Olestra Post-Marketing Surveillance

Lessons for GM foods

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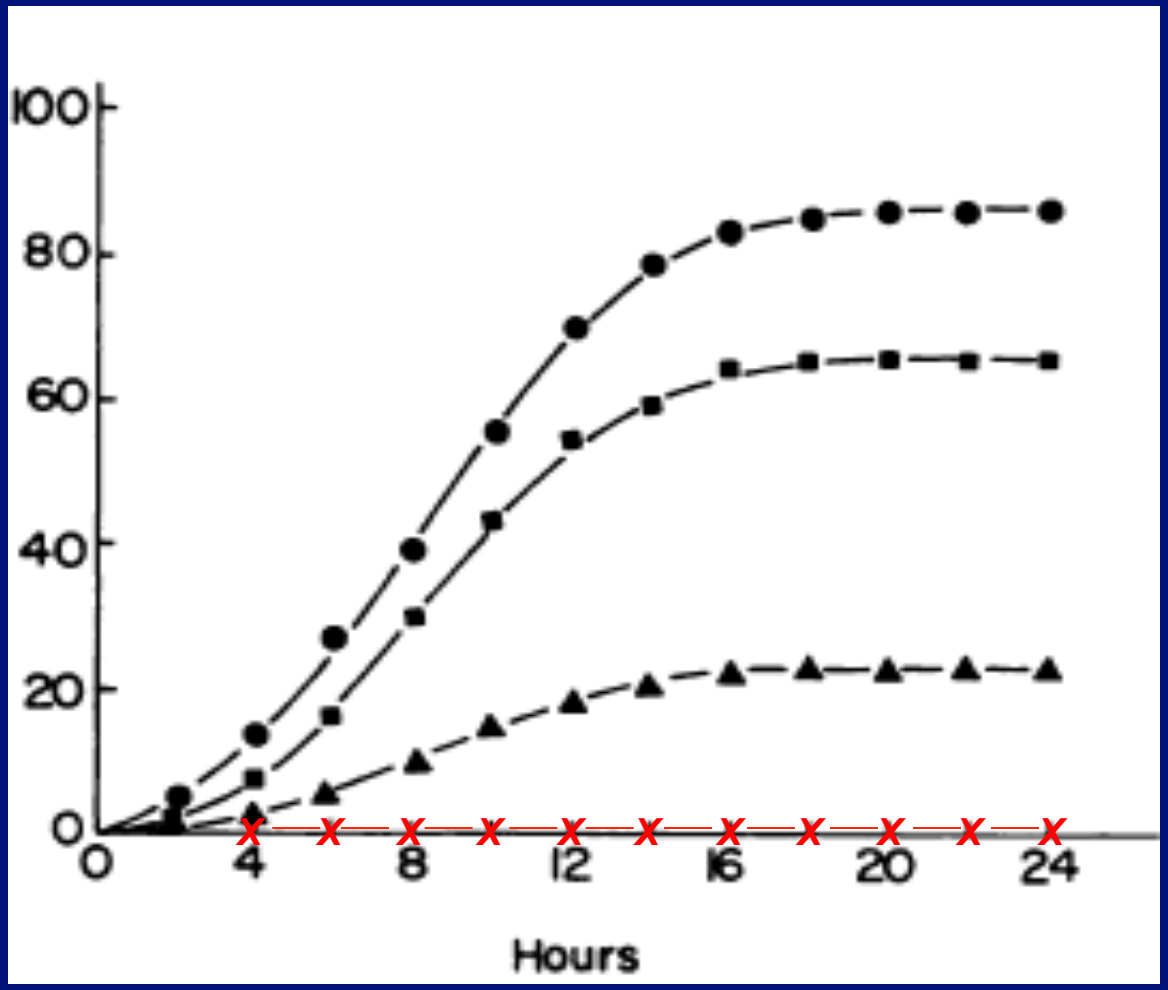
Absorption of Fats Decreases as Number of Fatty Acid Ester Groups Increase



Glycerol (3)

