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Supplemental information

**Circulating uridine dynamically and adaptively
regulates food intake in humans**

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Supplemental tables

Questionnaires and buffet composition

Table S1: Questionnaires

English translation of the prior activity questionnaire and the buffet questionnaire ; related to STAR Methods Methods details

	Study 1g	Study 0.5g
Prior activity questionnaire	<ul style="list-style-type: none"> - Which activities did you pursue yesterday? - How stressed did you feel yesterday? - Did you have breakfast, lunch, dinner yesterday? If yes, how big was your breakfast, lunch and dinner? - Did you have snacks in-between yesterday? If yes, how big were your snacks? - Did you eat anything after 10pm yesterday? - Did you do sports yesterday? - Did you drink alcohol yesterday? - How did you reach the testing site today (public transport, bike, car, walking)? 	<ul style="list-style-type: none"> - Did you have dinner yesterday? If yes, how big was your dinner? - Did you eat anything after dinner? If yes, how big was this meal? - Did you eat anything after midnight? If yes, how big was this meal? - Did you do sports yesterday? - Did you drink alcohol yesterday? - Was reaching the testing site physically exhausting for you?
Buffet questionnaire	<p>Measurement day 2 only</p> <p>For the buffet rating it was asked for:</p> <ul style="list-style-type: none"> - liking of the buffet - liking of the food - liking of the drinks - sufficient choice of different food items - food and drinks which were liked most - food and drinks which were disliked most <p>To indicate reasons for food intake, participants noted down the time point of food intake of both testing days and could choose from a list of answers for each time point. Possible answers included:</p> <ul style="list-style-type: none"> - Feeling hungry - Feeling appetite - Boredom 	<p>Measurement day 1</p> <ul style="list-style-type: none"> - Do you think you received UMP or placebo today? - What are your plans for tonight? - What did you do today during the testing period? <p>Measurement day 2</p> <ul style="list-style-type: none"> - Do you think you received UMP or placebo today? - What are your plans for tonight? - What did you do today during the testing period? - Did you notice/assume that we are measuring your food intake? - Do you think your evening plans on the first testing day affected

	<ul style="list-style-type: none"> - Urge to eat or habit of eating - Incentive values of the buffet - Emotional reasons for eating - Eating as reward - Further reasons, which the participant could note down 	<ul style="list-style-type: none"> - your food intake on the first testing day? - Do you think your evening plans on the second testing day affected your food intake on the second testing day?
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Table S2: Composition of the buffet (Study 1g)

Related to STAR Methods Methods details

Product number	Product name	Energy (kcal)	Fat (g)	Carbo-hydrates (g)	Sugar (g)	Protein (g)
1	Mayonnaise	713.0	78.0	2.2	2.1	1.0
2	Butter	745.0	82.0	1.0	1.0	0.6
3	Cream cheese	235.0	21.5	4.0	4.0	5.5
4	Boiled egg	153.4	11.0	0.6	0.5	13.0
5	Harz cheese	116.0	0.3	0.3	0.1	28.0
6	Turkey breast slices	110.0	2.0	1.0	1.0	22.0
7	Dates	360.0	3.9	68.8	2.2	9.8
8	Tomato ketchup	102.0	0.1	23.2	22.8	1.2
9	Jelly bears (packed)	343.0	0.5	77.0	46.0	6.9
10	Jelly bears	343.0	0.5	77.0	46.0	6.9
11	Liquorice wheel	317.0	0.7	74.0	47.0	3.0
12	Bread	254.0	3.7	45.0	3.9	8.5
13	Jam	245.0	0.2	58.0	54.0	0.5
14	Fitness bread	194.0	3.3	31.7	1.6	5.2
15	Pumpernickel	194.0	1.6	35.8	2.4	5.1
16	Rice cake	384.0	3.2	79.0	0.7	8.3
17	Fruchtzwerge	105.0	2.9	13.0	12.8	6.6
18	Rice pudding with cinnamon	109.0	2.4	18.5	12.7	3.2
19	Geramont cheese	356.0	32.0	0.5	0.5	17.0
20	Babybell cheese	302.0	24.0	0.1	0.1	21.5

Product number	Product name	Energy (kcal)	Fat (g)	Carbo-hydrates (g)	Sugar (g)	Protein (g)
21	Smoked salmon	180.0	11.0	0.5	0.5	21.0
22	Chicken meatballs	227.0	14.4	8.6	0.9	15.8
23	Pâté	378.0	36.0	1.5	1.0	12.0
24	Stickado Salami	522.0	44.2	2.0	1.0	29.0
25	Peanuts	622.0	50.0	14.0	5.4	25.0
26	Chocolate pudding	157.0	8.2	17.0	14.0	3.3
27	Bread roll with chocolate	416.0	22.0	46.0	13.0	7.0
28	Cake	435.0	20.0	57.0	32.0	5.3
29	Crisps	528.0	33.0	49.0	0.6	5.6
30	Kinder Schokolade (chocolate)	566.0	35.0	53.5	53.3	8.7
31	Hanuta mini (waffle with chocolate and nuts)	542.0	31.9	54.0	42.6	7.6
32	Raffaello	628.0	48.6	38.3	33.8	7.5
33	Nutella	547.0	31.8	56.9	55.9	6.6
34	Mars mini	443.0	15.7	70.9	61.9	3.9
35	Corny Milch classic (cereal bar)	444.0	19.1	59.3	29.2	5.8
36	Milchschnitte	422.0	27.9	34.0	29.5	8.0
37	Sandwich (Crispbread with cheese)	470.0	23.0	53.0	3.0	9.0
38	Muesli with chocolate	406.0	11.3	60.7	22.2	10.7
39	M&Ms	511.0	25.3	59.1	53.6	9.8
40	Carazza	377.0	22.0	33.0	9.1	11.0
41	Sandwich	264.0	12.0	28.0	1.5	9.3
42	Cucumber	12.0	0.1	1.7	1.7	0.6

Product number	Product name	Energy (kcal)	Fat (g)	Carbo-hydrates (g)	Sugar (g)	Protein (g)
43	Small tomatoes	18.0	0.2	3.9	2.6	0.9
44	Yoghurt, 1,5 % fat, 150 g	52.0	1.5	5.3	5.3	4.2
45	Apple Braeburn	50.0	0.2	11.6	11.0	0.0
46	Banana Chiquita	90.0	0.2	20.0	12.2	1.2
47	Green grapes	68.0	0.3	15.6	15.4	0.7
48	Cocoa, 200 ml	72.0	2.0	9.8	9.7	3.6
49	Gouda cheese in cubes	378.0	31.0	0.0	0.0	24.0
50	Fanta, 1 l	38.0	0.0	9.2	9.1	0.0
51	Smoothie Pineapple & Banana, 250 ml	65.0	0.7	13.0	12.0	0.6
52	Orange juice, 1 l	43.0	0.5	8.8	8.8	1.0
53	Milk, 1,5 %, 1 l	66.0	3.6	4.9	4.9	3.4
54	Apple juice, 1 l	44.0	0.5	10.4	9.9	1.0
55	Water					

Table S3: Content of the standardized breakfast (Study 0.5 g)
Related to STAR Methods Methods details

	Food item	Amount	kcal
1	Bread roll	1	176
2	Cheese (Gouda Holland, 48% Fett in Tr. Mittelalt)	1 slice (37 g)	146
3	Small tomatoes	3	10
4	Butter (Meggle)	8 g	62
5	Yoghurt (Almighurt)	1 x 125 g	143
6	Jam (Zentis)	1 x 25 g	61
7	Orange juice (Rewe Beste Wahl)	1 glass (200 ml)	88
		Total kcal:	686

Table S4: Composition of the buffet (Study 0.5 g)
Related to STAR Methods Methods details

