

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

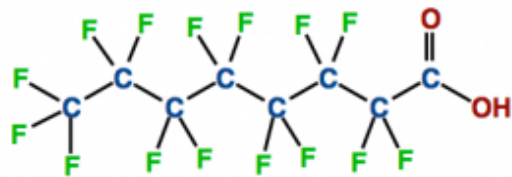
Qi Sun, MD, ScD
Associate Professor of Medicine

Channing Division of Network Medicine, Brigham and Women's Hospital and
Harvard Medical School
Department of Nutrition, Harvard School of Public Health

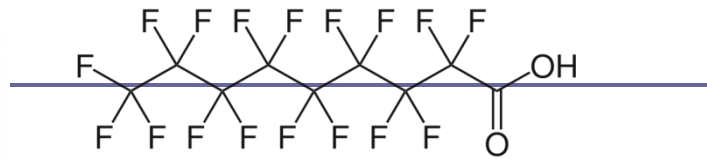
April 18, 2018



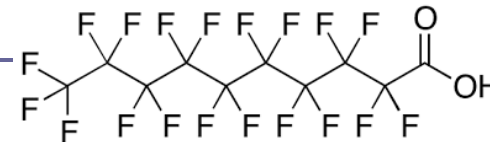
Background – PFASs



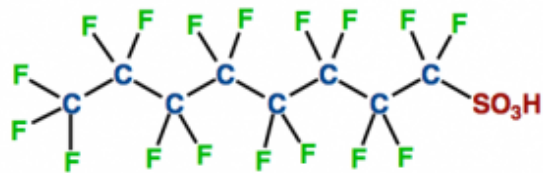
□ PFOA (C8)



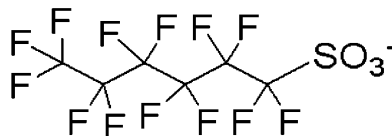
□ PFNA (C9)



□ PFDA (C10)



□ PFOS (C8)



□ PFHxS (C6)

□ PFUdA, PFDoA ...

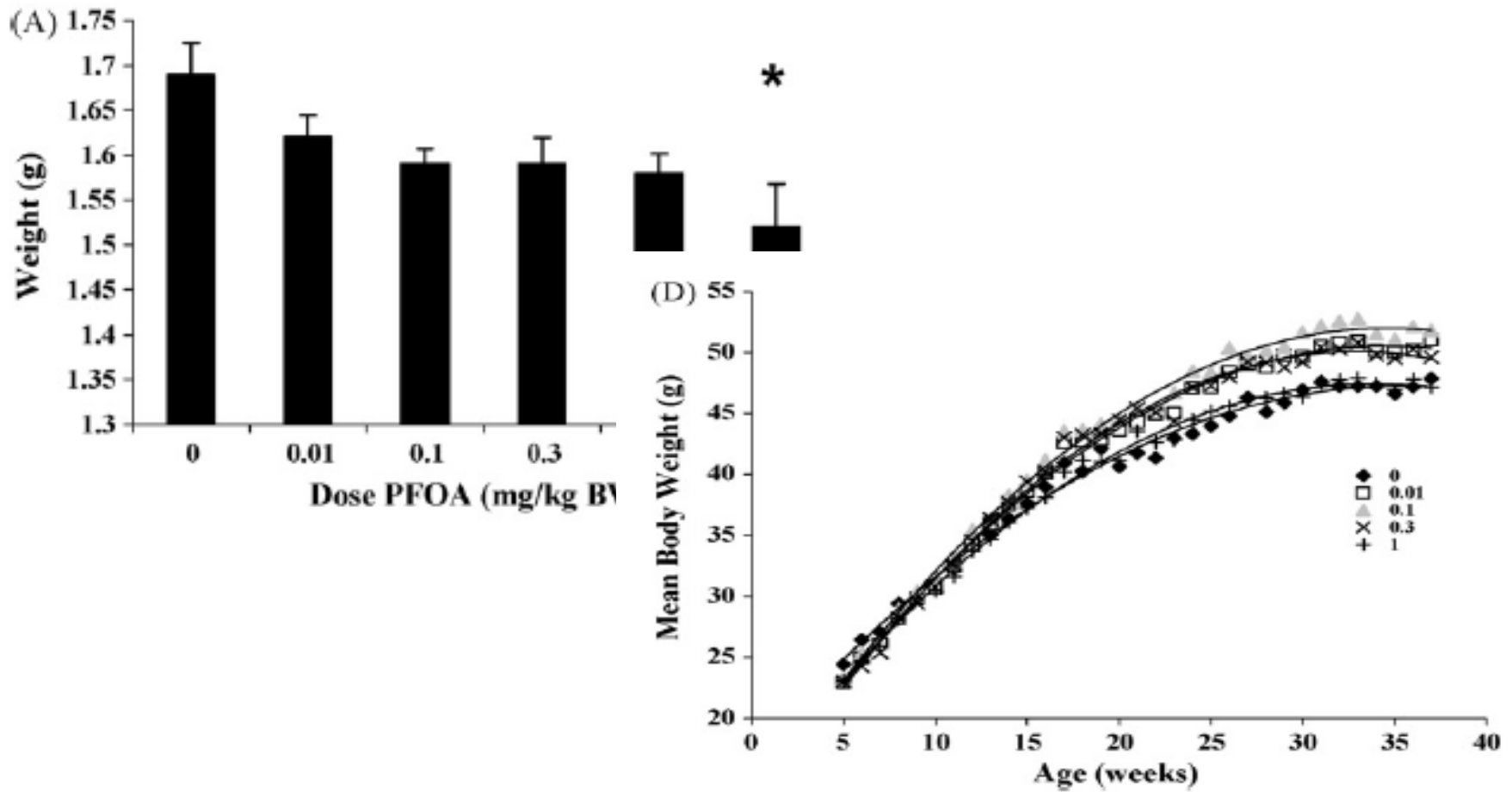
□ Elimination half-lives: **3-8** years

□ Exposure routes: **diet, drinking water, food packaging...**

PFASs are obesogens

- PFASs can modulate:
 - PPAR α and PPAR γ
 - Hepatocyte Nuclear Factor 4 α
 - Estrogen receptors
 - Thyroid hormones