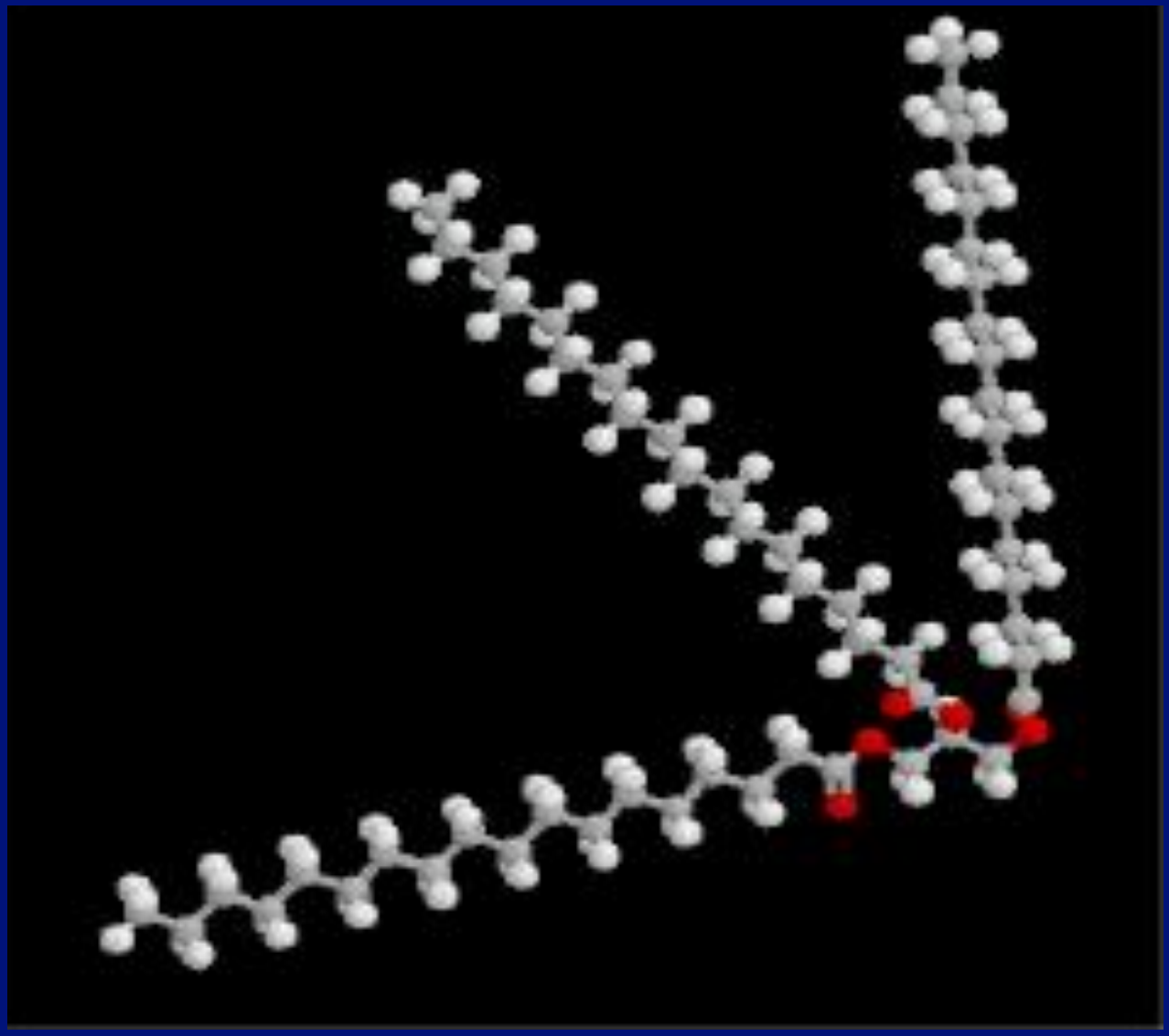
Erythritol (4)

Xylitol (5)