	Food item	Amount	kcal/100g
1	Vegetarian ravioli (Ravioli, Maggi, Gemüse)	1600 g	82
2	Ravioli with meat filling (Ravioli, Maggi, in pikanter Soße)	1600 g	87
3	Rice pudding (Milchreis, Milram)	1 kg	107
4	Sour cherries (Schattenmorellen, Rewe Beste Wahl)	740 g	74
5	Sugar (ja! Raffinade-Zucker)	50 g	400
6	Cinnamon (Zimt, Ostman)	1 g	243

Statistical analyses and results

Circulating uridine promotes food intake by dynamically stimulating hunger

Table S5: Effect of uridine on hunger [1 g, placebo]

Related to Figure 2B

hunger ~ uridine + uridine:timepoint + (1|ID)

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
uridine	1	44.71	29.04	<0.001	0.38	***
uridine:timepoint	2	55.62	5.76	.005	0.14	**

ω^2 = partial omega squared

Table S6: Effect of uridine on food intake [1 g, placebo]

Related to Figure 2F

intake_kcal ~ uridine + uridine:timepoint + (1|ID)

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
uridine	1	46.22	8.46	0.006	0.13	**
uridine:timepoint	2	57.23	1.88	0.161	0.03	

Table S7: mediation analysis uridine → hunger → food intake [1 g, placebo]

Related to Figure 2G

Model mediator: *hunger* ~ *uridine* + (1|ID)

Model full: *food_intake* ~ *uridine* + *hunger* + (1|ID)

	<i>Estimate</i>	<i>95% CI lower</i>	<i>95% CI upper</i>	<i>p-value</i>	
ACME	50.9	16.0	92.2	0.002	**
ADE	36.6	-19.2	93.2	0.199	
Total	87.5	38.8	136.7	<0.001	***
Prop. Mediated	0.58	0.17	1.39	0.002	**

Note. ACME = average causal mediation effects, ADE = average direct effects, Total = total effect of uridine and hunger on food intake, Prop. Mediated = proportion mediated, CI = confidence interval

Table S8: Effect of hunger on food intake [1 g, placebo]
Related to Figure 2E

$intake_kcal \sim hunger + hunger:timepoint$

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
hunger	1	55.59	25.73	<0.001	0.30	***
hunger:timepoint	2	55.07	5.48	0.007	0.13	**

Table S9: Effect of uridine on satiety [1 g, placebo]
Related to Figure 2

$satiety \sim uridine + uridine:timepoint + (1|ID)$

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
uridine	1	44.89	31.45	<0.001	0.39	***
uridine:timepoint	2	55.75	7.35	.001	.018	***

Table S10: Effect of uridine on appetite [1 g, placebo]
Related to Figure 2

$appetite \sim uridine + uridine:timepoint + (1|ID)$

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
uridine	1	48.43	22.93	<0.001	0.30	***
uridine:timepoint	2	51.51	2.83	.068	0.06	+

Table S10a: Effect of basal uridine on total intake [1 g, placebo]
Related to Figure 2

$intake_{totalkcal} \sim uridine@t0 + sports$

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
uridine@t0	1	19	1.28	0.273	0.01	
sports	1	19	1.58	0.224	0.03	

Note. uridine@t0 = baseline fasted uridine levels; sports = if participants did sports the day prior to the testing day

Table S10b: Effect of basal uridine on total intake [0.5 g, placebo]
Related to Figure 2

$$intake_{total_{kcal}} \sim uridine@t0 + sports + dinner_size$$

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
uridine@t0	1	13	0.001	0.979	-0.06	
sports	1	13	1.637	0.223	0.04	
dinner_size	1	13	3.443	0.086	0.13	+

Note. uridine@t0 = baseline fasted uridine levels; sports = if participants did sports the day prior to the testing day; dinner_size = size of the dinner the evening prior to the testing day

Table S10c: Effect of body composition on basal uridine [1 g]
Related to Figure 2

$$uridine@t0 \sim fatfree_mass_{kg} + fat_mass\% + (1|ID)$$

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
Fatfree_mass_kg	1	16.292	2.315	0.147	0.07	
Fat_mass_%	1	16.292	0.730	0.405	-0.01	

Table S10d: Effect of body composition on basal uridine [0.5 g]
Related to Figure 2

$$uridine@t0 \sim fatfree_mass_{kg} + fat_mass\% + (1|ID)$$

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
Fatfree_mass_kg	1	11.351	0.380	0.550	-0.05	
Fat_mass_%	1	11.351	0.105	0.752	-0.07	

Food intake downregulates serum uridine and hunger

Table S11: Effect of caloric intake on hunger [1 g, placebo]
Related to Figure 2I

$$\Delta hunger \sim ingested_calories + ingested_calories:timepoint + (1|ID)$$

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
ingested_calories	1	59.97	54.35	<0.001	0.46	***
Ingested_calories:timepoint	2	59.95	8.79	<0.001	0.20	***

Table S12: Effect of caloric intake on uridine levels [1 g, placebo]

Related to Figure 2H

$$\Delta\text{uridine} \sim \text{ingested_calories} + \text{ingested_calories:timepoint} + \text{sports} + (1|ID)$$

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
ingested_calories	1	37.73	19.29	<0.001	0.32	***
ingested_calories:timepoint	1	35.85	16.24	<0.001	0.13	***
sports	1	18.23	4.10	0.058	0.29	+

Table S13: Effect of uridine change on hunger change [1 g, placebo]

Related to Figure 2I

$$\Delta\text{hunger} \sim \Delta\text{uridine} + \Delta\text{uridine:timepoint} + (1|ID)$$

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
$\Delta\text{uridine}$	1	36.39	18.36	<0.001	0.31	***
$\Delta\text{uridine:timepoint}$	1	34.43	10.02	0.003	0.20	**

Table S14: mediation analysis ingested calories → uridine drop → hunger change [1 g, placebo]

Related to Figure 2K

$$\text{Model mediator: } \Delta\text{uridine} \sim \text{ingested_calories} + (1|ID)$$

$$\text{Model full: } \Delta\text{hunger} \sim \Delta\text{uridine} + \text{ingested_calories} + (1|ID)$$

	<i>Estimate</i>	<i>95% CI lower</i>	<i>95% CI upper</i>	<i>p-value</i>	
ACME	-.0002	-.00008	0	.034	*
ADE	-.0004	-.0006	0	<0.001	***
Total	-.0005	-.0007	0	<0.001	***
Prop. Mediated	0.17	.001	0.41	0.034	*

Note. ACME = average causal mediation effects, ADE = average direct effects, Total = total effect of uridine and hunger on food intake, Prop. Mediated = proportion mediated, CI = confidence interval

Table S15: Effect of uridine change on satiety change [1 g, placebo]
 Related to Figure 2

$$\Delta \text{satiety} \sim \Delta \text{uridine} + \Delta \text{uridine:timepoint} + (1|ID)$$

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
<i>Uridine</i>	1	38,95	28,28	<0.001	0.40	***
<i>Uridine:timepoint</i>	1	36,95	9.99	0.003	0.19	**

Table S16: Effect of uridine change on appetite change [1 g, placebo]
 Related to Figure 2

$$\Delta \text{appetite} \sim \Delta \text{uridine} + \Delta \text{uridine:timepoint} + (1|ID)$$

<i>regressor</i>	<i>numDF</i>	<i>denDF</i>	<i>F</i>	<i>p-value</i>	ω^2	
<i>Uridine</i>	1	40.96	13.09	<0.001	0.22	***
<i>Uridine:timepoint</i>	1	40.47	5.67	0.022	0.10	*

Oral UMP increases circulating uridine, potentiates hunger and food intake

Table S17: Effect of 0.5 g oral UMP supplementation on uridine levels [0.5 g]
 Related to Figure 3A

0.5g of oral UMP were administered and blood uridine levels were measured at baseline, after 2 hours and after 3.5hours.

$$\text{uridine} \sim \text{intervention} * \text{timepoint} + \text{intervention} \\
: (\text{fatfree_mass}_{kg} + \text{fat_mass}_{kg} + \text{sex}) + (1|ID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
intervention	1	78.04	0.519	0.473	-6.04e-03	
timepoint	2	78.04	39.77	<0.001	0.49	***
intervention:timepoint	2	78.04	13.48	<0.001	0.24	***
intervention:fatfree_mass_kg	2	17.24	0.72	0.499	-0.03	
intervention:fat_mass_kg	2	17.24	0.70	0.510	-0.03	
intervention:gender	2	17.24	1.45	0.261	0.04	

Table S18: Effect of UMP supplementation on uridine levels, post-hoc [0.5 g]
Related to Figure 3A

The posthoc-test revealed that uridine concentrations are significantly higher under 0.5 g UMP treatment after 2 and 3.5 hours.

