UNIVERSITAT ROVIRA I VIRGILI

EARNEST
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Gender differences in endocrine system and growth in response to protein intake early in life

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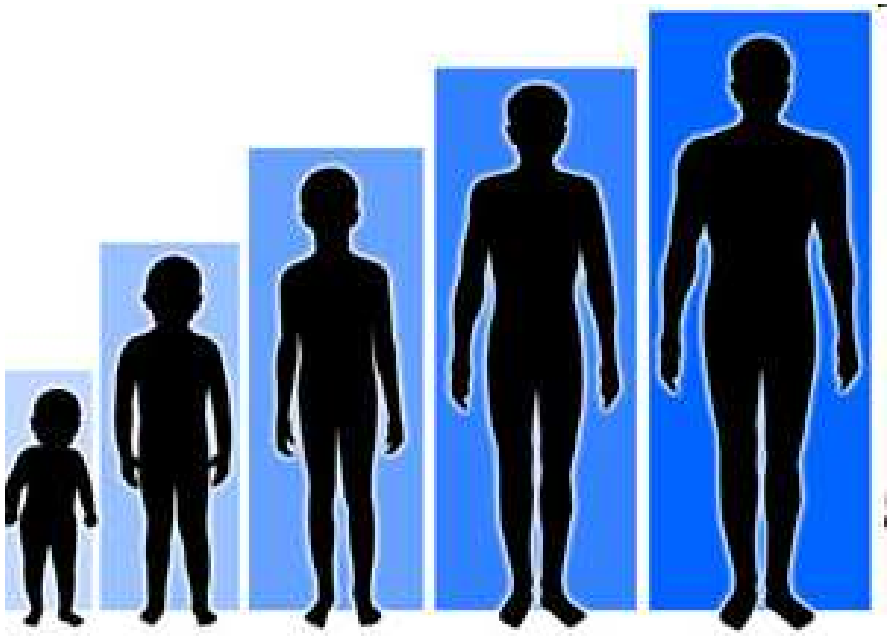
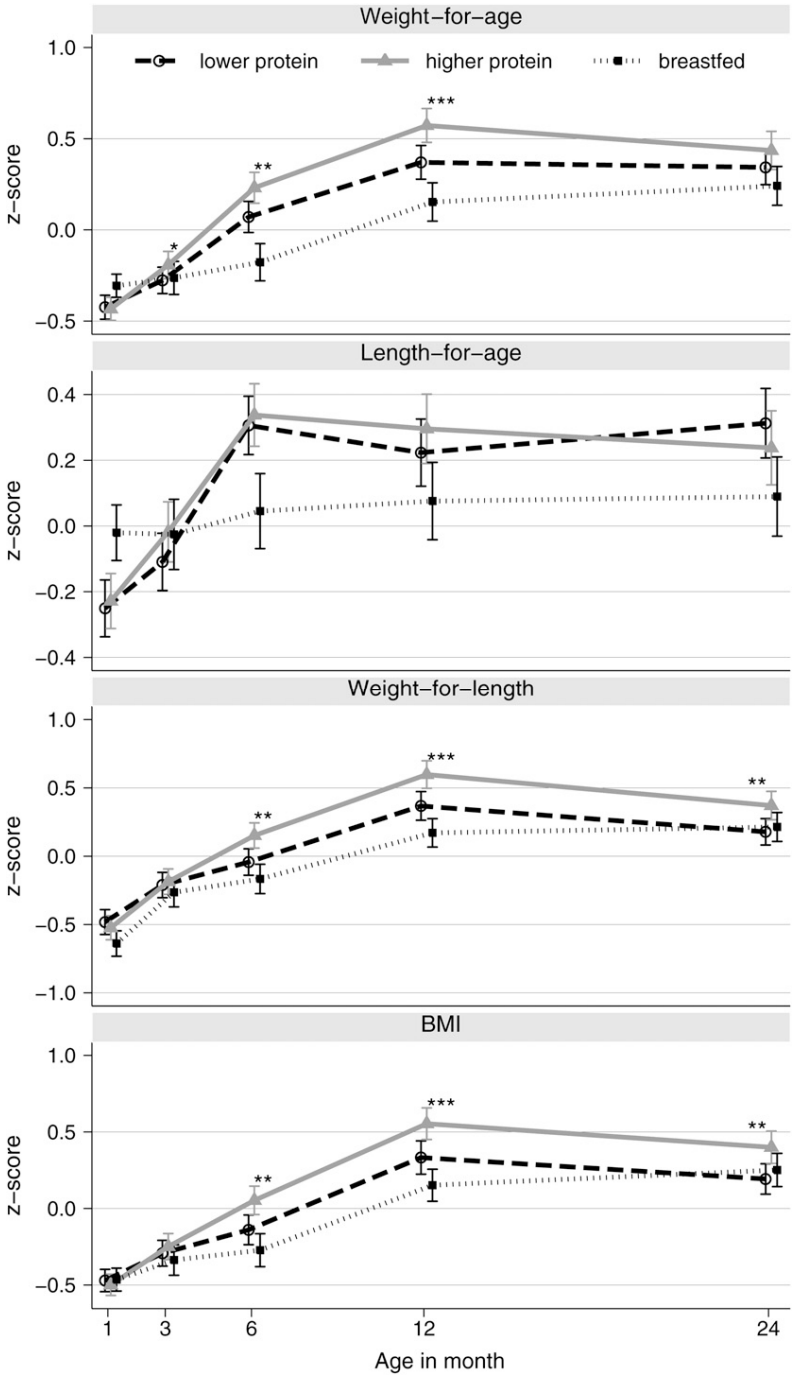
On behalf with CHOP Study Group

There is some evidence that protein intake plays a role on programming growth



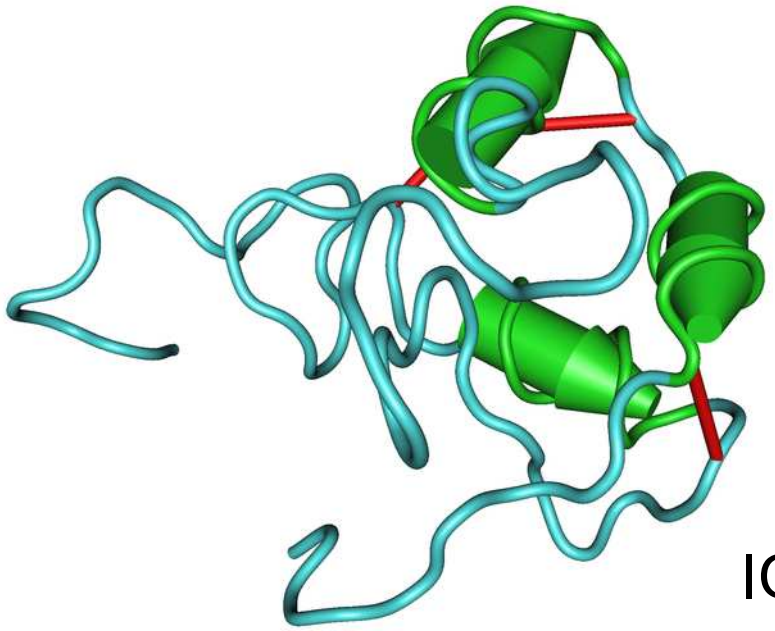


EU CHILDHOOD OBESITY
Early Programming by Infant Nutrition

Intervention for the first year of life produces differences on growth that are still significant at 24 months of age

