Getting the balance right: using nutritional geometry to optimise diet

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Charles Perkins Centre
Some big questions in nutrition

- What is a balanced diet?
- What are the consequences of an unbalanced diet?
- How does diet balance change across the life-course?

Nutritional Geometry: an integrating framework

The Nature of Nutrition
A Unifying Framework from Animal Adaptation to Human Obesity

Stephen J. Simpson and David Raubenheimer
Princeton University Press
Mapping the consequences of macronutrient balance

- Two nutrient dimensions
- Short-lived
Calorie restriction does not prolong life under *ad libitum* feeding conditions: it is the ratio of P to C that matters – in flies (and various other insects) at least ... *Mammals too?*

The Charles Perkins/ANZAC Study

- C57BL/6 wt mice
- 30 experimental diets differing systematically in
  ratio P:C:F and energy density

<table>
<thead>
<tr>
<th>Diet</th>
<th>% P</th>
<th>% C</th>
<th>% F</th>
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<tr>
<td>1</td>
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<td>23</td>
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<tr>
<td>STD</td>
<td>21</td>
<td>63</td>
<td>16</td>
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The Charles Perkins/ANZAC Study

- Fed ad libitum throughout life
- Cohort killed at 15 months
- Five diets (all 5% P) discontinued < 20 wks due to failure to grow.
Longevity greatest on low protein, high carb diets - as in flies

Macronutrient intake vs median lifespan

Actual lifespan

There was no life extension due to caloric restriction per se under *ad libitum* conditions - as in flies.
Mechanism related to *ageing biology*

Mitochondrial function enhanced (state III with pyruvate)

mTOR activation low on low P:C diets

... in turn reflected in blood levels of branched chain amino acids and glucose

mTOR driven by BCAA:glucose

Telomeres longest on low P:C diets
Levels of amino acids

Levels of glucose

TOR activity

AMPK activity

High P:C diet

Low P:C diet

Levels of amino acids

Levels of glucose

Nutrients

Leptin; insulin/IGF; etc.

Stress factors; sirtuins; etc

Insulin resistance; autophagy and repair inhibited

Insulin sensitivity; autophagy and repair promoted

Eat less

Eat more

Anabolic responses

Protein synthesis, lipogenesis, cell proliferation, growth, reproduction

Catabolic responses

Cell cycle arrest, inhibition of growth and reproduction, lipolysis, proteolysis

Die early

Live longer

In vitro studies: Hep G2 cells

Solon-Biet et al., unpublished.
Indicators of late-life health were optimal on low P:C diets BUT body fat was high due to ‘protein leverage’

(Le Couteur et al. (2015). J. Gerontol.)
Mice ate more on low protein diets to stabilise protein intake

“Healthy” obesity on a low protein, high carb diet than on a low protein, high fat diet, but obese nonetheless
The protein conundrum

Balance of dietary macronutrients
low protein : high carbohydrate

↑ food intake
↑ Obesity

↑ health

Protein leverage in humans

Meta-analysis of 38 trials in which subjects had \textit{ad libitum} access to diets differing in \% protein

%P range across all human populations with food sufficiency

Apparent even when macronutrient composition of the diet is disguised in clinical trials (Sydney and Jamaica)

Subjects ate 12% more total energy on 10% protein diets by increased snacking between meals, favouring savoury flavoured foods – indicative of protein seeking behaviour.


% P has fallen in the western diet by 1-2% since 1960: Why?

1. Economics: protein is more expensive than fat and carbs

2. Evolutionary legacy: fats and simple sugars were rare and prized – now superabundant, supernormal stimuli

3. More sedentary lifestyle – need less non-P energy to fuel metabolism

4. Rising atmospheric CO$_2$? There has been an average 54% increase in CHO:P ratio in plants (Robinson et al. 2012, *New Phytologist* 194:321-336)

How can the protein leverage effect be managed?

- Intermittent fasting (or maybe just not snacking) – implication of ad libitum studies is that fasting, rather than calories per se, underlies benefits of CR

- Increase energy expenditure – exercise and thermogenesis

- Choose dietary protein sources with low levels of branched chain and sulphur amino acids (Hine et al. 2014, Cell)

- Drugs that dampen protein appetite? FGF21 is a new candidate target molecule, with associated beneficial metabolic effects (Laeger et al. 2014 JCI)
Comparing *ad libitum* low P:C diet vs CR in mice

FGF21 is elevated on low protein/high carb diets

A. Circulating FGF21 *in vivo* (ng/ml)

B. FGF21 *in vitro* – Hep G2 cells

Solon-Biet et al., unpublished
BUT, as in flies, maximising reproductive potential needs higher protein intake

Conclusions: for mice at least

<table>
<thead>
<tr>
<th>Low P:High C:Low F</th>
<th>High P:Low C:High F</th>
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<tbody>
<tr>
<td>Increased food intake</td>
<td>Reduced food intake</td>
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<tr>
<td>Excess energy intake</td>
<td>Reduced energy intake</td>
</tr>
<tr>
<td>Increased adiposity</td>
<td>Decreased adiposity, increased lean mass</td>
</tr>
<tr>
<td>Better health outcomes</td>
<td>Worse health outcomes</td>
</tr>
<tr>
<td>Increased lifespan</td>
<td>Shorter lifespan</td>
</tr>
<tr>
<td>“Healthy” microbiome</td>
<td>“Unhealthy” microbiome</td>
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<tr>
<td>Reduced reproductive potential</td>
<td>Increased reproductive potential</td>
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<table>
<thead>
<tr>
<th>Low P:High F:Low C</th>
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<tbody>
<tr>
<td>Massively increased food intake</td>
</tr>
<tr>
<td>Vast excess energy intake</td>
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<tr>
<td>Maximal adiposity</td>
</tr>
<tr>
<td>Very poor health outcomes</td>
</tr>
<tr>
<td>Decreased lifespan</td>
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<tr>
<td>Reduced reproductive potential</td>
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Data are suggesting the same in humans too …

Protein and amino acid restriction, aging and disease: from yeast to humans

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Health effects of protein intake in healthy adults: a systematic literature review

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¹ DTU Food, National Food Institute, Lyngby, Denmark; ² Clinical Nutrition Unit, Rigshospitalet University Hospital, Copenhagen, Denmark; ³ Department of Surgery, The University of Texas Medical Branch, Galveston, TX, USA
Moderate protein, high carbohydrate diets associated with better cognitive function in older men
Maternal macronutrition and its effects *in utero*
Method

- The Women & Their Children’s Health (WATCH) Study

- 179 Australian women enrolled during pregnancy

- Measurements: diet, mother’s health, child’s health, body composition etc.

Two key questions:

1) How did energy intake relate to macronutrient balance?

2) How did the child’s body composition (fat) relate to maternal diet?
1) How did energy intake relate to macronutrient balance?

i. Energy intake peaked at low % P (16%), supporting the protein leverage hypothesis.

ii. But was only high when low P was combined with high Fat (44%).

iii. And not high Carbohydrate.

iv. Suggests protein leverage is particularly strong for Fat – as in mice.

2) How did the child’s body composition (fat) relate to maternal diet?

Differed according to site of fat depot

Would you rather:

1. Lose weight?
2. Live longer and stay healthier?
3. Look younger?
4. Have healthy children?

Diet can help achieve each of these – but not all on the same diet composition!

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