Low-dose PFASs Exposures Led to Weight Gain in Mouse Model



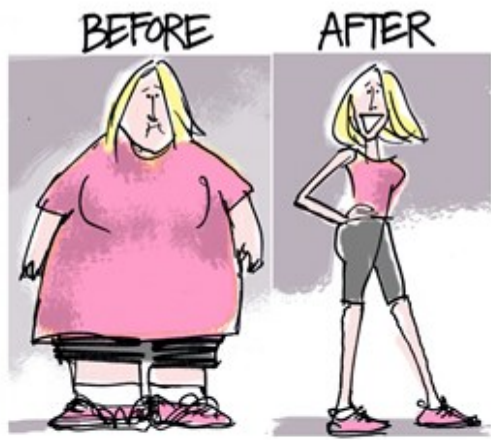
Human Studies are Mixed

“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)].”

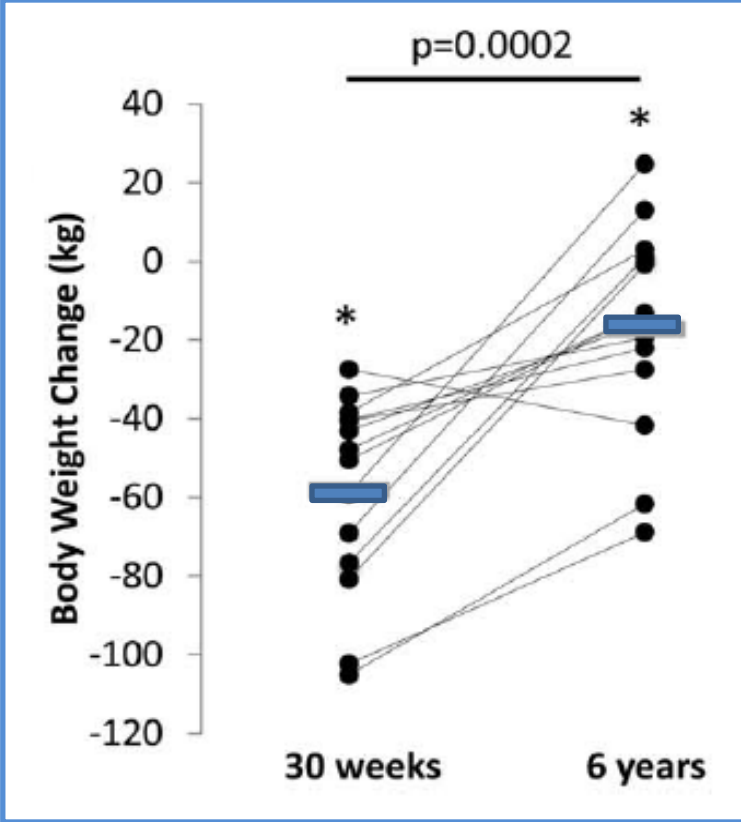
Did we ask the right
question?



Background – Weight Regain in Common



Winner of Season 8
Before show: 430 lbs.
After show: 191 lbs.
After 6 years: 295 lbs.