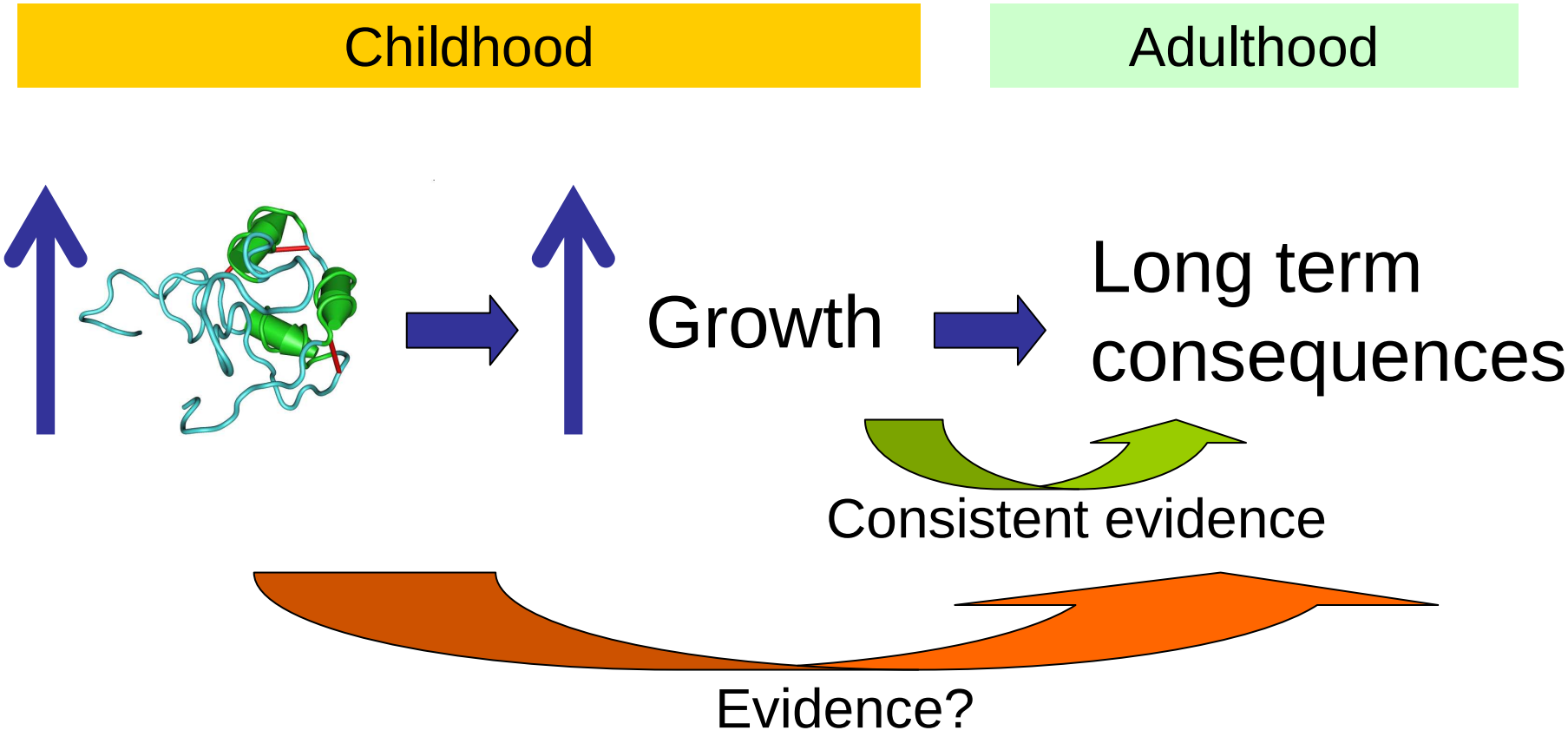
Koletzko B *et al*. Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial. *Am J Clin Nutr 2009;89:1–10.*

Protein intake is clearly related with IGF-1 axis



IGF-1

Is there any gender difference?



Results from EU CHOP could clarify some of these aspects

Aim

- Are there any specific gender differences in growth and biochemical parameters in response to protein intake early in life?

Methods

- RCT
- 5 European countries
- 2 Infant / Follow-on formulas (HP, LP)
- Observational control group (BF)
- Birth – 6 months

Koletzko B *et al*. Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial. *Am J Clin Nutr 2009;89:1–10.*

Main outcome measures

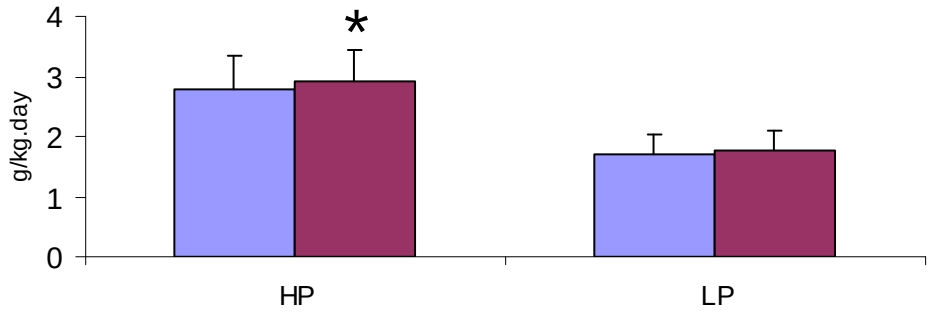
- Anthropometry (0-6 mo)
- Dietary intake (energy, protein)
- Biochemical parameters:
  - Blood parameters (6 mo): IGF-1 axis, leptin, leptin BP, adiponectin.
  - Urinary parameters (6 mo): c-peptide
- Kidney ultrasonography (6 mo)

Results

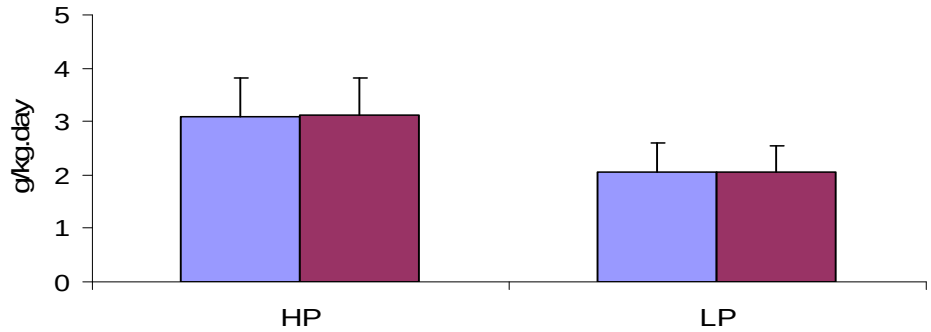
- Dietary intake by feeding groups (by gender)

Protein intake

3 mo



6 mo

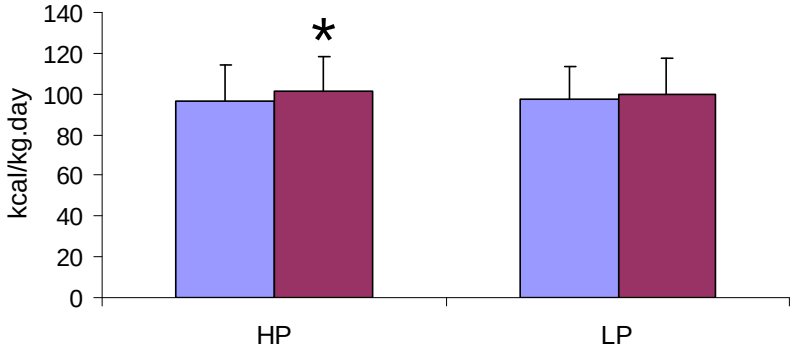


There were no differences between genders in protein intake adjusted for body weight (at 6 mo or later)