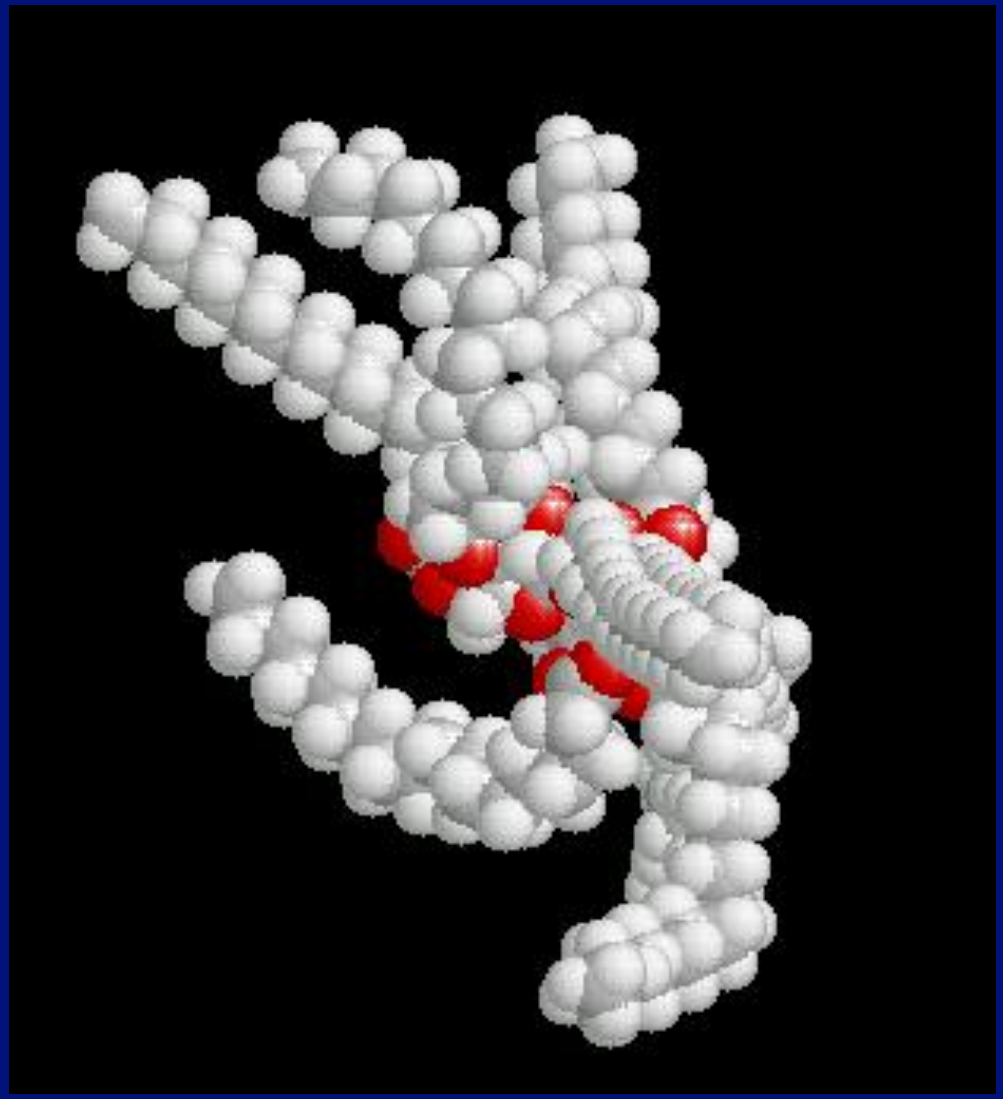
Sucrose (8)

Mattson FH, Volpenhein RA, J Nutr 102: 1972

Triglycerides Readily Absorbed



Sucrose Octa-Ester Resistant to Pancreatic Lipases and Bacterial Metabolism



1971 *Proctor and Gamble first meets with U.S. Food and Drug Administration*

1987 *Proctor and Gamble applies for market approval as general purpose fat substitute*

1990 *Proctor and Gamble narrows application to savory snacks*

1995 *Congressional sub-committee holds hearings on FDA food additive petitions*

1995 *Regulatory decision team votes 17-5 for approval*

1996 *Approval, conditional upon Post-Marketing Surveillance*

FDA 1997 Final Ruling

The Procter and Gamble Co. has made a commitment to the agency that it will conduct the studies outlined in the letter to FDA…