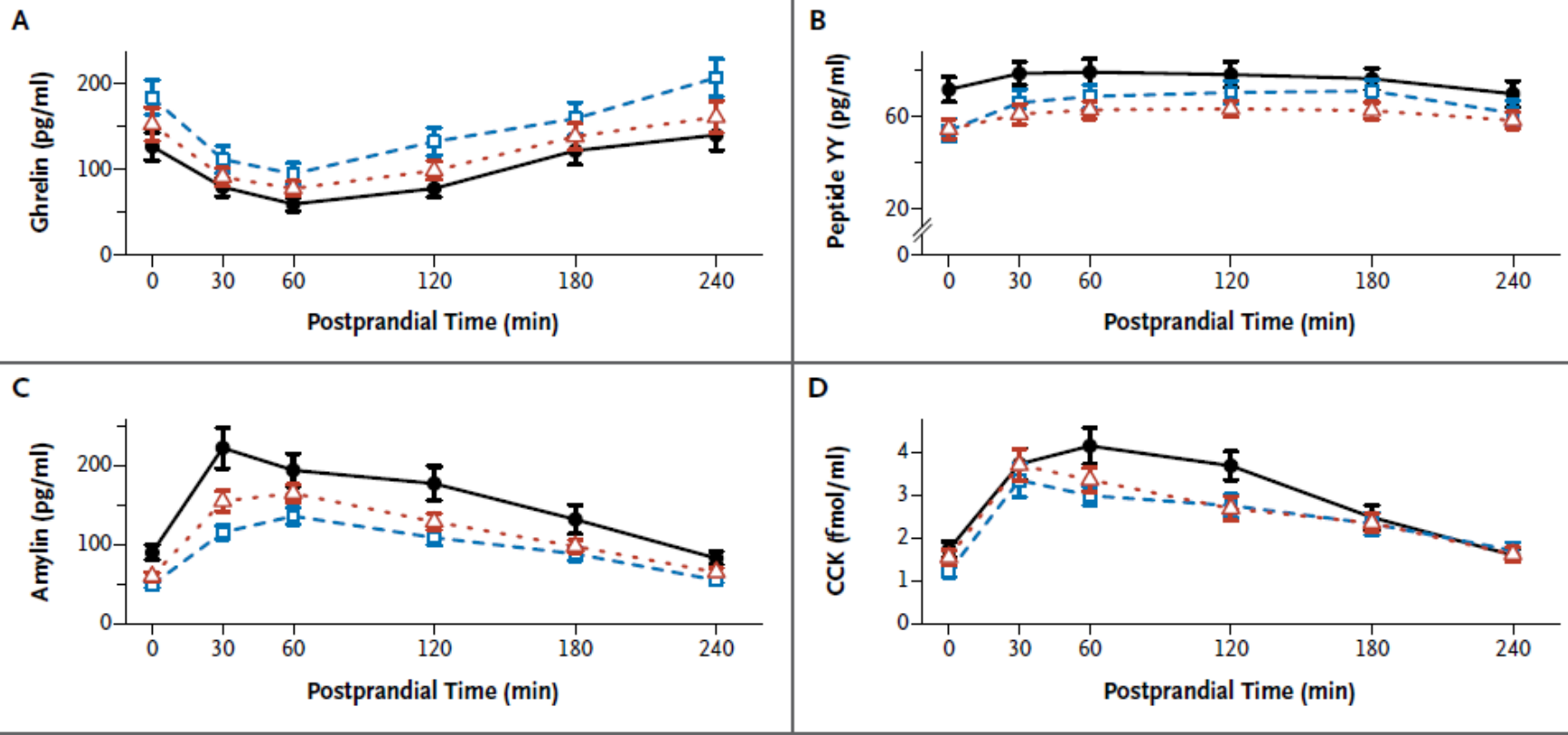
Challenges for observational studies

- 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

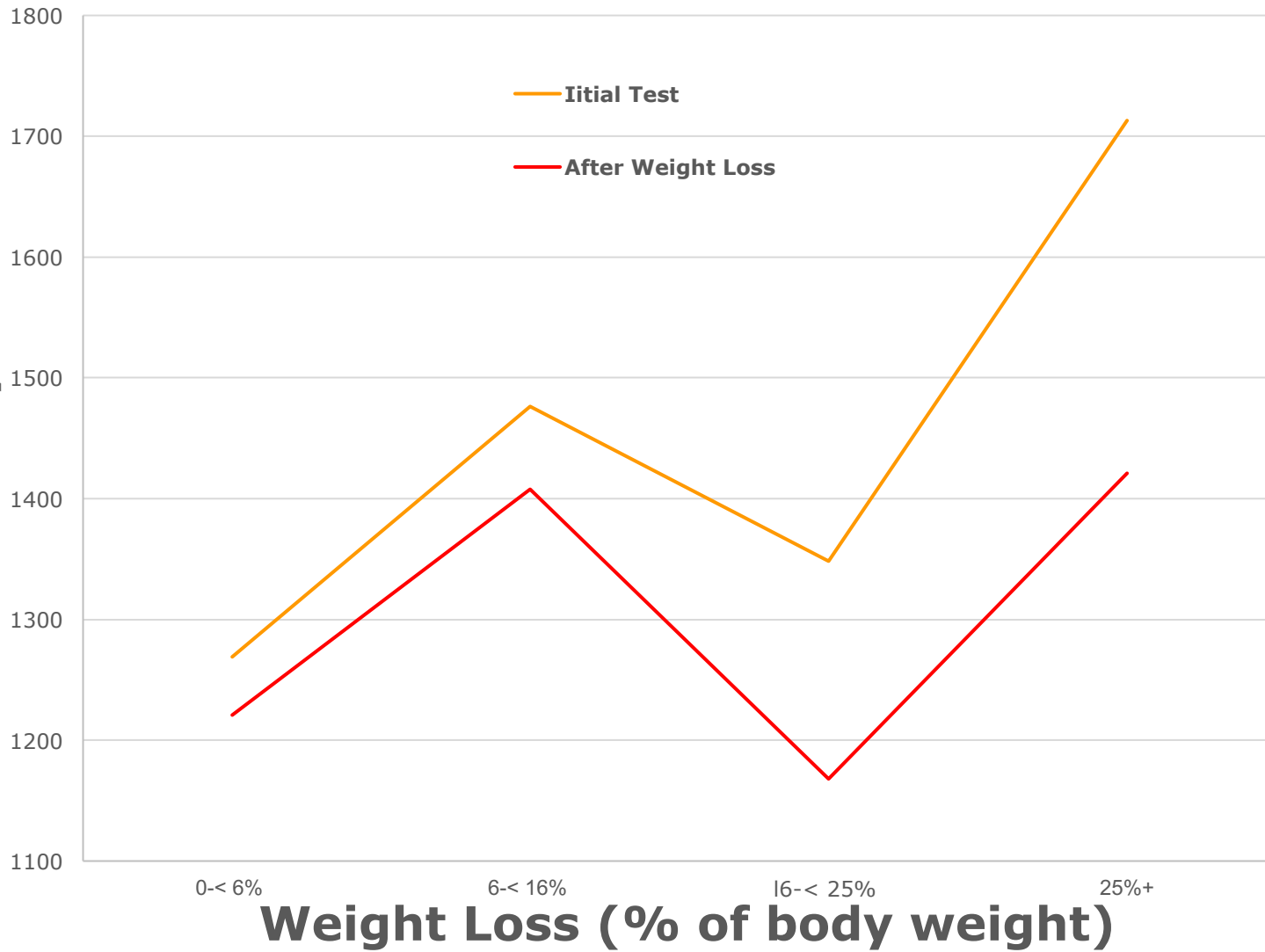
Persistence of Hormonal Adaptations to Weight Loss

—●— Baseline —□— Week 10 —△— Week 62



□ Adapted from P Sumithran et al, *N Engl J Med*, 2011

Resting Metabolic Rate (kcal/24 hour)