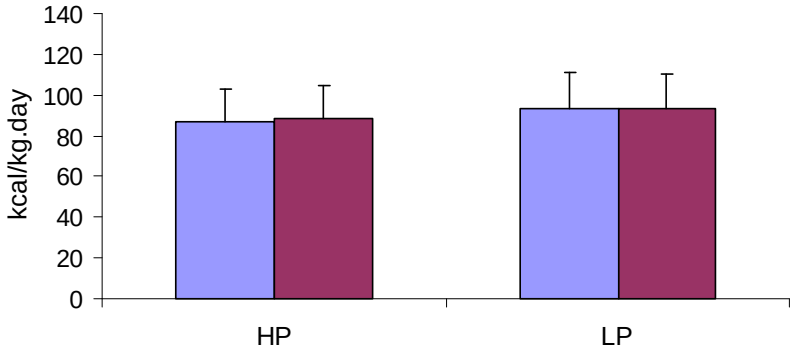
Males Females *: p<0.05 vs males

Energy intake

3 mo



6 mo



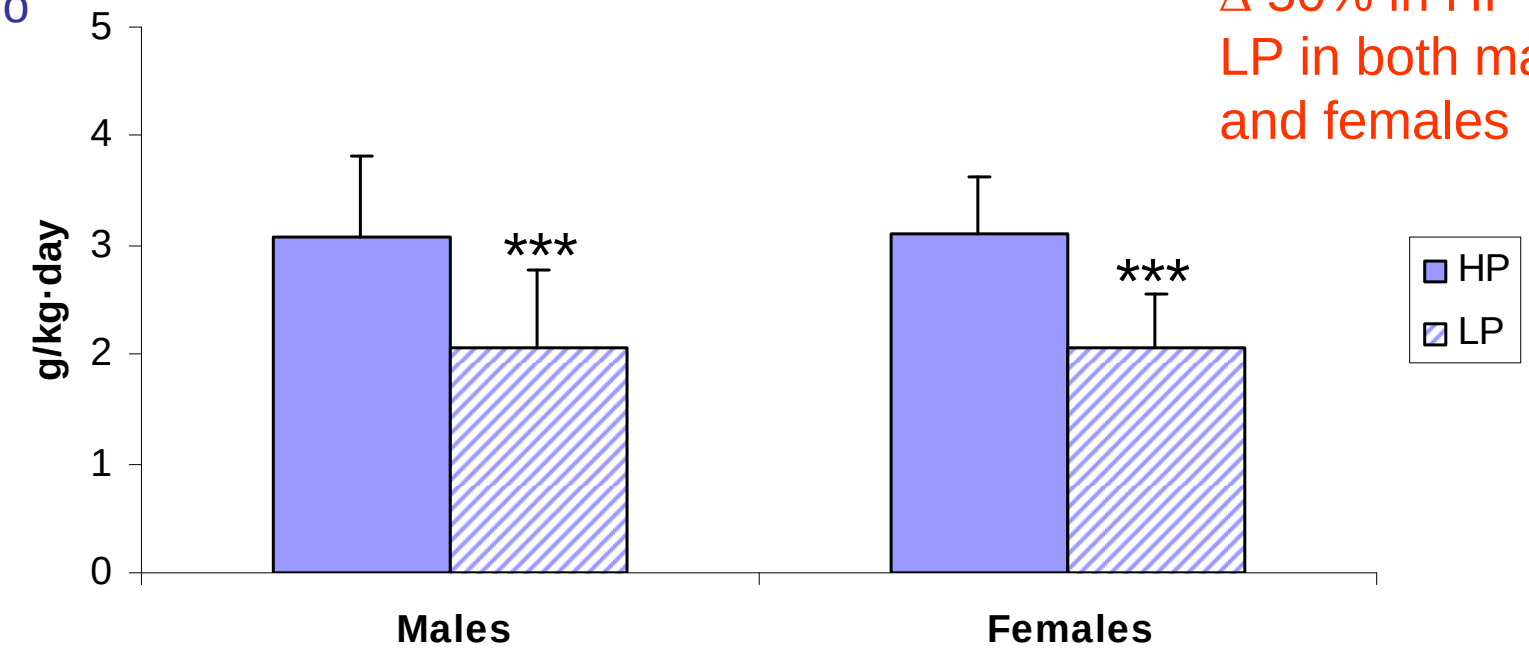
There were no differences between genders in total energy intake adjusted for body weight (at 6 mo or later)

Males Females *: p<0.05 vs males

Protein intake

6 mo

Δ 50% in HP vs LP in both males and females



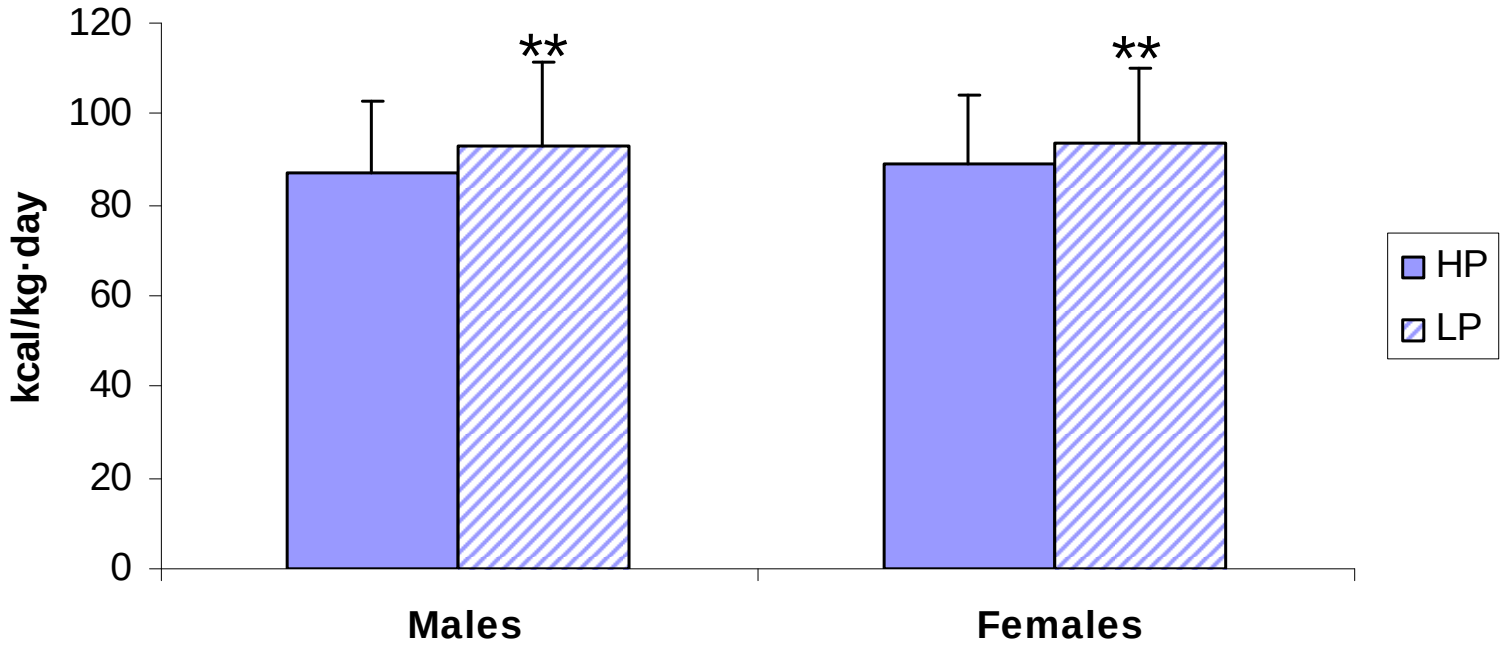
Between feeding groups there were significant statistical differences regardless of gender

These differences were constant during all the intervention period (until 1y, including after complementary feeding introduction).

***:p<0.001 vs HP

6 mo

Energy intake



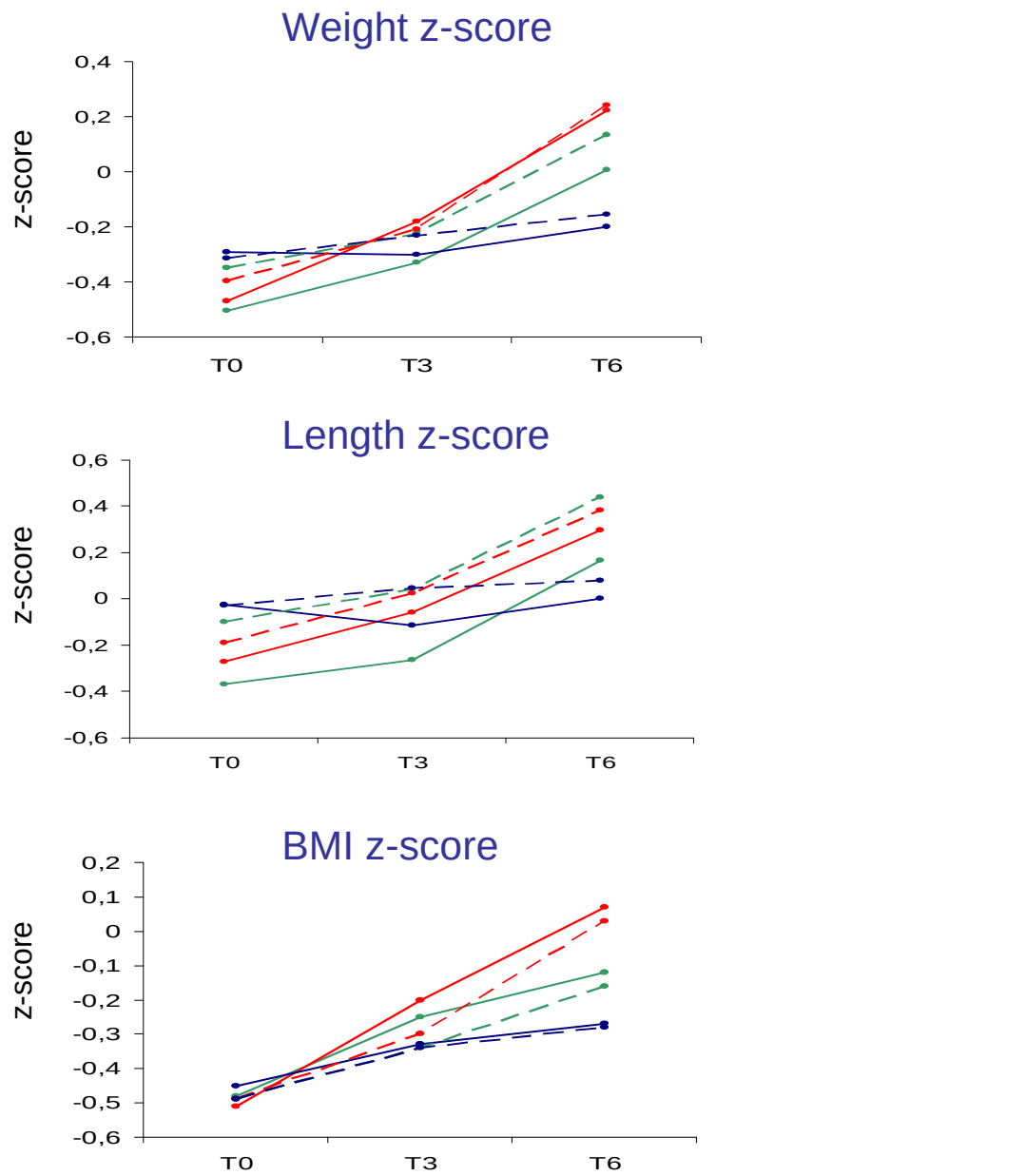
At 6 mo total energy intake was slight higher in LP vs HP. There were no differences in energy intake at other time points. The differences were similar in both genders.

