strengths. First, its controlled design, with body composition and RMR measured after a 4-week weight stabilization phase, with participants in EB. This is important, as EB has been shown to modulate the magnitude of MA [4]. Second, S_I, AIRg and RMR were measured using gold standard methods: IVGTT for S_I (and AIRg), and indirect calorimetry for RMR. However, this study also presents with some limitations. First, SM and organ mass were not measured,

which would require CT or MRI. Instead, limb and trunk LBM, measured with DXA were used as proxies of SM and organ mass, respectively. However, limb LBM measured using DXA has been shown to correspond reasonably well to SM measured by CT or MRI [14, 15]. Additionally, changes in trunk LBM are likely to reflect a decrease in organ mass, as it accounts for < 25% of total SM [35]. Nevertheless, future studies should investigate the contribution of organ versus SM mass loss, measured with CT or MRI, on the exaggerated reduction in RMR observed with weight loss. Finally, this study was limited to premenopausal women with overweight, which limits the generalizability of the results to other populations.

In conclusion, in overweight premenopausal women who lost weight through diet alone, or combined with aerobic or resistance training, loss of trunk, but not limb, LBM contributes to MA variability measured after a 4-week weight stabilization period, suggesting that loss of organ mass might be more important than loss of SM in modulating the magnitude of MA.

Author Contributions

GRH designed and conducted the study; CM performed the statistical analysis and had primary responsibility for final content; CM, GRH and BAG wrote the manuscript; and all authors: assisted with data interpretation and read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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