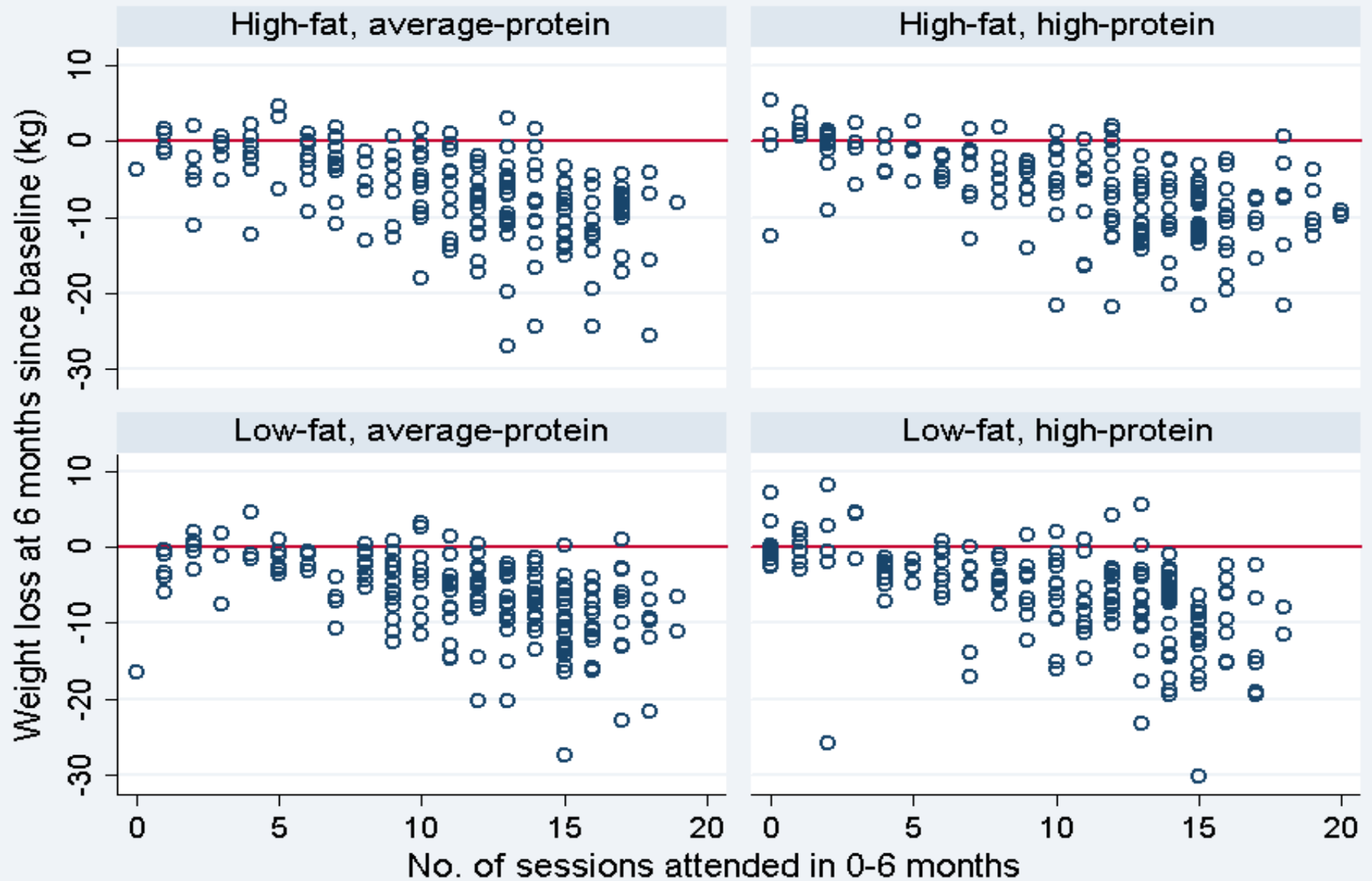


Adapted from Stanley Heshka, et al, AJCN

Weight gain and weight loss



Background — Weight Loss and Regain Varies between Individuals

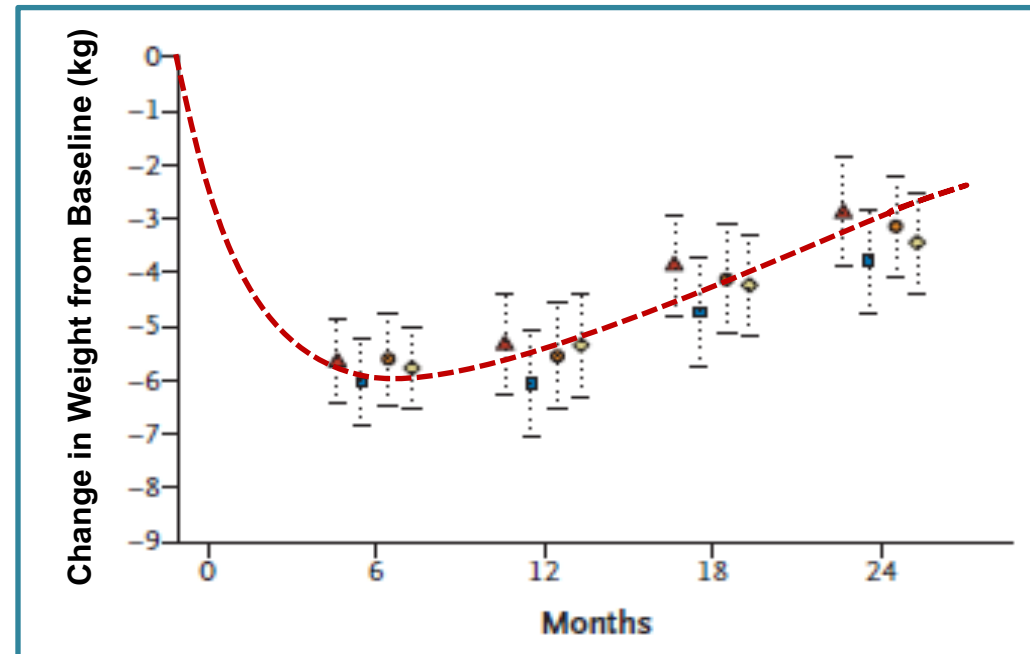


Study Population



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)



