PFASs and Changes in Body Weight and Resting Metabolic Rate in Response to Weight-loss Diets

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Background — PFASs

- PFOA (C8)
- PFOS (C8)
- PFNA (C9)
- PFDA (C10)
- PFHxS (C6)
- PFUdA, PFDoA...

- Elimination half-lives: 3-8 years
- Exposure routes: diet, drinking water, food packaging...

PFASs are Obesogens

- PFASs can modulate:
  - PPARα and PPARγ
  - Hepatocyte Nuclear Factor 4α
  - Estrogen receptors
  - Thyroid hormones
Low-dose PFASs Exposures Led to Weight Gain in Mouse Model

E.P. Hines et al. / Molecular and Cellular Endocrinology 304 (2009) 97–105
“The strongest effects were seen with PFOS among males. In males 12–19 and 20–59 years of age, BMI decreased with increasing PFOS exposure. Teenage boys in the highest PFOS quartile had BMIs that were 2.8 points (95% CI, –4.1 to –1.4) lower than those in the lowest quartile ($p$-value for trend $= 0.004$). In men 60–80 years of age, on the other hand, increasing PFOS exposure was associated with increased BMI [effect estimate for the top quartile compared with lowest of 1.6 (95% CI, 0.14–3.0)].“
Did we ask the right question?
Background — Weight Regain in Common

Winner of Season 8

Before show: 430 lbs.
After show: 191 lbs.
After 6 years: 295 lbs.

E Fothergill et al, Obesity, 2016
Challenges for observational studies

- Intentional weight change versus unintentional weight change
- Weight loss trials: causes of weight change are well-defined.
Background — We are Engineered to Maintain Body Weight

Persistence of Hormonal Adaptations to Weight Loss

Adapted from P Sumithran et al, N Engl J Med, 2011
Resting Metabolic Rate (RMR) is the rate at which body burns energy when at complete rest.

![Graph showing the relationship between Resting Metabolic Rate (kcal/24 hour) and Weight Loss (% of body weight).](Adapted from Stanley Heshka, et al, AJCN)
Weight gain and weight loss
Background — Weight Loss and Regain Varies between Individuals
The POUNDS LOST trial

- **2-year** randomized clinical dietary intervention trial
- **4** energy-reduced diets with different macronutrients
- **811** overweight and obese participants (30-70 years)

• Study hypotheses:
  – Higher PFASs levels are associated with slower weight loss.
  – Higher PFASs levels are associated with faster weight regain.
• Study design:
  – Baseline PFASs levels
  – Weight loss through 6 months
  – Weight regain between 6 and 24 month
  – RMR changes
• Statistical analyses
  – Linear mixed-effects model
## Results

### PFASs & Metabolic Parameters (at baseline)

<table>
<thead>
<tr>
<th></th>
<th>PFOA</th>
<th>PFHxS</th>
<th>PFNA</th>
<th>PFDA</th>
<th>PFOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAT fat mass</td>
<td>0.13</td>
<td>0.13</td>
<td><strong>0.24</strong></td>
<td>0.17*</td>
<td>0.10</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td><strong>0.10</strong>*</td>
<td>0.09*</td>
<td><strong>0.18</strong>***</td>
<td>0.06</td>
<td><strong>0.15</strong>***</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.05</td>
<td>0.04</td>
<td><strong>0.15</strong>***</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>Insulin</td>
<td><strong>0.10</strong>*</td>
<td>0.07</td>
<td><strong>0.14</strong>***</td>
<td>0.04</td>
<td><strong>0.10</strong>*</td>
</tr>
<tr>
<td>HbA1C</td>
<td>-0.03</td>
<td>-0.03</td>
<td>0.01</td>
<td>0.02</td>
<td>-0.01</td>
</tr>
<tr>
<td>HOMA_IR</td>
<td><strong>0.10</strong>*</td>
<td>0.07</td>
<td><strong>0.15</strong>***</td>
<td>0.05</td>
<td><strong>0.10</strong>*</td>
</tr>
<tr>
<td>Triglycerides</td>
<td><strong>0.08</strong>*</td>
<td>0.04</td>
<td>0.003</td>
<td>-0.07</td>
<td>-0.02</td>
</tr>
<tr>
<td>Free T3</td>
<td><strong>0.15</strong>***</td>
<td><strong>0.11</strong>**</td>
<td><strong>0.09</strong>*</td>
<td>0.04</td>
<td><strong>0.12</strong>**</td>
</tr>
<tr>
<td>Free T4</td>
<td>0.06</td>
<td><strong>0.10</strong>*</td>
<td><strong>0.09</strong>*</td>
<td>0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>Leptin</td>
<td><strong>0.09</strong>*</td>
<td>0.08</td>
<td>0.06</td>
<td>0.01</td>
<td>0.05</td>
</tr>
</tbody>
</table>

- Date are adjusted for demographics, lifestyle factors, and diet groups.

Results – PFASs Predict Weight Regain

- Baseline PFASs ↑ Weight Regain

Data are least-square means, with multivariate adjustment including lifestyle factors, diet groups, and baseline body weight

G Liu et al, PLoS Medicine. 2018
Results — PFASs & Weight Change in Men

Data are least-square means, with multivariate adjustment including diet groups, and baseline body weight.
Results — PFASs & Weight Change in Women

Data are least-square means, with multivariate adjustment including diet groups, and baseline body weight.
Results — PFASs & RMR

Data are least-square means, with multivariate adjustment including diet groups, and baseline resting metabolic rate.
Alternative explanations?

• Chance findings?
• Confounding by an obesogenic habitual diet?
Implications

• PFASs may contribute to the obesity epidemic by promoting weight regain after intentional weight loss.
• We need to understand how PFASs promote weight regain and prevent RMR regression.
• Need to confirm the current findings in other weight loss trials.
• Animal studies can help elucidate the mechanisms.
Conclusion

- In this diet-induced weight-loss setting, higher baseline PFASs predict more weight regain, especially in women, possibly explained by the suppressed RMR levels associated with higher PFASs levels.

- A novel role of PFASs in weight regulation may help identify individuals more responsive to weight-loss diets.
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Thank You