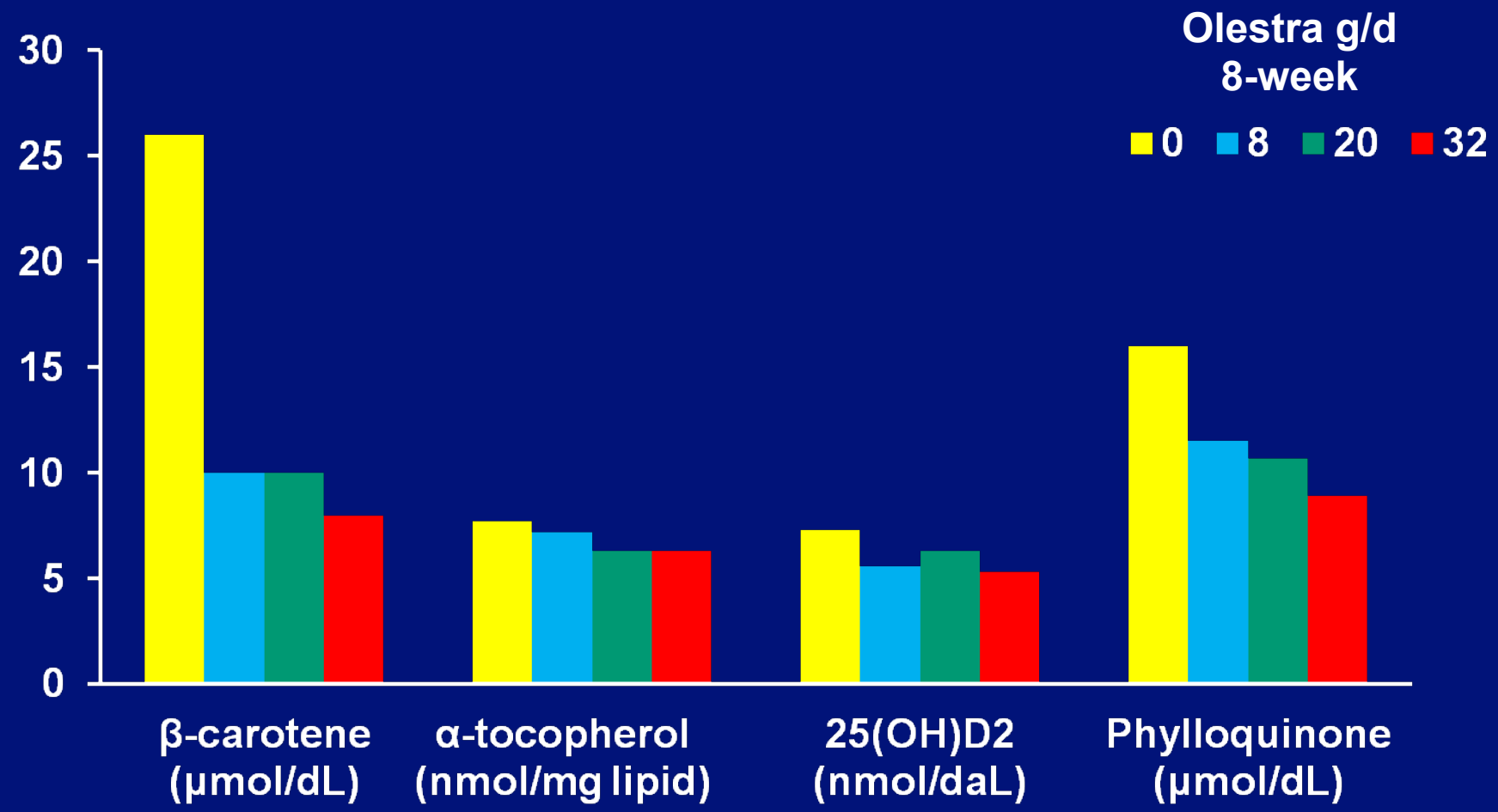
If Procter and Gamble does not conduct the identified studies …., FDA will consider the approval set forth in this document to be void…

FDA 1997 Final Ruling

It is the agency's responsibility….to review and evaluate the data generated by Procter and Gamble's studies, as well as any new data that bear on the safety of olestra (such as data and information on the health significance of carontenoids) to determine whether there continues to be a basis for a reasonable certainty that the use of olestra in savory snacks is not harmful.