Adapted from FM Sacks et al, N Engl J Med, 2009

- 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)

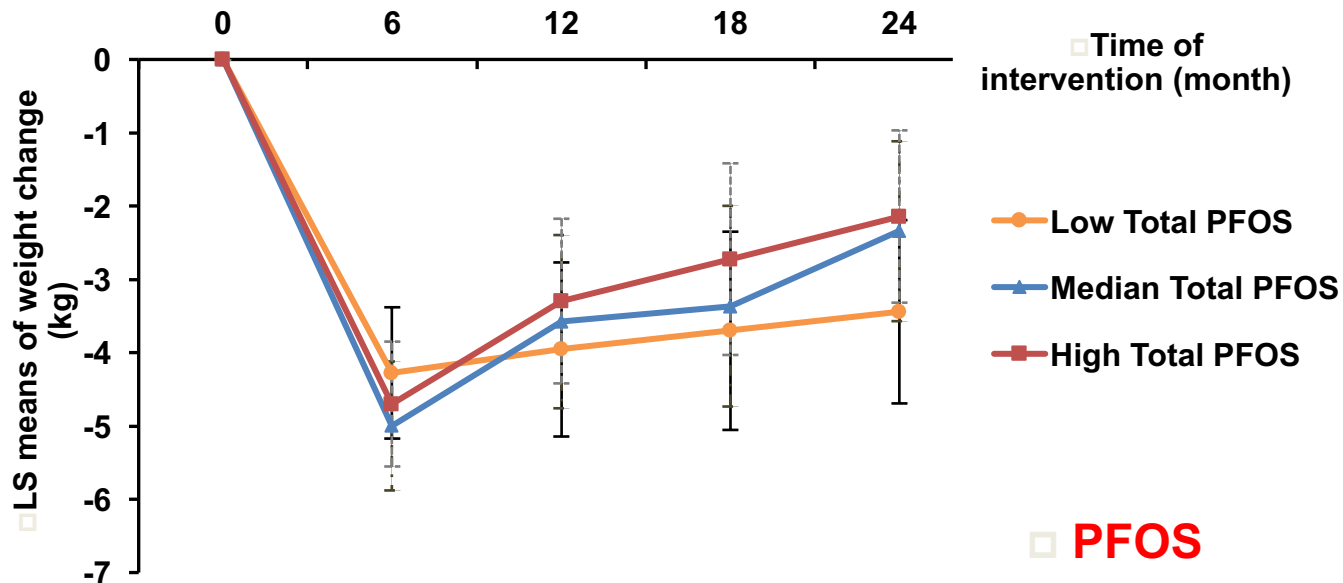
	PFOA	PFHxS	PFNA	PFDA	PFOS
VAT fat mass	0.13	0.13	0.24**	0.17*	0.10
Diastolic blood pressure	0.10*	0.09*	0.18***	0.06	0.15***
Glucose	0.05	0.04	0.15***	0.08	0.08
Insulin	0.10*	0.07	0.14***	0.04	0.10*
HbA1C	-0.03	-0.03	0.01	0.02	-0.01
HOMA_IR	0.10*	0.07	0.15***	0.05	0.10*
Triglycerides	0.08*	0.04	0.003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

□ Data are adjusted for demographics, lifestyle factors, and diet groups.