Δ 6.3% in males ($p<0.01$) and Δ 5.1% in females ($p<0.01$)

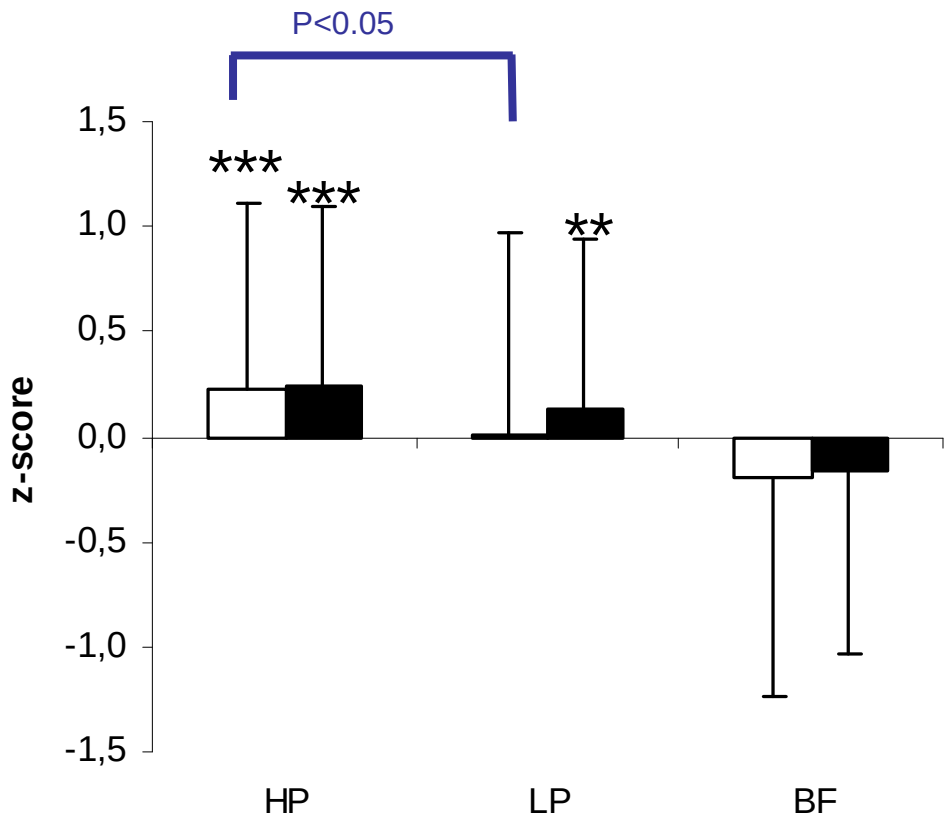
**: $p<0.05$ vs HP

Results

- Effect of protein intake on anthropometrical parameters by gender


Weight z-score
z-score
0,4
0,2
0
-0,2
-0,4
-0,6
T0
T3
T6
Length z-score
z-score
0,6
0,4
0,2
0
-0,2
-0,4
-0,6
T0
T3
T6
BMI z-score
z-score
0,2
0,1
0
-0,1
-0,2
-0,3
-0,4
-0,5
-0,6
T0
T3
T6
HP, males
HP, females
LP, males
LP, females
BF, males
BF, females

Weight z-score (6mo)



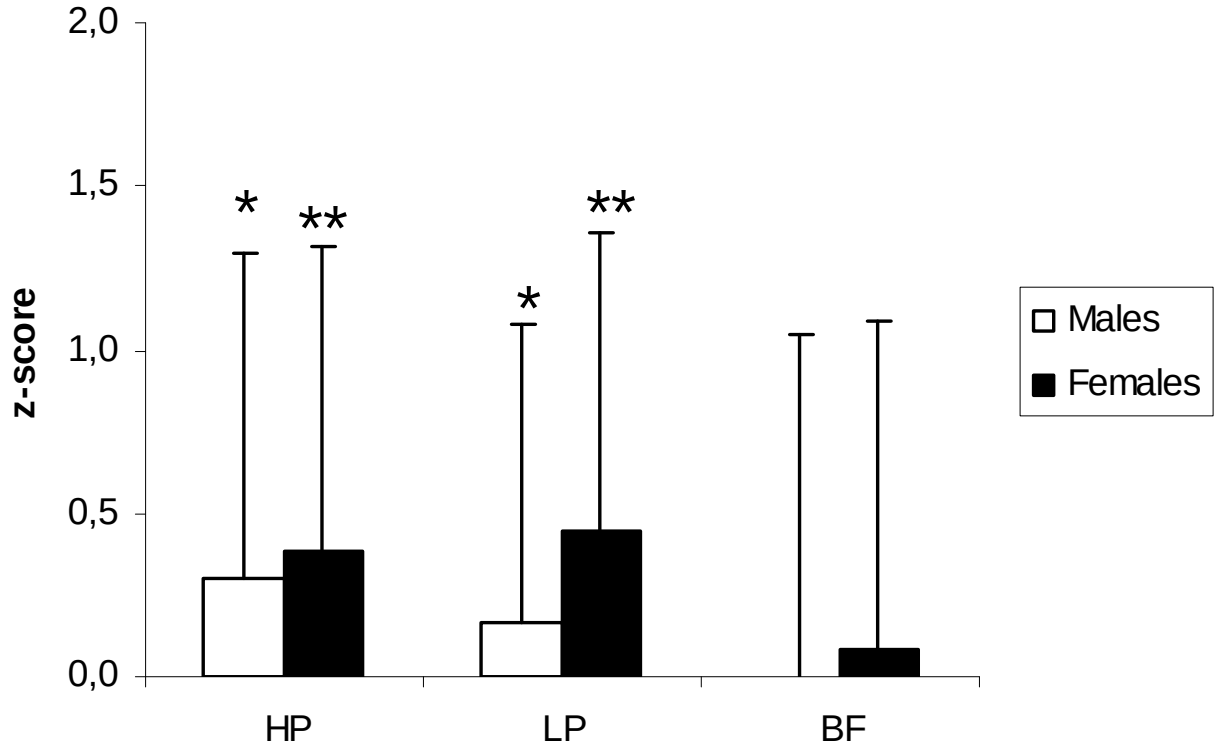
Δ 0.21 SD in HP vs LP among males (p<0.05)

Δ 0.11 SD in HP vs LP among females (NS)