	<i>Estimate</i>	<i>Std. error</i>	<i>t</i>	<i>p-value</i>	
U@t0 – P@t0	0.117	0.26	0.444	0.658	
U@t+2 – P@t+2	2.036	0.26	7.760	<0.001	***
U@t+3.5 – P@t+3.5	1.113	0.26	4.237	<0.001	***

Note. Std. error = Standard error, P= placebo U = treatment with UMP, @t0 = initial timepoint, @t+2 = after 2 hours, @t+3.5 = after 3.5 hours.

Table S19: Effect of UMP supplementation on hunger ratings [0.5 g]
Related to Figure 3C-D

Initial hunger ratings were subtracted from the average hunger ratings during the buffet.

$$hunger@buffet - hunger@t0 \sim intervention * fatfree_mass_{kg} + sport + alcohol + (1|ID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
intervention	1	14.96	5.21	0.038	0.20	*
intervention:fatfree_mass_kg	1	15.19	5.44	0.034	-0.03	*
fatfree_mass_kg	1	12.48	0.58	0.459	0.02	
sport	1	25.13	1.65	0.211	0.18	
alcohol	1	21.21	6.18	0.021	0.21	*

Note. sport = if the participant did sports the day prior to the testing day, alcohol = if the participant drank alcohol the day prior to the testing day

Table S20: Effect of UMP supplementation on caloric intake [0.5 g]
Related to Figure 3E-F

$$intake_{kcal} \sim intervention * fatfree_mass_{kg} + fatmass_{kg} + dinner_size + sport + evening_food + (1|ID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
intervention	1	16.22	4.04	0.061	0.14	+
intervention:fatfree_mass_kg	1	15.94	5.53	0.032	0.68	*
Fatfree mass_kg	1	13.17	32.94	<0.001	0.38	***
fatmass_kg	1	13.62	10.75	0.006	0.19	**
dinner_size	1	25.89	7.71	0.010	0.22	*
sport	1	25.19	8.62	0.007	0.17	**

evening_food	1	25.51	6.55	0.017	0.20	*
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Note. Dinner_size = size of the dinner the evening prior to the testing day, sport = if the participant did sports the day prior to the testing day, evening_food = if the participant had food after dinner the evening prior to the testing day

A single-dose of oral UMP does not alter markers of the post-ingestive metabolic response

Table S21: Effect of adiposity on fasting HOMA-IR [0.5g]

Related to Figure 4A

$$HOMA-IR \sim intervention * fatmass_pc + (1|subjectID)$$

	numDF	denDF	F-value	p-value	ω^2	
intervention	1	15	4.69	0.047	0.18	*
fat_mass_pc	1	15	0.01	0.964	-0.06	
intervention:fat_mass_pc	1	15	1.58	0.228	0.03	

Table S22: Effect of UMP intervention on serum insulin levels [0.5g]

Related to Figure 4B

$$Insulin \sim intervention * timepoint + (1|ID)$$

	numDF	denDF	F-value	p-value	ω^2	
timepoint	2	80	42.0	<0.001	0.5	***
intervention	1	80	0.09	0.753	-0.01	
intervention:timepoint	2	80	0.46	0.633	-0.01	
t-contrast						
			t-value	p-value		
Timepoint 0h vs. 2h			-8.65	<0.001		***
Timepoint 0h vs. 3.5h			-1.69	0.256		
Timepoint 2h vs. 3.5h			6.96	<0.001		***

Table S23: Effect of UMP intervention on serum glucose levels [0.5g]

Related to Figure 4D

$$Glucose \sim intervention * timepoint + (1|ID)$$

	numDF	denDF	F-value	p-value	ω^2	
timepoint	2	80	12.5	<0.001	0.22	***
intervention	1	80	1.1241	0.292	<0.01	
intervention:timepoint	2	80	1.8129	0.170	0.02	
t-contrast						
			t-value	p-value		

Timepoint 0h vs. 2h			4.91	<0.001		***
Timepoint 0h vs. 3.5h			1.64	0.281		
Timepoint 2h vs. 3.5h			-3.27	0.005		**

Table S24: Effect of adiposity on (log-) fasting leptin [0.5g]

Related to Figure 4D

$$\log(\text{leptin}) \sim \text{intervention} * \text{fatmass_pc} + (1|\text{subjectID})$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
fat_mass_pc	1	15	127.77	<0.001	0.88	***
intervention	1	15	1.16	0.298	<0.01	
intervention:fat_mass_pc	1	15	0.94	0.348	<0.01	

Table S25: Effect of (log-) fasting leptin on total food intake [0.5g]

Related to Figure 4E

$$\text{total intake}_{kcal} \sim \text{intervention} * \log(\text{leptin}) + (1|\text{subjectID})$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
log(leptin)	1	16.9	25.65	<0.001	0.58	***
intervention	1	14.9	0.04	0.848	-0.06	
intervention: log(leptin)	1	15.1	0.87	0.366	<0.01	

Table S26: Effect of UMP intervention on (log-) serum leptin levels [0.5g]

Related to Figure 4F

$$\log(\text{leptin}) \sim \text{intervention} * \text{timepoint} + (1|ID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
timepoint	2	80	5.70	0.005	0.10	**
intervention	1	80	0.58	0.447	<0.001	
intervention:timepoint	2	80	1.53	0.590	-0.01	
t-contrast						
			<i>t-value</i>	<i>p-value</i>		
Timepoint 0h vs. 2h			3.36	0.004		**
Timepoint 0h vs. 3.5h			1.97	0.150		
Timepoint 2h vs. 3.5h			-1.40	0.420		