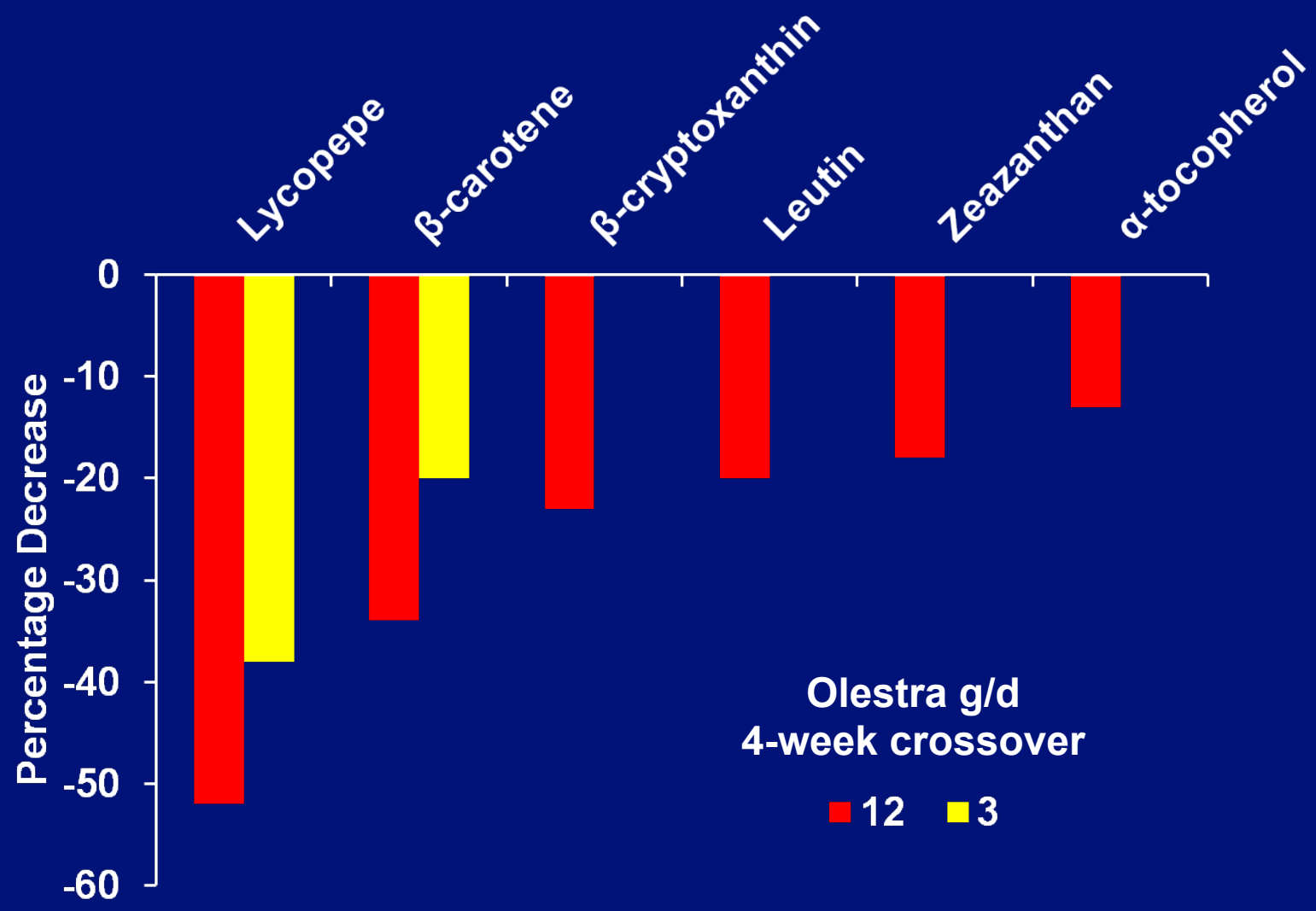

Lay's
WOW!
FAT FREE
Original
Doritos
WOW!
Nacho Cheesier
Ruffles
WOW!
FAT FREE
Original