The intervention was associated with an increased Weight z-score in both genders

**: p<0.01; ***:p<0.001 vs BF

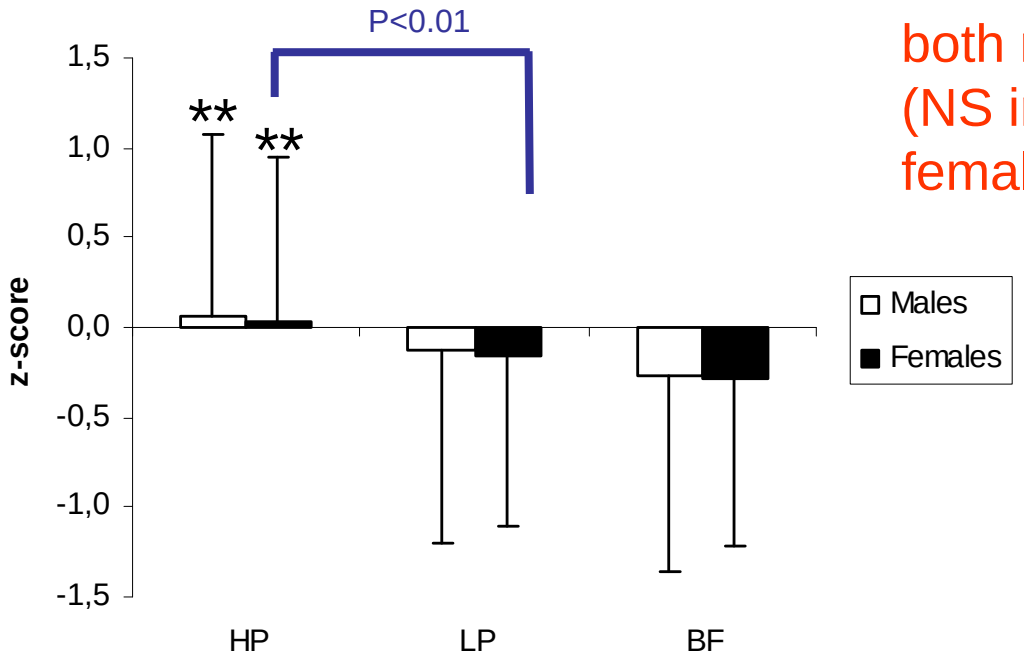
Length z-score (6mo)



There were no differences between formula fed groups in length z-score regardless of gender

**: p<0.01; ***:p<0.001 vs BF

BMI z-score (6mo)



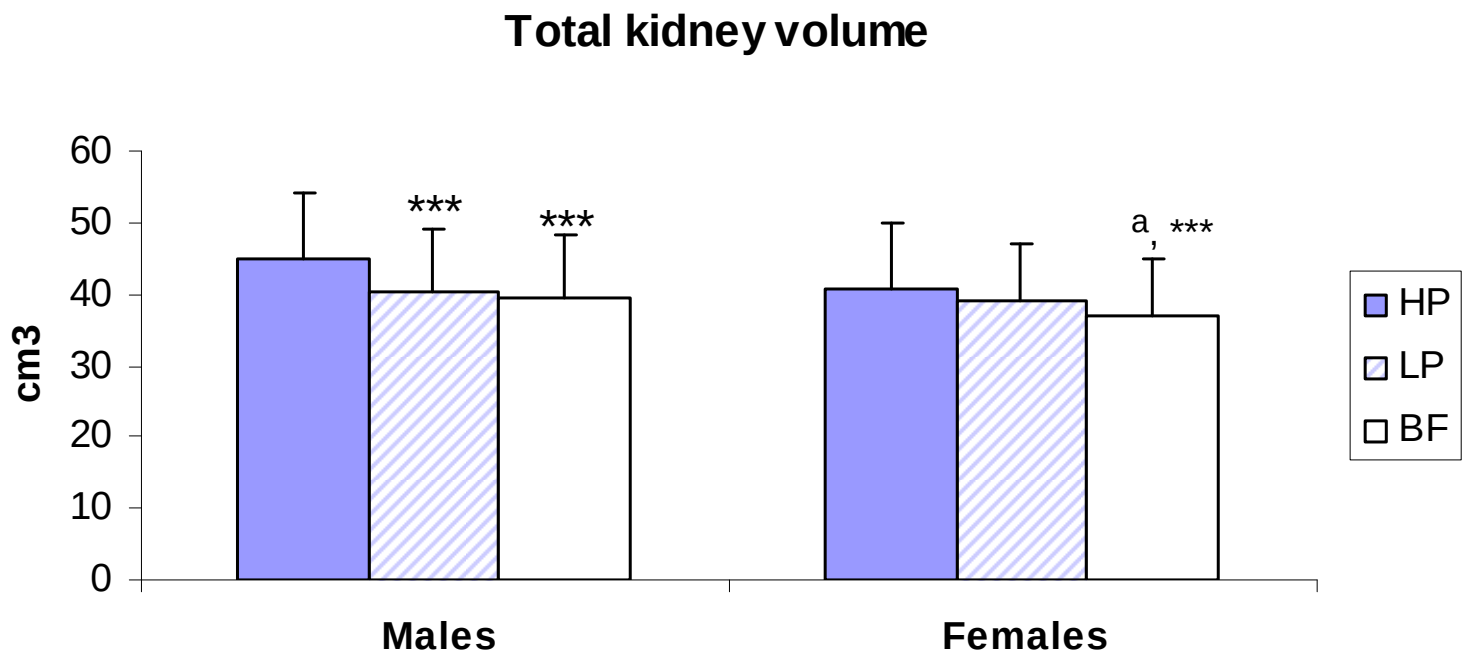
Δ 0.19 SD in HP vs LP in both males and females (NS in males, p<0.01 in females)

The intervention was associated with an increased BMI z-score in both genders

**: p<0.01 vs BF

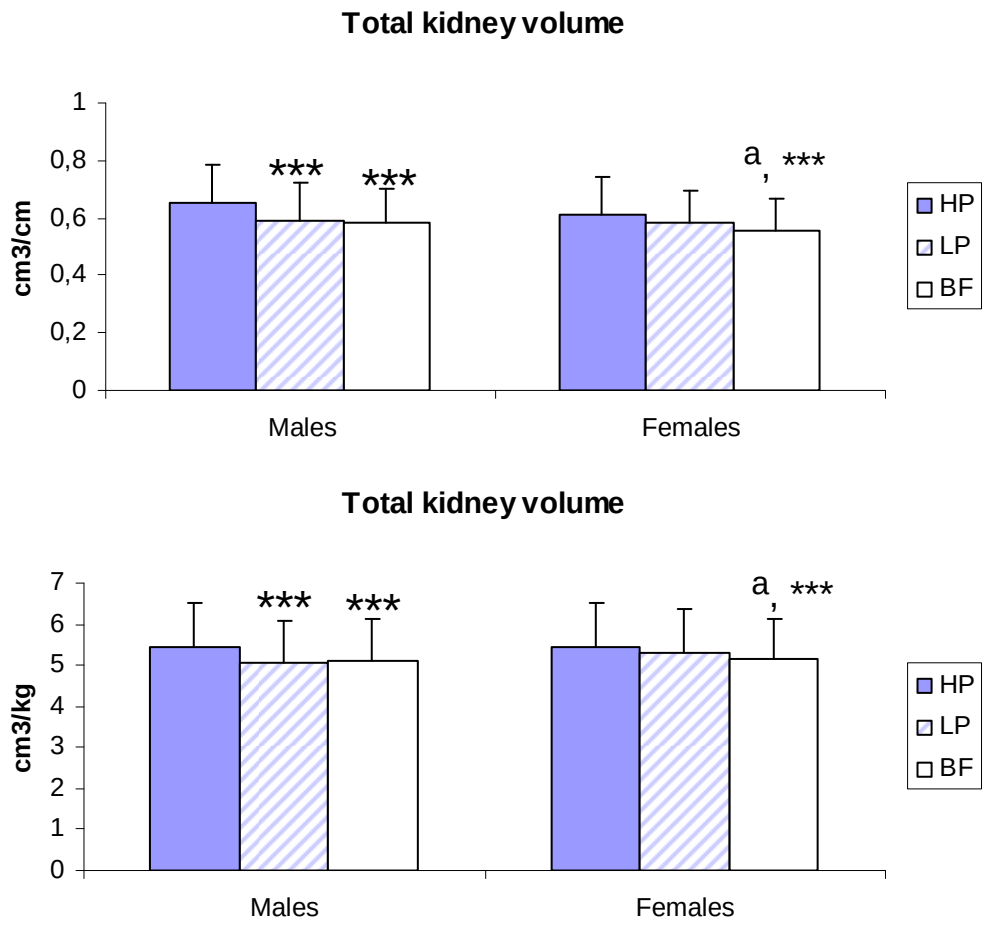
Results

- Effect of protein intake on kidney volume by gender



HP formula was associated with increased total kidney volume among males but not among females

***:p<0.001 vs HP; [a]:p<0.05 vs LP



These differences between HP and LP among males persisted when kidney volume was adjusted for body length or body weight