Table S27: Effect of UMP intervention on serum amino acids levels [0.5g]
 Related to Figure 4G

$$\text{amino acid} \sim \text{intervention} * \text{timepoint} + (1|ID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	<i>Bonferroni corrected p-value</i>	²	
Alanine							
timepoint	2	2.89E+07	7.62	<0.001	0.010	<0.001	*
intervention	1	3.48E+07	1.88	0.170	3.399	<0.001	
intervention:timepoint	2	2.89E+07	2.00	0.136	2.715	<0.001	
t-contrast							
			<i>t-value</i>	<i>p-value</i>			
Timepoint 0h vs. 2h			-3.87	<0.001			***
Timepoint 0h vs. 3.5h			2.44	0.044			*
Arginine							
timepoint	2	3.69E+07	2.23	0.107	2.144	<0.001	
intervention	1	4.45E+07	3.30	0.069	1.387	<0.001	
intervention:timepoint	2	3.69E+07	1.63	0.196	3.920	<0.001	
Asparagine							
timepoint	2	1.25E+07	6.87	0.001	0.021	<0.001	*
intervention	1	1.51E+07	3.02	0.082	1.647	<0.001	
intervention:timepoint	2	1.25E+07	0.88	0.417	8.332	<0.001	
t-contrast							
			<i>t-value</i>	<i>p-value</i>			
Timepoint 0h vs. 2h			-3.59	0.001			**
Timepoint 0h vs. 3.5h			2.63	0.025			*
Aspartic Acid							
timepoint	2	78.997	2.04	0.136	2.723	0.02	
intervention	1	79	0.64	0.427	8.545	-4.50E-03	
intervention:timepoint	2	78.997	0.70	0.498	9.962	-7.29E-03	
Cysteine							
timepoint	2	79.109	0.85	0.430	8.610	-3.62E-03	
intervention	1	79.109	3.01	0.087	1.734	0.02	
intervention:timepoint	2	79.109	0.48	0.621	12.419	-0.01	
Glutamic Acid							
timepoint	2	1.72E+08	0.01	0.990	19.789	<0.001	
intervention	1	2.07E+08	0.48	0.487	9.745	<0.001	
intervention:timepoint	2	1.72E+08	0.20	0.819	16.382	<0.001	
Glutamine							
timepoint	2	3.28E+07	1.95	0.142	2.841	<0.001	
intervention	1	3.95E+07	3.12	0.077	1.542	<0.001	.
intervention:timepoint	2	3.28E+07	0.81	0.443	8.863	<0.001	

Glycine							
timepoint	2	79.131	0.60	0.549	10.975	-9.72E-03	
intervention	1	79.132	3.33	0.072	1.438	0.03	
intervention:timepoint	2	79.131	1.11	0.335	6.703	2.63E-03	
Histidine							
timepoint	2	2.28E+07	2.17	0.114	2.288	<0.001	
intervention	1	2.74E+07	1.73	0.187	3.756	<0.001	
intervention:timepoint	2	2.28E+07	1.10	0.331	6.639	<0.001	
Isoleucine							
timepoint	2	3.51E+07	4.43	0.011	0.238	<0.001	
intervention	1	4.23E+07	1.12	0.290	5.810	<0.001	
intervention:timepoint	2	3.51E+07	1.55	0.212	4.236	<0.001	
Leucine							
timepoint	2	3.24E+07	4.46	0.012	0.232	<0.001	
intervention	1	3.90E+07	1.38	0.240	4.797	<0.001	
intervention:timepoint	2	3.24E+07	1.54	0.213	4.255	<0.001	
Lysine							
timepoint	2	2.00E+07	4.21	0.015	0.297	<0.001	
intervention	1	2.42E+07	0.99	0.320	6.396	<0.001	
intervention:timepoint	2	2.00E+07	1.72	0.180	3.591	<0.001	
Methionine							
timepoint	2	1.36E+07	5.06	0.006	0.127	<0.001	
intervention	1	1.64E+07	4.00	0.045	0.908	<0.001	
intervention:timepoint	2	1.36E+07	1.86	0.155	3.102	<0.001	
Phenylalanine							
timepoint	2	1.43E+07	4.39	0.012	0.247	<0.001	
intervention	1	1.73E+07	2.22	0.136	2.722	<0.001	
intervention:timepoint	2	1.43E+07	1.30	0.272	5.442	<0.001	
Proline							
timepoint	2	1.62E+07	14.09	<0.001	<0.001	<0.001	***
intervention	1	1.95E+07	4.97	0.026	0.515	<0.001	
intervention:timepoint	2	1.62E+07	1.59	0.204	4.074	<0.001	
				t-contrast			
			<i>t-value</i>	<i>p-value</i>			
Timepoint 0h vs. 2h			-5.25	<0.001			
Timepoint 0h vs. 3.5h			-3.28	0.003			
Serine							
timepoint	2	2.20E+07	2.27	0.103	2.068	<0.001	
intervention	1	2.65E+07	5.42	0.020	0.399	<0.001	
intervention:timepoint	2	2.20E+07	1.11	0.328	6.569	<0.001	
Threonine							
timepoint	2	1.69E+07	3.11	0.044	0.887	<0.001	
intervention	1	2.03E+07	7.40	0.007	0.130	<0.001	
intervention:timepoint	2	1.69E+07	1.08	0.341	6.822	<0.001	
Tryptophane							
timepoint	1	1.31E+22	0.53	0.468	4.675	<0.001	

intervention	1	1.66E+08	0.14	0.711	3.282	<0.001	
intervention:timepoint	1	5.62E+22	2.65	0.104	4.225	<0.001	
Tyrosine							
timepoint	2	2.04E+07	5.36	0.005	0.094	<0.001	
intervention	1	2.46E+07	2.34	0.126	2.525	<0.001	
intervention:timepoint	2	2.04E+07	1.49	0.225	4.509	<0.001	
Valine							
timepoint	2	3.90E+07	2.57	0.077	1.531	<0.001	
intervention	1	4.70E+07	1.90	0.168	3.354	<0.001	
intervention:timepoint	2	3.90E+07	1.35	0.258	5.160	<0.001	

Table S28: Effect of adiposity on fasting HOMA-IR [1g]

Related to Figure 4

$$HOMA-IR \sim intervention * fatmass_pc + (1|subjectID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
intervention	1	17	4.91	0.041	0.17	*
fat_mass_pc	1	17	0.65	0.431	-0.02	
intervention:fat_mass_pc	1	17	2.29	0.149	0.06	

Table S29: Effect of UMP intervention on serum insulin levels [1g]

Related to Figure 4

$$insulin \sim intervention * timepoint + (1|ID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
timepoint	2	90	32.77	<0.001	0.41	*
intervention	1	90	1.76	0.20	<0.01	
intervention:timepoint	2	90	1.59	0.21	<0.01	
t-contrast						
			<i>t-value</i>	<i>p-value</i>		
Timepoint 0h vs. 2h			-7.89	<0.001		***
Timepoint 0h vs. 4h			-5.89	<0.001		***
Timepoint 2h vs. 4h			2.02	0.132		

Table S30: Effect of UMP intervention on serum glucose levels [1g]

Related to Figure 4

$$Glucose \sim intervention * timepoint + (1|ID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
timepoint	2	90	3.2800	0.042	0.05	*
intervention	1	90	0.5078	0.477	<0.01	

intervention:timepoint	2	90	0.4461	0.64	-0.01	
	t-contrast					
			<i>t-value</i>	<i>p-value</i>		
Timepoint 0h vs. 2h			2.16	0.096		.
Timepoint 0h vs. 4h			2.27	0.075		.
Timepoint 2h vs. 4h			0.10	0.999		

Table S31: Effect of adiposity on (log-) fasting leptin [1g]
Related to Figure 4

$$\log(\text{leptin}) \sim \text{intervention} * \text{fatmass_pc} + (1|\text{subjectID})$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
fat_mass_pc	1	17	62.31	<0.001	0.76	***
intervention	1	17	0.70	0.702	-0.05	
intervention:fat_mass_pc	1	17	0.01	0.905	-0.05	

Table S32: Effect of (log-) fasting leptin on total food intake [1g]
Related to Figure 4

$$\text{total intake}_{kcal} \sim \text{intervention} * \log(\text{leptin}) + (1|\text{subjectID})$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
log(leptin)	1	20.0	4.09	0.057	0.12	.
intervention	1	16.9	3.83	0.067	0.13	.
intervention: log(leptin)	1	17.0	0.96	0.340	<0.01	