□ G Liu et al, *PLoS Medicine*. 2018

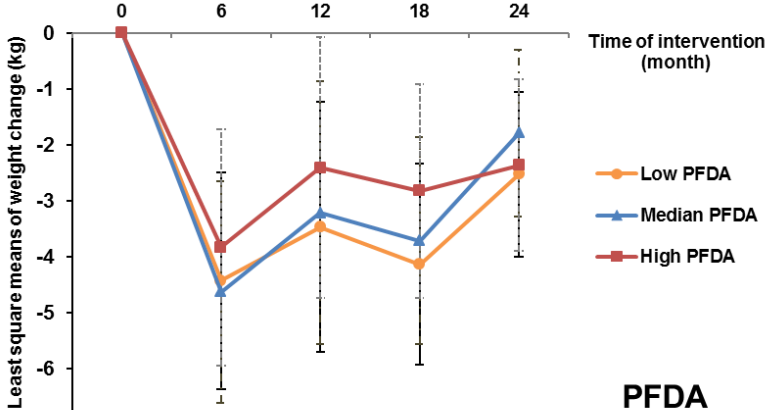
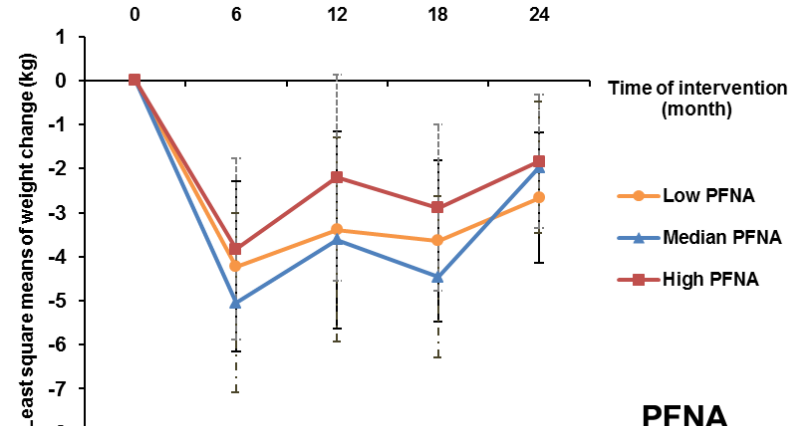
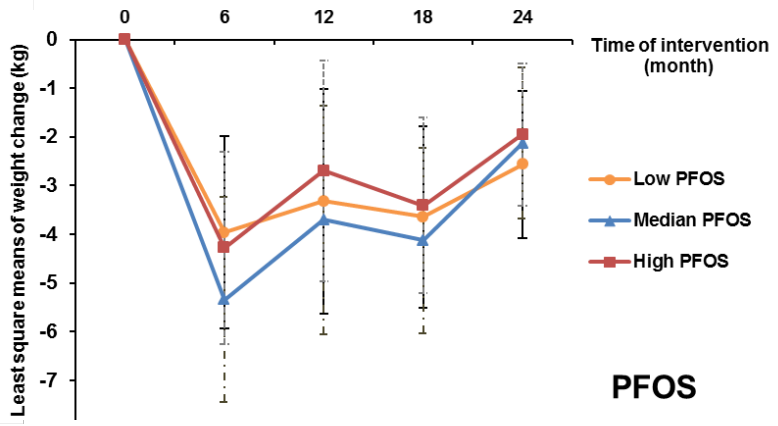
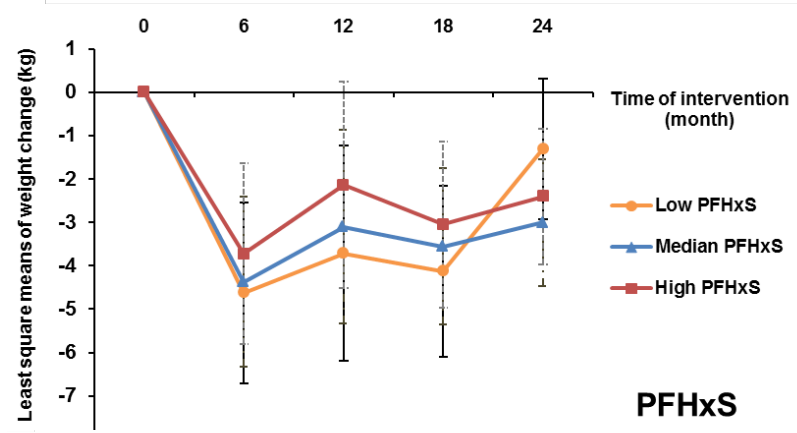
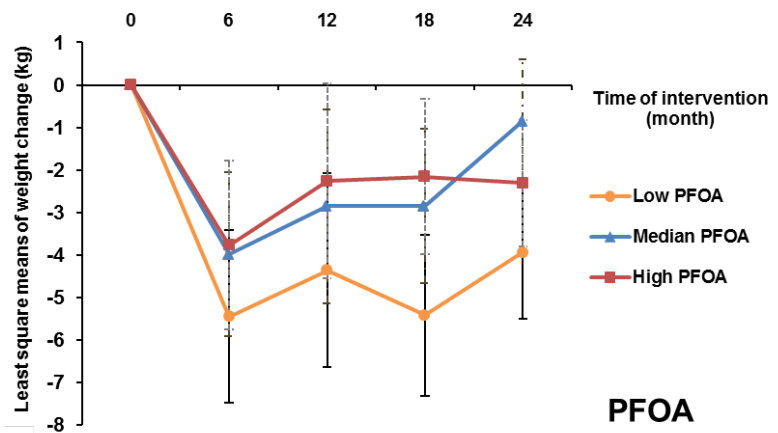
Results – PFASs Predict Weight Regain