***:p<0.001 vs HP; [a]:p<0.05 vs LP

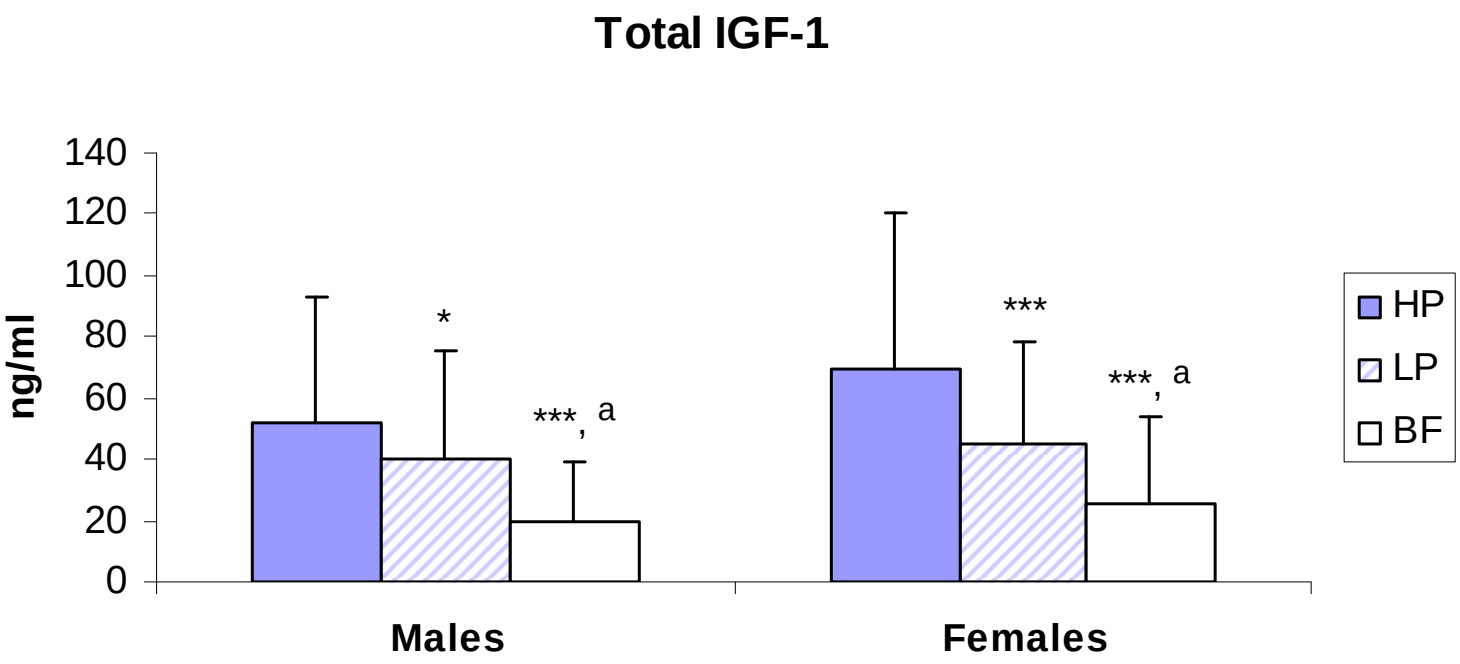
Results

- Effect of protein intake on IGF-1 axis parameters by gender

Gender differences on IGF-1 axis (by feeding group)

		Total IGF-1 (ng/mL)	Free IGF-1 (ng/mL)	IGFBP2 (ng/mL)	IGFBP3 (ng/mL)
HP	♂	51.8 ± 40.8	0.72 ± 0.56	846.7 ± 385.5	2897.9 ± 718.9
	♀	69.5 ± 51.2 **	0.89 ± 0.68 *	804.2 ± 349.9	3148.3 ± 690.5 **
LP	♂	40.6 ± 34.3	0.55 ± 0.46	1117.8 ± 417.5	2848.2 ± 702.6
	♀	45.1 ± 33.4	0.675 ± 0.56 (p=0.051)	1215.0 ± 437.1	3040.1 ± 655.6 *
BF	♂	19.9 ± 19.6	0.39 ± 0.29	1333.4 ± 515.0	2436.4 ± 634.1
	♀	25.5 ± 28.5	0.49 ± 0.53	1528.3 ± 541.5 **	2465.4 ± 665.5

*: $p<0.05$; **:$p<0.01$ vs males (Mann-Whitney U Test)



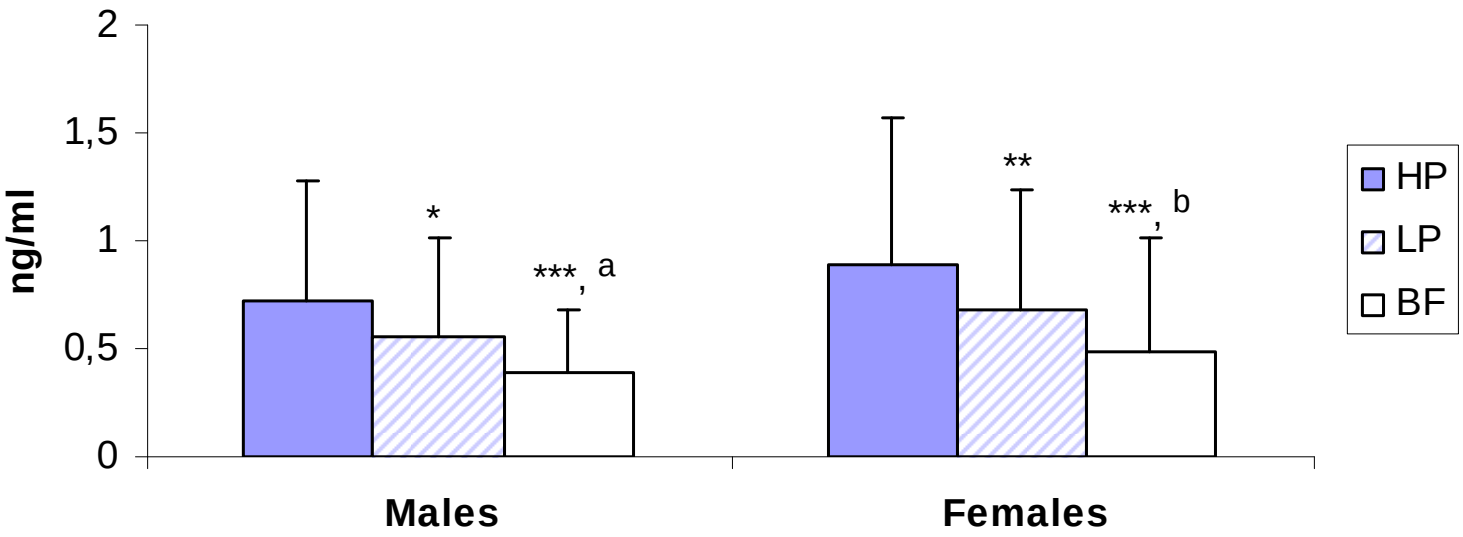
HP formula was associated with higher total IGF-1 vs LP. Females showed higher response

Δ 27% in HP vs LP among males ($p<0.05$)

Δ 53% in HP vs LP among females ($p<0.001$)

*: $p<0.05$, ***:$p<0.001$ vs HP; [a]:$p<0.001$ vs LP

Free IGF-1



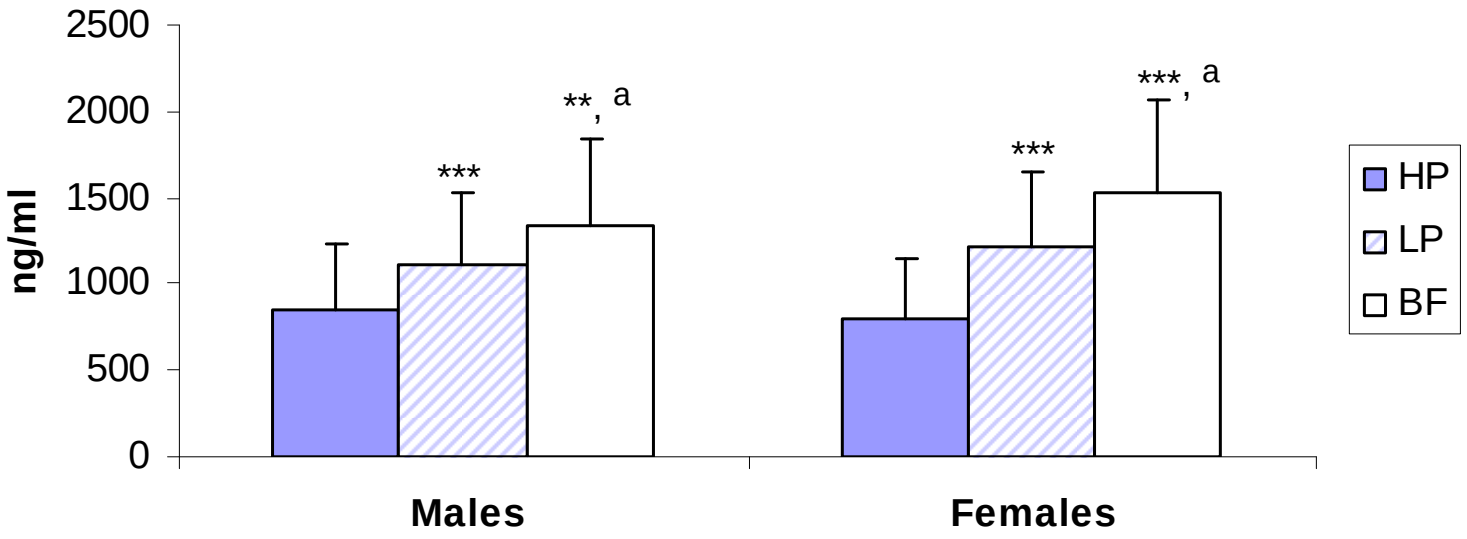
HP formula was associated with higher free IGF-1 vs LP with a similar response in both genders