Table S33: Effect of UMP intervention on (log-) serum leptin levels [1g]
Related to Figure 4

$$\log(\text{leptin}) \sim \text{intervention} * \text{timepoint} + (1|ID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
timepoint	2	90	4.60	0.013	0.07	*
intervention	1	90	2.34	0.129	0.01	
intervention:timepoint	2	90	0.15	0.862	-0.02	
	t-contrast					
			<i>t-value</i>	<i>p-value</i>		
Timepoint 0h vs. 2h			2.99	0.011		*
Timepoint 0h vs. 4h			1.05	0.650		
Timepoint 2h vs. 4h			-1.94	0.159		

Table S34: Effect of UMP intervention on serum amino acids levels [1g]
 Related to Figure 4

$$\text{amino acid} \sim \text{intervention} * \text{timepoint} + (1|ID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	<i>Bonferroni corrected p-value</i>	ω^2	
Alanine							
timepoint	2	14910311	33.49	<0.001	<0.001	<0.001	***
intervention	1	3187520	<0.01	0.9822	19.644	<0.001	
intervention:timepoint	2	14493229	0.36	0.7007	14.014	<0.001	
t-contrast							
			<i>t-value</i>	<i>p-value</i>			
Timepoint 0h vs. 2h			-7.163	<0.001			***
Timepoint 0h vs. 4h			-7.04003	<0.001			***
Arginine							
timepoint	2	15526522	2.08	0.1254	2.508	<0.001	
intervention	1	3315863	0.67	0.4132	8.265	<0.001	
intervention:timepoint	2	15089554	0.02	0.9777	19.555	<0.001	
Asparagine							
timepoint	2	5716132	15.05	<0.001	<0.001	<0.001	***
intervention	1	1262563	0.06	0.8115	16.229	<0.001	
intervention:timepoint	2	5586817	1.07	0.3414	6.8275	<0.001	
t-contrast							
			<i>t-value</i>	<i>p-value</i>			
Timepoint 0h vs. 2h			-4.77483	<0.001			***
Timepoint 0h vs. 4h			-4.74728	<0.001			***
Aspartic Acid							
timepoint	2	91.48	9.7046	0.0001506	0.003	0.16	**
intervention	1	91.746	0.6803	0.4116174	8.232	-3.42E-03	
intervention:timepoint	2	91.483	0.4446	0.642453	12.849	-0.01	
t-contrast							
			<i>t-value</i>	<i>p-value</i>			
Timepoint 0h vs. 2h			-3.721	<0.001			***
Timepoint 0h vs. 4h			-4.403	<0.001			***
Cysteine							
timepoint	2	91.071	0.5314	0.5896	11.791	-0.01	
intervention	1	91.169	1.2211	0.272	5.441	2.37E-03	
intervention:timepoint	2	91.073	0.5817	0.561	11.221	-8.97E-03	
Glutamic Acid							
timepoint	2	22544376	3.0162	0.04899	0.980	<0.001	
intervention	1	4775514	0.0057	0.93972	18.794	<0.001	

intervention:timepoint	2	21879080	0.2205	0.80211	16.042	<0.001	
		Glutamine					
timepoint	2	50586338	3.6148	0.02692	0.538	<0.001	
intervention	1	10576927	0.0686	0.79338	15.867	<0.001	
intervention:timepoint	2	48981843	0.899	0.40699	8.140	<0.001	
		Glycine					
timepoint	2	91.048	0.6012	0.5503	11.006	-8.55E-03	
intervention	1	91.114	0.1287	0.7207	14.413	-9.45E-03	
intervention:timepoint	2	91.049	0.0123	0.9878	19.756	-2.00E-02	
		Histidine					
timepoint	2	2611389	4.877	0.00762	0.152	<0.001	
intervention	1	602405	2.3304	0.12687	2.537	<0.001	
intervention:timepoint	2	2570026	1.0202	0.36052	7.210	<0.001	
		Isoleucine					
timepoint	2	9312478	2.5281	0.07981	1.596	<0.001	
intervention	1	2017368	0.9192	0.33768	6.754	<0.001	
intervention:timepoint	2	9072415	0.7068	0.49321	9.864	<0.001	
		Leucine					
timepoint	2	12545827	2.8267	0.05921	1.184	<0.001	
intervention	1	2693797	1.4466	0.22907	4.581	<0.001	
intervention:timepoint	2	12204017	0.5586	0.57201	11.440	<0.001	
		Lysine					
timepoint	2	10137859	4.9152	0.007334	0.147	<0.001	
intervention	1	2191024	0.0557	0.813502	16.270	<0.001	
intervention:timepoint	2	9872603	0.1278	0.880013	17.600	<0.001	
		Methionine					
timepoint	2	7596567	7.8485	0.0003903	0.867	<0.001	
intervention	1	1657912	2.5129	0.112916	7.867	<0.001	
intervention:timepoint	2	7409971	0.3708	0.6901931	16.155	<0.001	
		Phenylalanine					
timepoint	2	7596567	7.8485	0.0003903	0.008	<0.001	**
intervention	1	1657912	2.5129	0.112916	2.258	<0.001	
intervention:timepoint	2	7409971	0.3708	0.6901931	13.804	<0.001	
		t-contrast					
			<i>t-value</i>	<i>p-value</i>			
Timepoint 0h vs. 2h			-3.73	<0.001			***
Timepoint 0h vs. 4h			-3.01	0.008			**
		Proline					
timepoint	2	25777920	30.6972	<0.001	<0.001	<0.001	***
intervention	1	5446540	1.1415	0.2853	5.707	<0.001	
intervention:timepoint	2	25006100	0.3181	0.7275	14.551	<0.001	
		t-contrast					
			<i>t-value</i>	<i>p-value</i>			
Timepoint 0h vs. 2h			-5.72	<0.001			***
Timepoint 0h vs. 4h			-7.51	<0.001			***

Serine							
timepoint	2	1886950	0.8161	0.4421	8.843	<0.001	
intervention	1	447934	1.1767	0.278	5.561	<0.001	
intervention:timepoint	2	1865065	0.6102	0.5433	10.865	<0.001	
Threonine							
timepoint	2	9888738	4.0434	0.01754	0.351	<0.001	
intervention	1	2138334	0.0002	0.9902	19.803	<0.001	
intervention:timepoint	2	9630878	0.1724	0.84162	16.832	<0.001	
Tryptophane							
timepoint	2	20229362	5.0641	0.006319	0.126	<0.001	
intervention	1	4294519	4.7597	0.029134	0.583	<0.001	
intervention:timepoint	2	19639832	1.3101	0.269788	5.396	<0.001	
Tyrosine							
timepoint	2	37606979	5.2049	0.00549	0.110	<0.001	
intervention	1	7895630	1.0297	0.31024	6.205	<0.001	
intervention:timepoint	2	36440584	0.3136	0.73084	14.617	<0.001	
Valine							
timepoint	2	21364714	5.5714	0.003805	0.076	<0.001	
intervention	1	4529931	1.2786	0.258166	5.163	<0.001	
intervention:timepoint	2	20737647	0.9576	0.383832	7.677	<0.001	

Supraphysiological circulating uridine does not alter food behavior

Table S35: Effect of 1 g oral UMP supplementation on uridine levels [1 g]

Related to Figure 5A

$$\begin{aligned}
 & \text{uridine} \sim \text{treatment} * \text{timepoint} + \text{treatment: drymass}_{kg} + \text{treatment: fatmass}_{kg} \\
 & + \text{treatment: sex} + (1 | \text{subjectID})
 \end{aligned}$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
intervention	1	103.12	8.09	0.005	0.06	**
timepoint	2	103.12	80.16	<0.001	0.60	***
intervention:timepoint	2	103.12	108.87	<0.001	0.67	***
intervention:fatfree_mass_kg	2	25.70	0.96	0.397	-2.88e-03	
intervention:fat mass kg	2	25.70	0.83	0.448	-0.01	
intervention:gender	2	25.70	0.77	0.474	-0.02	

Table S36: Effect of UMP supplementation on uridine levels, post-hoc [1 g]

Related to Figure 5A

Post-analysis of the effect of treatment on blood uridine levels; the posthoc-test revealed that uridine concentrations are significantly higher under UMP treatment after 2 and 4 hours.