↑ Baseline PFASs ↑ Weight Regain



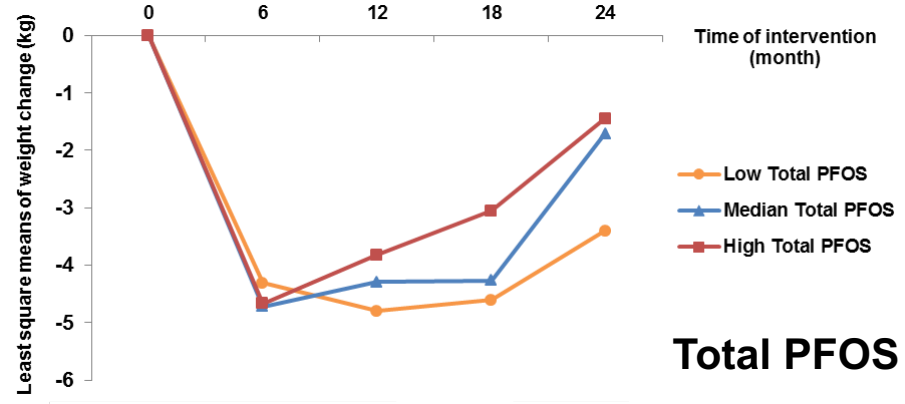
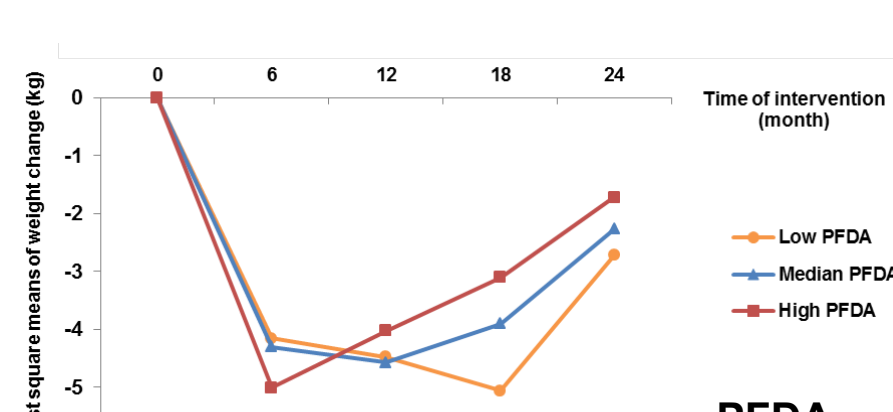
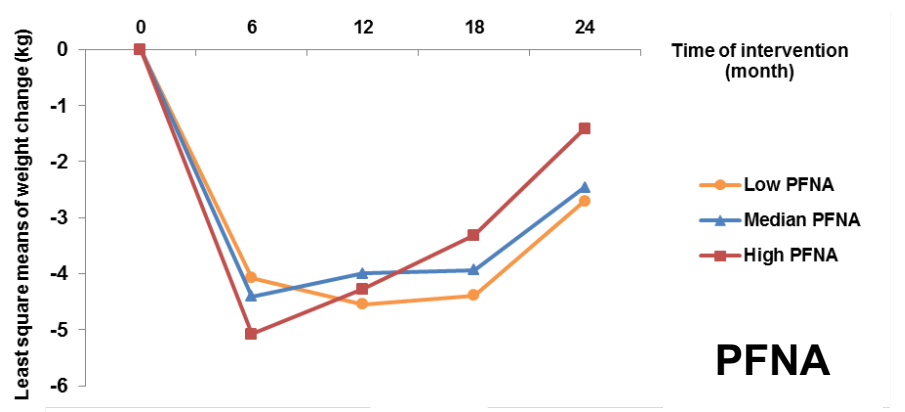
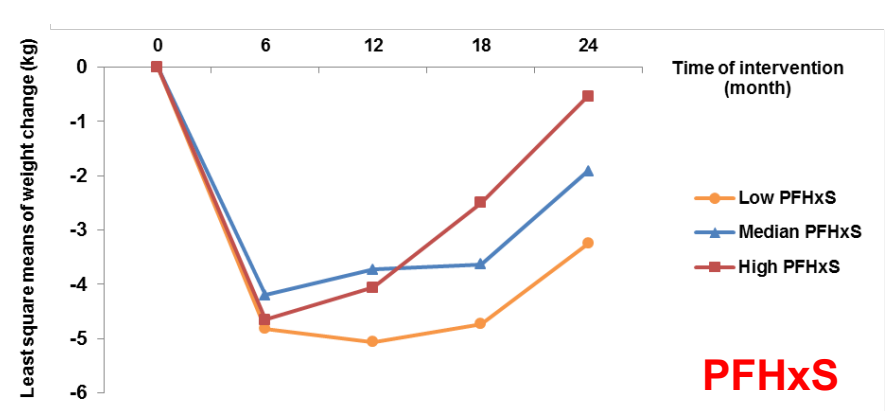
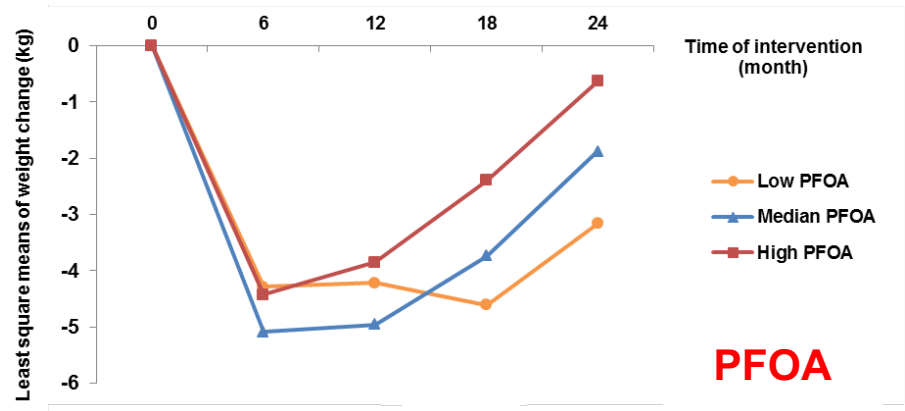
Data are least-square means, with multivariate adjustment including lifestyle factors, diet groups, and baseline body weight