Δ 31% in HP vs LP among males ($p<0.05$)

Δ 31.9% in HP vs LP among females ($p<0.01$)

*: $p<0.05$, **: $p<0.01$, ***:$p<0.001$ vs HP; [a]:$p<0.05$; [b]:$p<0.001$ vs LP

IGF BP2

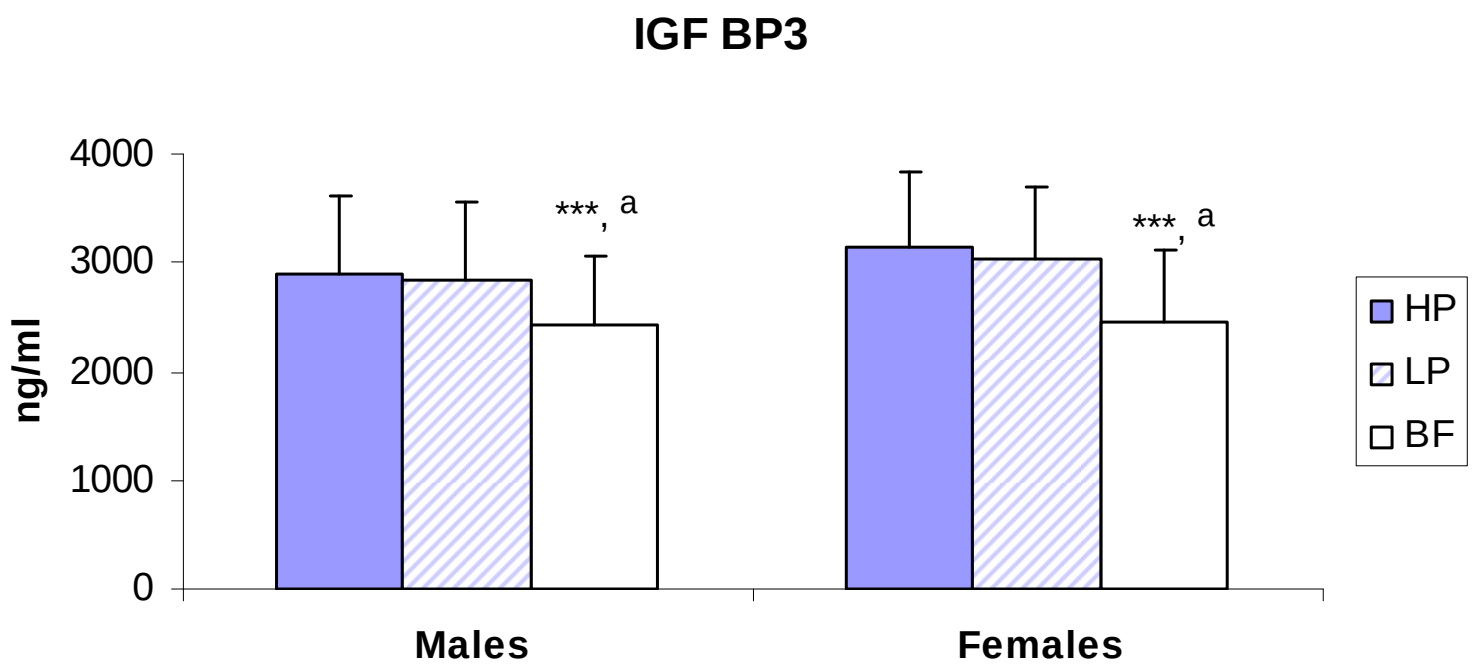


HP formula was associated with lower IGFBP2 vs LP with a similar response in both genders

Δ -24.3% in HP vs LP among males (p<0.001)

Δ -33.8% in HP vs LP among females (p<0.001)

**: p<0.01, ***:p<0.001 vs HP; [a]:p<0.001 vs LP



There were no differences between formula fed groups regardless of gender. BF children showed lower IGFBP3 than formula fed ones.

***:p<0.001 vs HP; [a]:p<0.001 vs LP

Total IGF-1 at 6 mo

	β (ng/ml)	*P*
Study formula (HP vs LP)	17.66	< 0.001
Gender (females vs males)	11.01	< 0.001

R^2 corrected: 0.058, P<0.001

	β (ng/ml)	*P*
Protein intake (1 g/kg·day)	8.85	< 0.001
Gender (females vs males)	12.60	< 0.01

R^2 corrected: 0.046, P<0.001

Males: 6.50, R^2 corrected: 0.015, p<0.05

Females: 11.37, R^2 corrected: 0.035, p<0.01

Results

- Correlations:
  - Intake - IGF-1
  - IGF-1 – anthropometry

Correlation coefficients between protein intake and IGF-1 axis

R Spearman	
	Protein intake (g/kg·day)
Total IGF-1 (ng/mL)	0.186***
Free IGF-1 (ng/mL)	0.208***
IGF-1 BP2 (ng/mL)	-0.304***
IGF-1 BP3 (ng/mL)	0.034

Correlation coefficients between protein intake and IGF-1 axis

R Spearman	
	Protein intake (g/kg·day)
Total IGF-1 (ng/mL)	0.186***
Free IGF-1 (ng/mL)	0.208***
IGF-1 BP2 (ng/mL)	-0.304***
IGF-1 BP3 (ng/mL)	0.034

R Spearman	Protein intake (g/kg·day)	
	♂	♀
Total IGF-1 (ng/mL)	0.195**	0.184**
Free IGF-1 (ng/mL)	0.183**	0.239***
IGF-1 BP2 (ng/mL)	-0.276***	-0.332***
IGF-1 BP3 (ng/mL)	0.121	-0.059

Correlation coefficients between anthropometry and IGF-1 axis

N= 699	Total IGF-1 (ng/mL)	Free IGF-1 (ng/mL)	IGFBP2 (ng/mL)	IGFBP3 (ng/mL)
Weight z-score	0.287***	0.271***	-0.232***	0.314***
Length z-score	0.158***	0.160***	-0.102**	0.192***
Weight/length z-score	0.239***	0.214***	-0.211***	0.245***
BMI z-score	0.237***	0.213***	-0.211***	0.244***
Tricipital SKf z-score	0.044	0.142***	-0.063	-0.029
Subscapular SKf z-score	0.127**	0.188***	-0.025	0.113†

*p<0.05, **p<0.01, ***p<0.001

Correlation coefficients between anthropometry and IGF-1 axis

	Total IGF-1 (ng/mL)		Free IGF-1 (ng/mL)	
N= 699	♂	♀	♂	♀
Weight z-score	0.250***	0.324***	0.281***	0.266***
Length z-score	0.121*	0.187***	0.146**	0.165**
Weight/length z-score	0.222***	0.264***	0.233***	0.207**
BMI z-score	0.215***	0.266***	0.229***	0.210***
Tricipital SKf z-score	0.064	0.032	0.126*	0.162**
Subscapular SKf z-score	0.94	0.153**	0.154**	0.213***