	<i>Estimate</i>	<i>Std. error</i>	<i>t</i>	<i>p-value</i>	
U@t0 – P@t0	- 0.386	0.469	0.882	0.413	
U@t+2 – P@t+2	9.174	0.469	19.558	<0.001	***
U@t+4 – P@t+4	3.018	0.469	6.435	<0.001	***

Note. Std. error = Standard error, P= placebo U = treatment with UMP, @t0 = initial timepoint, @t+2 = after 2 hours, @t+4 = after 4 hours.

Table S37: Effect of UMP supplementation on hunger ratings [1 g]

Related to Figure 5

Initial hunger ratings were subtracted from the average hunger ratings during the buffet.

$$hunger@buffet - hunger@t0 \sim intervention * fatfree_mass_{kg} + day + sex + (1|ID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
intervention	1	20.03	0.016	0.901	-0.05	
intervention:fatfree_mass_kg	1	19.87	0.005	0.947	0.07	
fatfree_mass_kg	1	15.86	2.435	0.138	0.11	
day	1	19.95	3.674	0.70	0.08	+
Gender	1	15.873	2.560	0.129	-0.05	

Note. Day = measurement day (day1 or day 2)

Table S38: Effect of UMP supplementation on caloric intake [1 g]

Related to Figure 5

$$intake_kcal \sim intervention * fatfree_mass_{kg} + fat_mass_{kg} + (1|ID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
intervention	1	20.99	0.015	0.902	-0.04	
intervention:fatfree_mass_kg	1	20.995	0.0324	0.859	0.12	
fatfree_mass_kg	1	17.593	3.656	0.072	-0.04	+

Table S39: Effect of uridine levels on caloric intake [1 g]

Related to Figure 5B

$$intake_{kcal} \sim uridine_{t-1} + uridine_{t-1}^2 + (1|ID)$$

	<i>numDF</i>	<i>denDF</i>	<i>F-value</i>	<i>p-value</i>	ω^2	
Uridine_tm1	1	128.72	5.609	0.019	0.03	*
Uridine_tm1 ^2	1	127.58	5.432	0.021	0.03	*

