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Addendum: Hypercaloric diets with high meal frequency, but not increased meal size, increase intrahepatic triglycerides: a randomized controlled trial

Mireille J Serlie[1], **Kasper W ter Horst**[1], and **Andrew W Brown**[2]

Mireille J Serlie: m.j.serlie@amc.uva.nl; Kasper W ter Horst: k.w.terhorst@amc.uva.nl; Andrew W Brown: awbrown@uab.edu

[1]Department of Endocrinology & Metabolism, Academic Medical Centre Amsterdam, the Netherlands [2]Office of Energetics and Nutrition Obesity Research Center, University of Alabama at Birmingham, Birmingham, AL, USA

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To the Editor

One of us (MJS, on behalf of *the authors*) published an article entitled “Hypercaloric diets with high meal frequency, but not increased meal size, increase intrahepatic triglycerides: a randomized controlled trial” (1), which compared a ‘high-sugar’ (HS) vs ‘high-fat, high-sugar’ (HFHS) diet, and ‘meal frequency’ (F) vs ‘meal size’ (S) in a two-factor, randomized, controlled design. Another of us (AWB and colleagues, hereafter *the readers*) read the article with interest, but raised concerns about the analysis. This letter identifies clarifications that need to be made regarding those concerns.

First, there are differences in baseline values in Tables 1 and 3 in the article. These describe the same participants, and baseline values should have been identical. This is explained by the fact that Table 1 reflected data from participants with complete (meaning all study measurements) datasets only (corrected in Supplementary Table 1)..

Second, we would like to clarify the between-group outcome comparisons. In Tables 3 and 4, outcomes were expressed as changes from baseline within treatments. The readers were concerned that some results were potentially consistent with the ‘differences in nominal significance’ error. This can occur when within-group changes are compared instead of between-group differences, resulting in Type I error rates up to 87.5% for four groups(2). Conclusions such as “hypercaloric diets with increased meal frequency … increase IHTG and abdominal fat in lean men whereas similar diets with increased meal size do not,” describe within-group (rather than between-group) comparisons. The authors reanalyzed the data by two-way analysis of variance of change scores (post minus pre values; Table 1). The readers did not have access to the raw data, but both agree that the results presented below add detail to the originally reported results, and show a significant overall between-group effect for suppression of endogenous glucose production (EGP suppression), subcutaneous adipose tissue (SQAT), and intrahepatic triglyceride (IHTG) content. For EGP suppression and SQAT, the interaction effect with *post-hoc* between-group differences between HFHS-F and HFHS-S for EGP suppression shows a trend (Bonferroni corrected $p=0.07$) and is significant for SQAT (Bonferroni corrected $p<0.05$). Finally, for IHTG there is a significant main effect of S vs F ($p=0.028$), as previously reported (1).

These analyses confirm the original conclusion that a hypercaloric diet with high meal frequency compared to high meal size increased IHTG. However, the conclusions that "high meal frequency increased … abdominal fat" and "snacking … contributes to obesity" should have been phrased more cautiously as the interaction effect suggests that the effect on SQAT is dependent both on the HFHS/HS factor and the F/S factor and there are no significant between-group differences for other obesity-related variables (BMI, and intraabdominal or visceral adipose tissue).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

EGP	Endogenous Glucose Production
F	Meal Frequency
HS	High-Sugar
HFHS	High-Fat, High-Sugar
IHTG	Intrahepatic Triglycerides
S	Meal Size
SQAT	Subcutaneous Adipose Tissue

Table 1

Between-group analysis of variance

	HFHS-S		HFHS-F		HS-S		HS-F		p	p	p	p
	Delta	SD of delta	Delta	SD of delta	Delta	SD of delta	Delta	SD of delta	overall	S vs F	HFHS vs HS	Interaction
BMI (kg/m2)	0.6	0.6	0.8	0.5	0.8	0.3	0.5	0.6	0.502	0.655	0.705	0.165
REE (kcal/day)	47	152	37	88	185	99	-21	198	0.063	**0.048**	0.449	0.071
Glucose (mmol/l)	0.0	0.5	0.0	0.2	-0.1	0.3	0.1	0.3	0.790	0.453	0.902	0.540
Insulin (pmol/l)	7	21	5	12	12	11	-1	16	0.453	0.207	0.930	0.304
Cortisol (nmol/l)	-66	235	35	105	10	83	-74	167	0.454	0.881	0.783	0.122
Glucagon (ng/l)	-10	23	4	19	9	13	-8	25	0.284	0.849	0.645	0.059
Leptin (ng/ml)	0.8	1.0	1.7	1.7	0.9	0.8	1.4	2.0	0.596	0.196	0.834	0.751
Triglycerides (mmol/l)	0.1	0.5	0.3	0.2	0.2	0.3	0.2	0.4	0.793	0.488	0.948	0.485
FFA (mmol/l)	0.0	0.1	-0.1	0.2	-0.2	0.2	-0.2	0.3	0.280	0.278	0.148	0.485
EGP (umol/kg/min)	-0.1	1.4	0.2	1.2	0.0	1.1	0.4	1.0	0.886	0.461	0.789	0.955
EGP suppression (%)	6.2	10.4	**-9.4**†	**13.2**	-4.9	10.1	2.3	9.7	**0.046**	0.305	0.939	**0.009**
Rd (umol/kg/min)	-0.4	10.4	-0.2	7.8	-2.7	8.6	-2.3	5.3	0.906	0.930	0.467	0.976
FFA suppression (%)	0.0	9.5	-4.6	4.5	-5.4	9.0	-1.2	5.7	0.431	0.945	0.706	0.110
IAAT (l)	0.00	0.06	0.06	0.04	0.05	0.09	0.05	0.05	0.278	0.235	0.494	0.194
SQAT (l)	-0.02	0.05	**0.04** **	**0.03**	0.03	0.04	0.03	0.02	**0.027**	0.066	0.257	**0.035**
VAT (l)	0.02	0.03	0.02	0.03	0.02	0.06	0.02	0.03	1.000	0.985	0.912	0.985
IHTG content (%)	0.2	0.4	0.4	0.5	0.1	0.9	**1.6** *	1.7	**0.028**	**0.028**	0.132	0.087

† p=0.07 vs HFHS-S with Bonferroni correction for multiple testing.

** p<0.05 vs HFHS-S with Bonferroni correction for multiple testing.

* p=0.06 vs HS-S with Bonferroni correction for multiple testing.