*p<0.05, **p<0.01, ***p<0.001

Correlation coefficients between anthropometry and IGF-1 axis

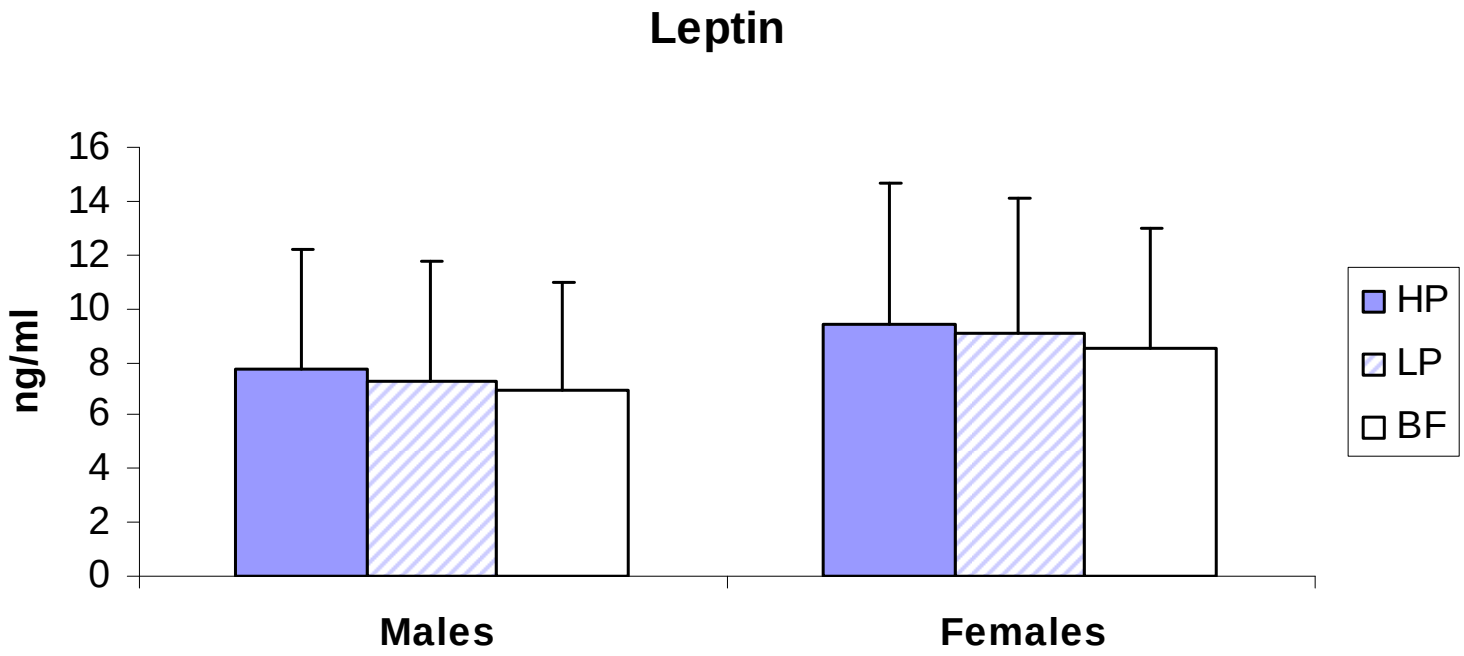
	IGFBP2 (ng/mL)		IGFBP3 (ng/mL)	
N= 699	♂	♀	♂	♀
Weight z-score	-0.183**	-0.287***	0.297***	0.331***
Length z-score	-0.066	-0.148**	0.207***	0.165**
Weight/length z-score	-0.172**	-0.250***	0.209***	0.289***
BMI z-score	-0.171**	-0.250***	0.205***	0.291***
Tricipital SKf z-score	-0.085	-0.041	-0.041	-0.014
Subscapular SKf z-score	0.003	-0.062	0.082	0.136*

*p<0.05, **p<0.01, ***p<0.001

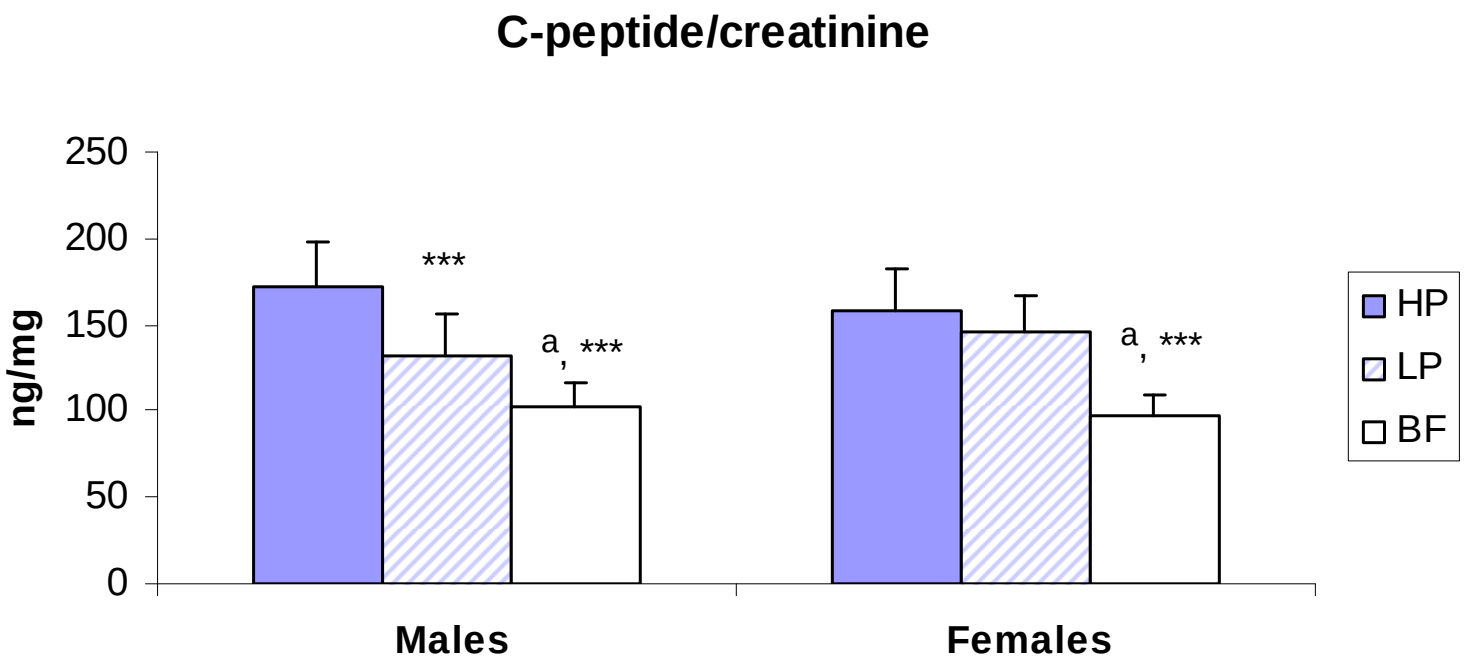
Gender differences on blood parameters (by feeding group)

		Blood leptin (ng/mL)	Blood leptin BP (ng/mL)	Blood adiponectin (µg/mL)	C-peptide/creatinine (ng/mg)
HP	♂	7.76 ± 4.46	69.4 ± 39.1	22.4 ± 5.8	171.1 ± 138.7
	♀	9.42 ± 5.29 **	61.0 ± 31.1	21.3 ± 6.7	158.8 ± 114.3
LP	♂	7.28 ± 4.49	60.5 ± 30.5	21.7 ± 6.7	132.7 ± 90.9
	♀	9.02 ± 5.04 **	58.4 ± 29.6	21.7 ± 6.6	145.5 ± 105.4
BF	♂	6.91 ± 4.02	68.5 ± 43.5	22.7 ± 5.7	102.5 ± 125.0
	♀	8.52 ± 4.50 **	66.9 ± 36.0	22.5 ± 5.7	98.0 ± 108.2

*: $p<0.05$; **:$p<0.01$; ***:$p<0.001$ vs males



Formula feeding was not associated with any change in leptin, regardless of gender



HP formula was associated with increased urinary C-peptide/creatinine among males

Δ 29% in HP vs LP among males (p<0.001)

Δ 9% in HP vs LP among females (NS)

***:p<0.001 vs HP [a]:p<0.001 vs LP

Conclusions

- HP formula was associated with increased weight among males.
- HP formula induced and increase in kidney volume in males but not in females.
- HP formula induced IGF-1 secretion, especially in females who showed a higher response.
- HP formula was associated with increased c-peptide excretion in males.
- Anthropometrical parameters were correlated with IGF-1 axis.
- Leptin values were always higher in females and the intervention maintained these differences.

Open questions / further research…

- Are there any differences in growth / fat mass by gender?
- Can IGF-1 influence “the timing” of adiposity rebound?
- Can IGF-1 influence gender differences in pubarche/ puberty?
- Can IGF-1 influence mental performance?
- Is there any relationship between sex hormones and IGF-1 ?