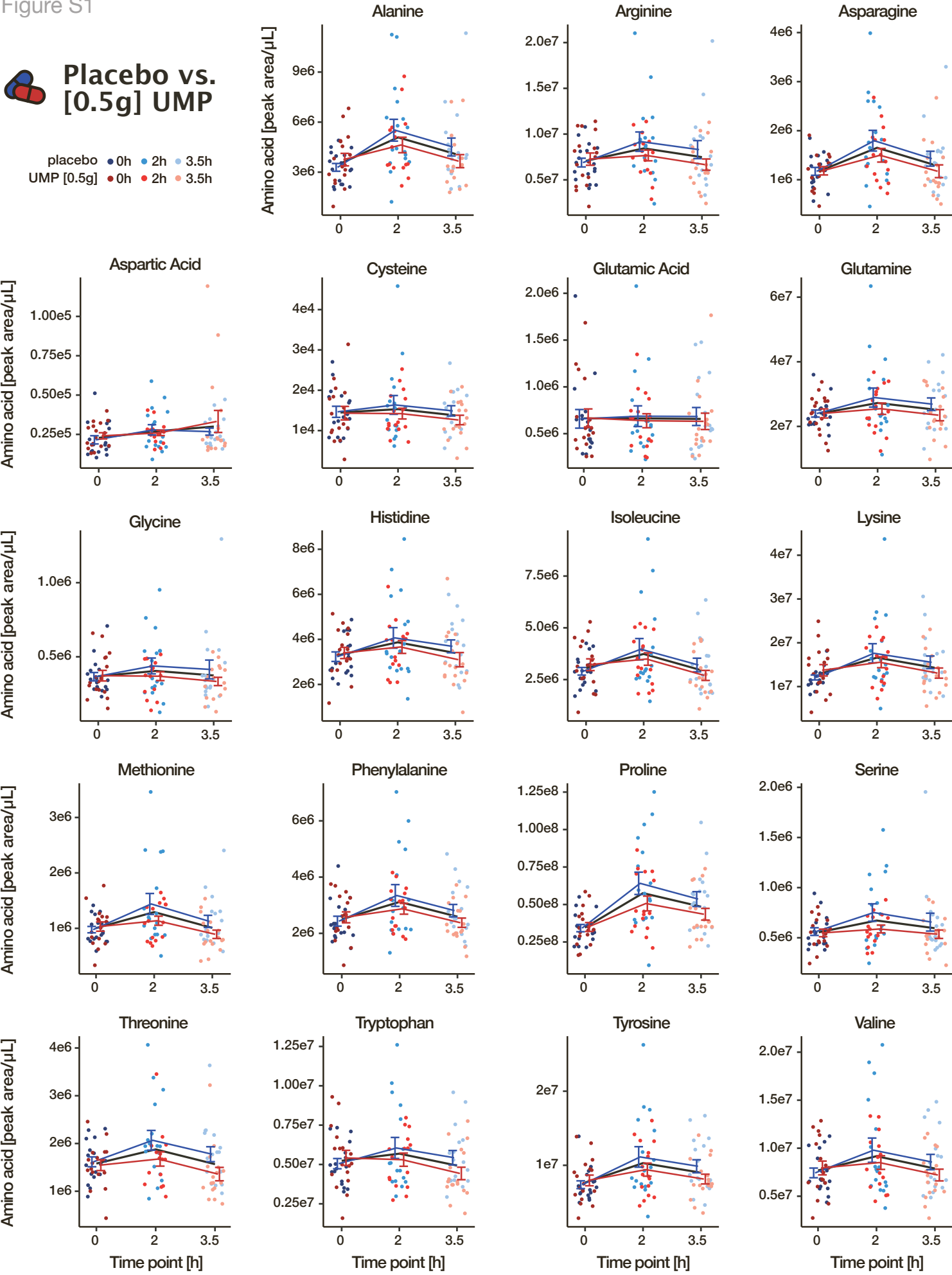
Supplementary Figures

Figure S1



Placebo vs. [0.5g] UMP

placebo ● 0h ● 2h ● 3.5h
UMP [0.5g] ● 0h ● 2h ● 3.5h

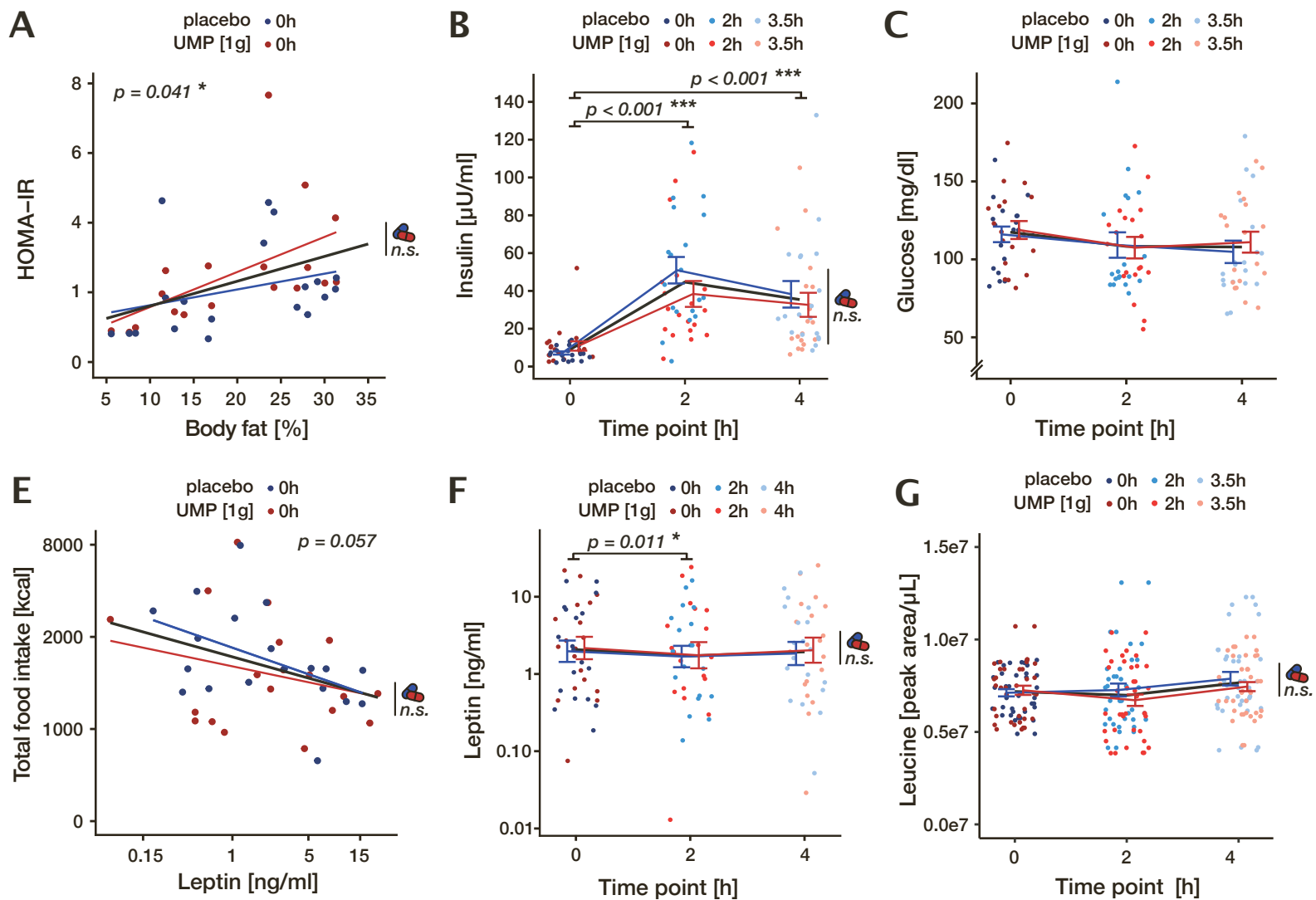


Supplemental Figure 1: Serum amino acids as a function of time in the study [0.5g]. In all panels, placebo and intervention (0.5g UMP) are shown in blue and red respectively. Thin lines and error bars represent the mean and standard error for each session, thick black lines the grand average, and lighter colors mean later time points. Related to Figure 4.

Figure S2



Placebo vs. [1g] UMP



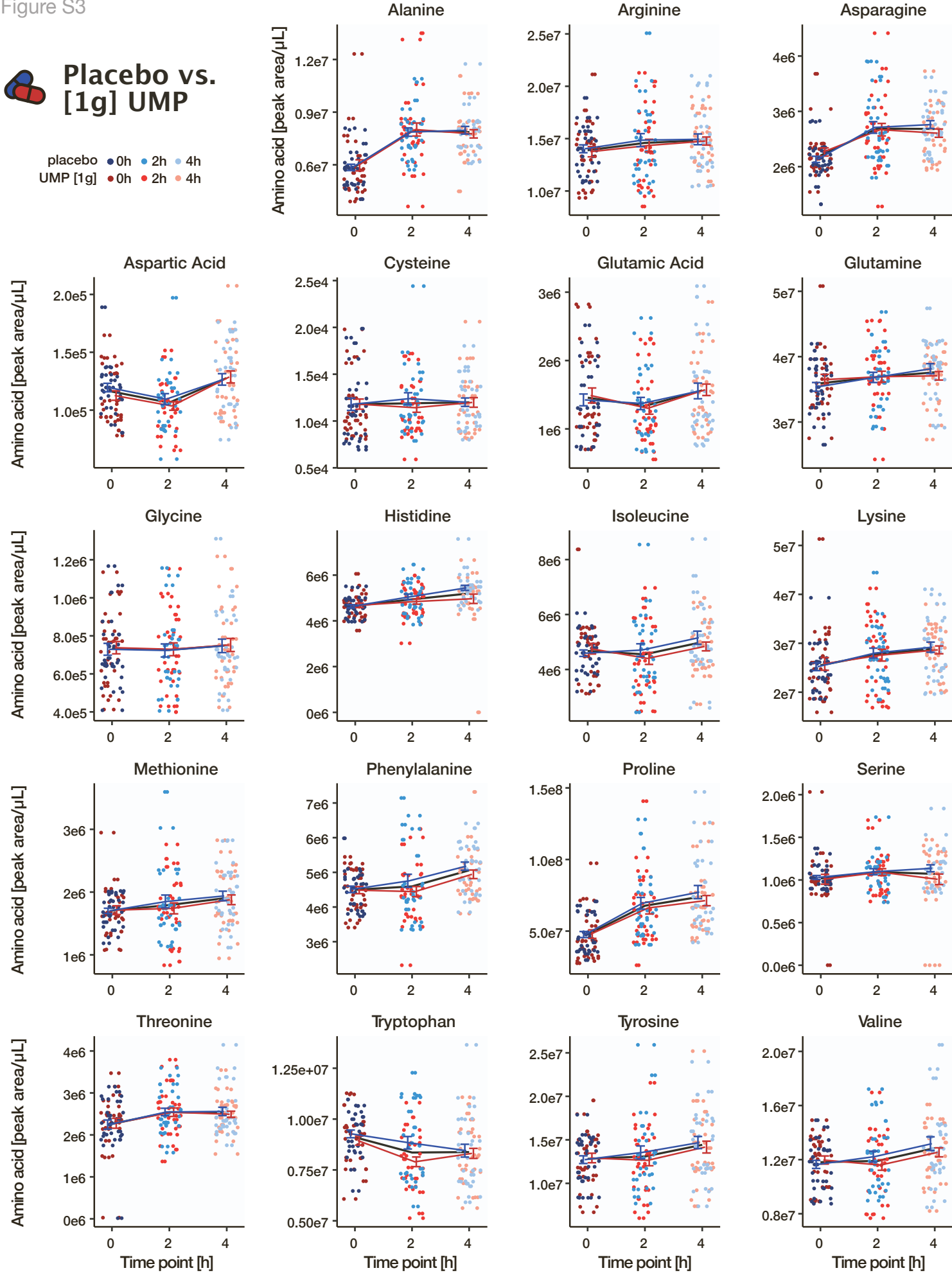
Supplemental Figure 2: Metabolic profile of the participants in the study [1g]. **A** Insulin resistance, as measured by HOMA-IR = (fasting glucose [mg/dL] x fasting insulin [mU/L]) / 405, as function of adiposity. Linear fit. Table S28. **B-C** Serum insulin (B) and glucose (C) as a function of time. Statistics correspond to the *post-hoc* comparison between time-points. Table S29 and S30. **D** Basal serum leptin increases exponentially as a function of adiposity. Statistics correspond to the fitted model: $\text{Leptin} \sim \beta_0 + \exp(\beta_1 * \text{bodyfat})$. Table S31. **E** Total food intake as a function of the (log-) basal serum leptin. Linear fit. Table S32. **F** Serum leptin (log scale) as a function of time. Statistics correspond to the *post-hoc* comparison between time-points. Table S33. **G** Serum leucine as a function of time. Statistics correspond to the *post-hoc* comparison between time-points. Table S34. In all panels, placebo and intervention (1g UMP) are shown in blue and red respectively. Thin lines and error bars represent the mean and standard error (B-C, F-G) or the best fit (A, D, E) for each session, thick black lines the grand average, and lighter colors mean later time points. The pill symbol with “n.s.” indicate the absence of any significant difference (main effect or interaction) between the UMP and the placebo conditions. Related to Figure 4.