Results — PFASs & Weight Change in Men



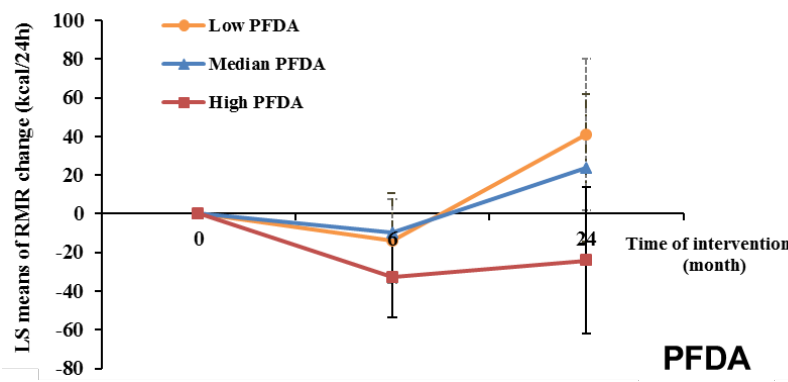
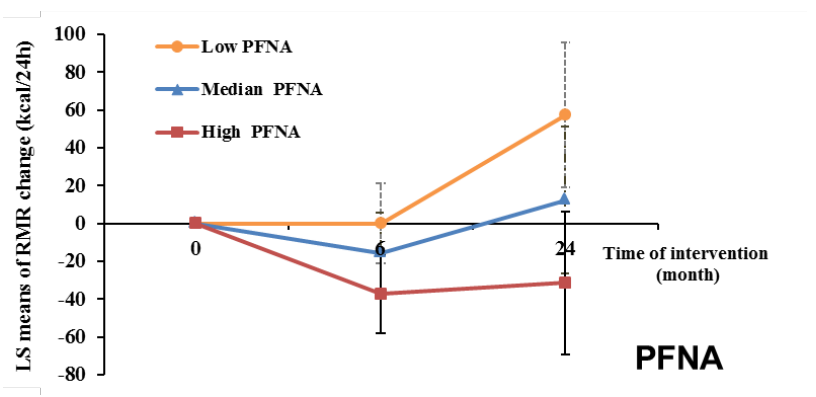
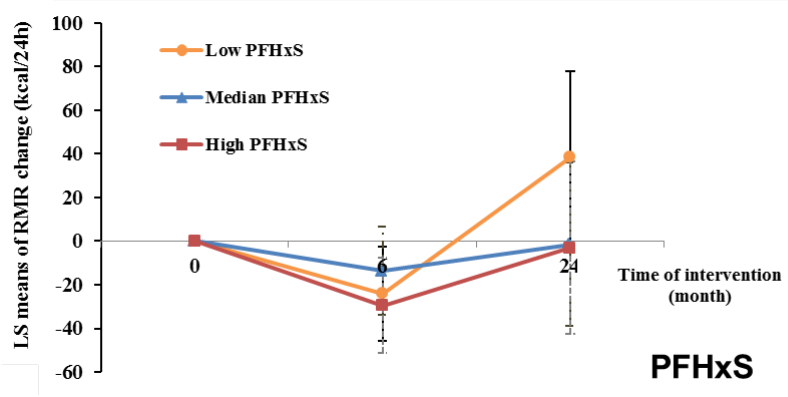
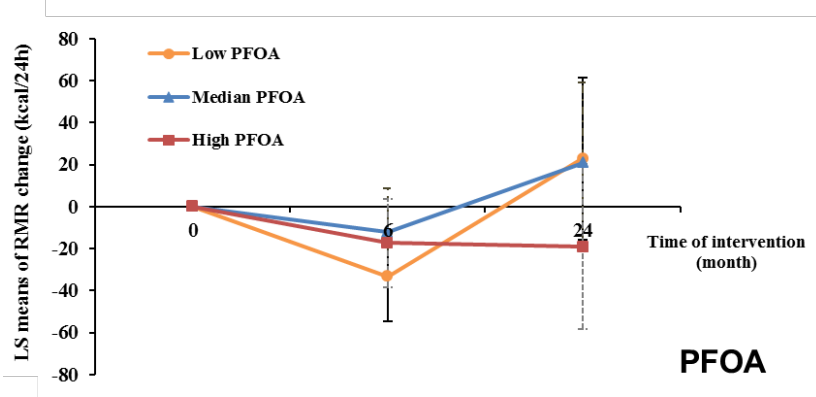
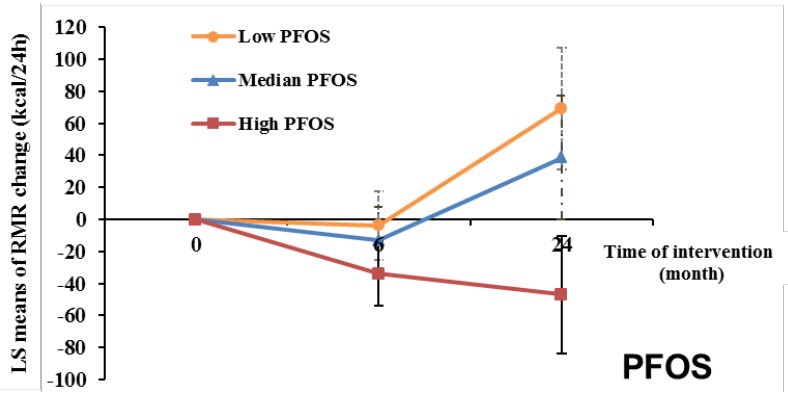
□ Data are least-square means, with multivariate adjustment including diet groups, and baseline body weight

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?

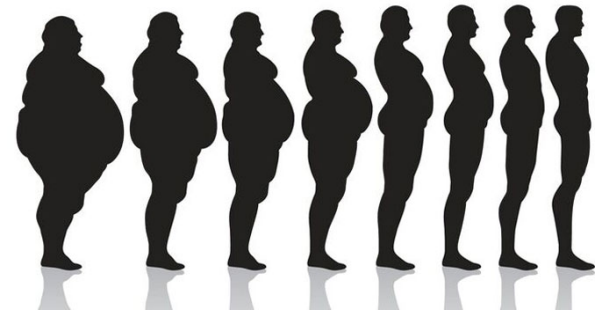
- Chance findings?
- Confounding by an obesogenic habitual diet?

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

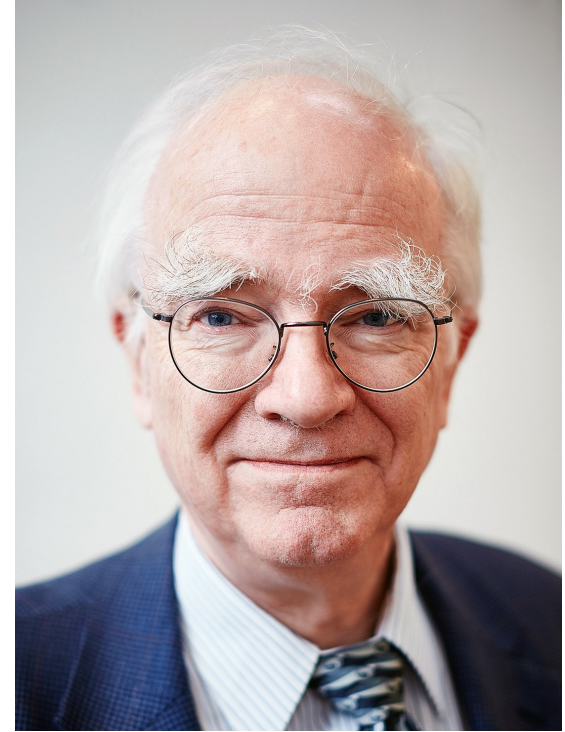
- In this diet-induced weight-loss setting, higher baseline **PFASs** predict more **weight regain**, especially in **women**, possibly explained by the **suppressed RMR** levels associated with higher PFASs levels
- A novel role of **PFASs** in weight regulation may help identify individuals **more responsive** to weight-loss diets



Acknowledgment



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Thank You