Figure S3

Placebo vs. [1g] UMP

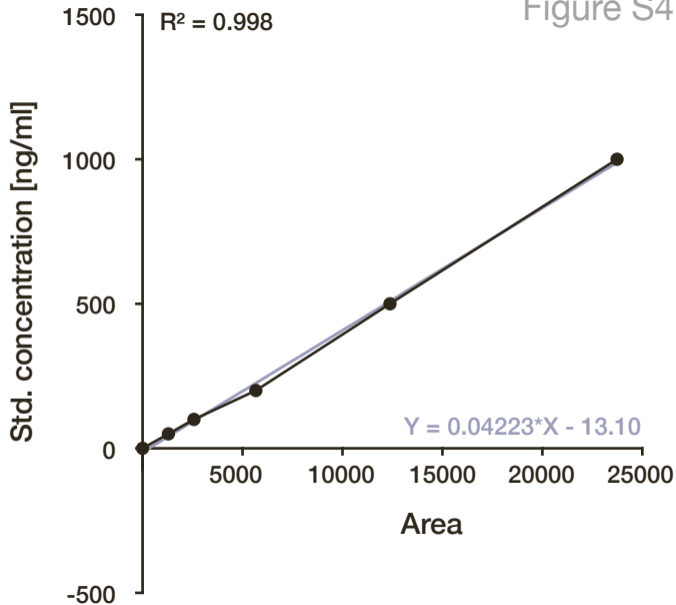


placebo ● 0h ● 2h ● 4h
UMP [1g] ● 0h ● 2h ● 4h

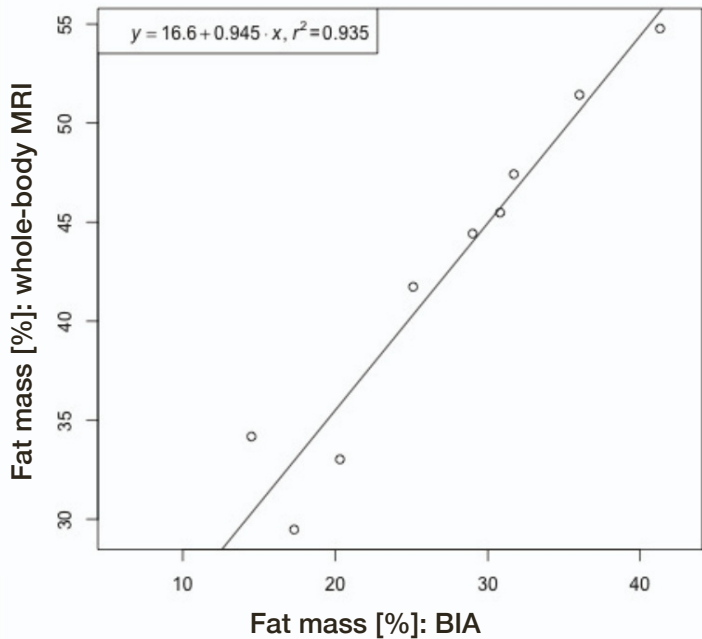
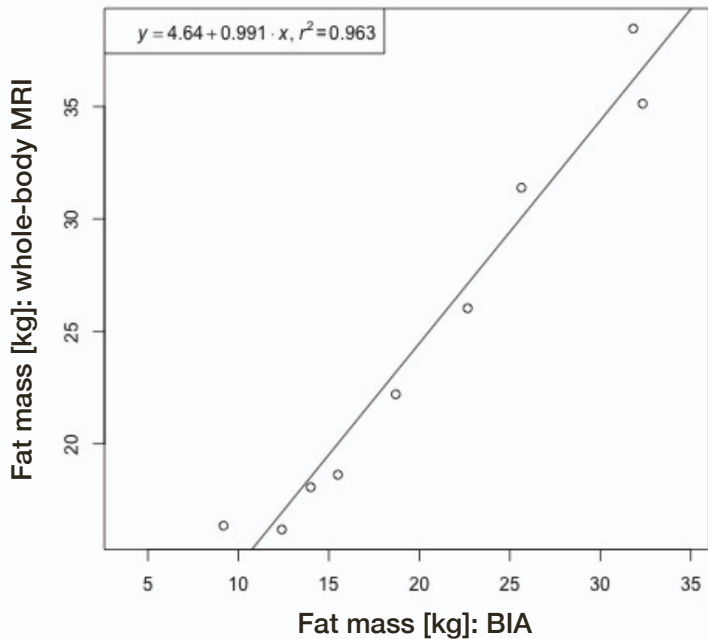


Supplemental Figure 3: Serum amino acids as a function of time in the study [1g]. In all panels, placebo and intervention (1g UMP) are shown in blue and red respectively. Thin lines and error bars represent the mean and standard error for each session, thick black lines the grand average, and lighter colors mean later time points. Complementary statistics can be found in Table S34. Related to Figure 4.

Figure S4

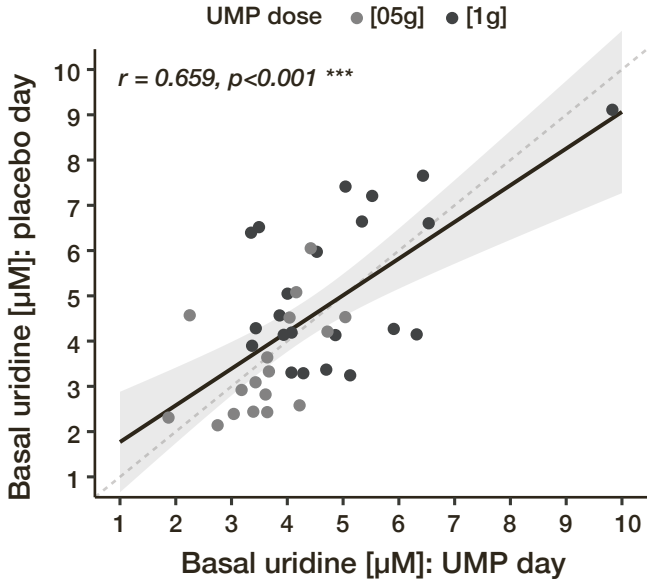


Supplemental Figure 4: Standard Curve of the UPLC. Standard Curve of the UPLC for the measurement of uridine concentration in serum. Black dots and the black line are the measured standards, the grey line is standard curve (linear fit, equation given in the bottom right). Related to Ultra-Performance Liquid Chromatography (UPLC) in STAR METHODS.

A**B**

Supplemental Figure 5: Correlation between BIA and whole-body MRI measures of body composition. Relative (A) and absolute (B) body fat as estimated by the mBCA 515 Bioelectrical Impedance Scale (x-axis) and by whole-body Magnetic Resonance Imaging (y-axis). Lines represent the best linear fit detailed on the top-left corner of each plot. Related to Body Composition in STAR METHODS.

Figure S6



Supplemental Figure 6: Correlation between basal uridine levels across testing days. Serum uridine levels measured either before the placebo (x-axis) or before the UMP intervention (y-axis) in the study [0.5g] (gray) and the study [1g] (black). The black line and the shaded area represent respectively to the estimated correlation and its 95% confidence interval. Statistics: Pearson correlation. Related to Figure 3.