Olestra Lowers Absorption of β-carotene and Vitamins E, D and K in Humans



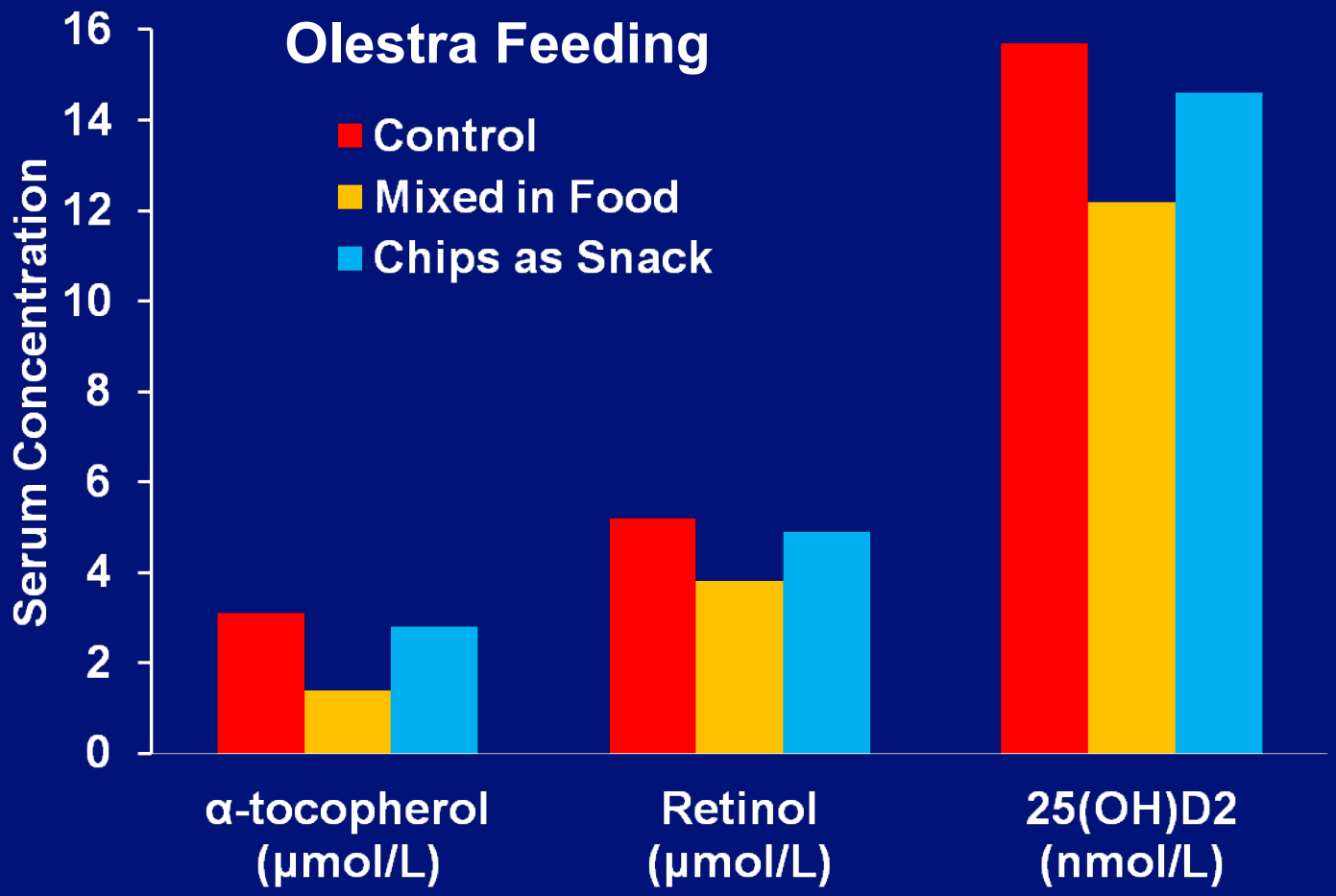
Schlagheck, J Nutr 1997

Olestra Substantially Decreases Serum Carotenoid Concentrations



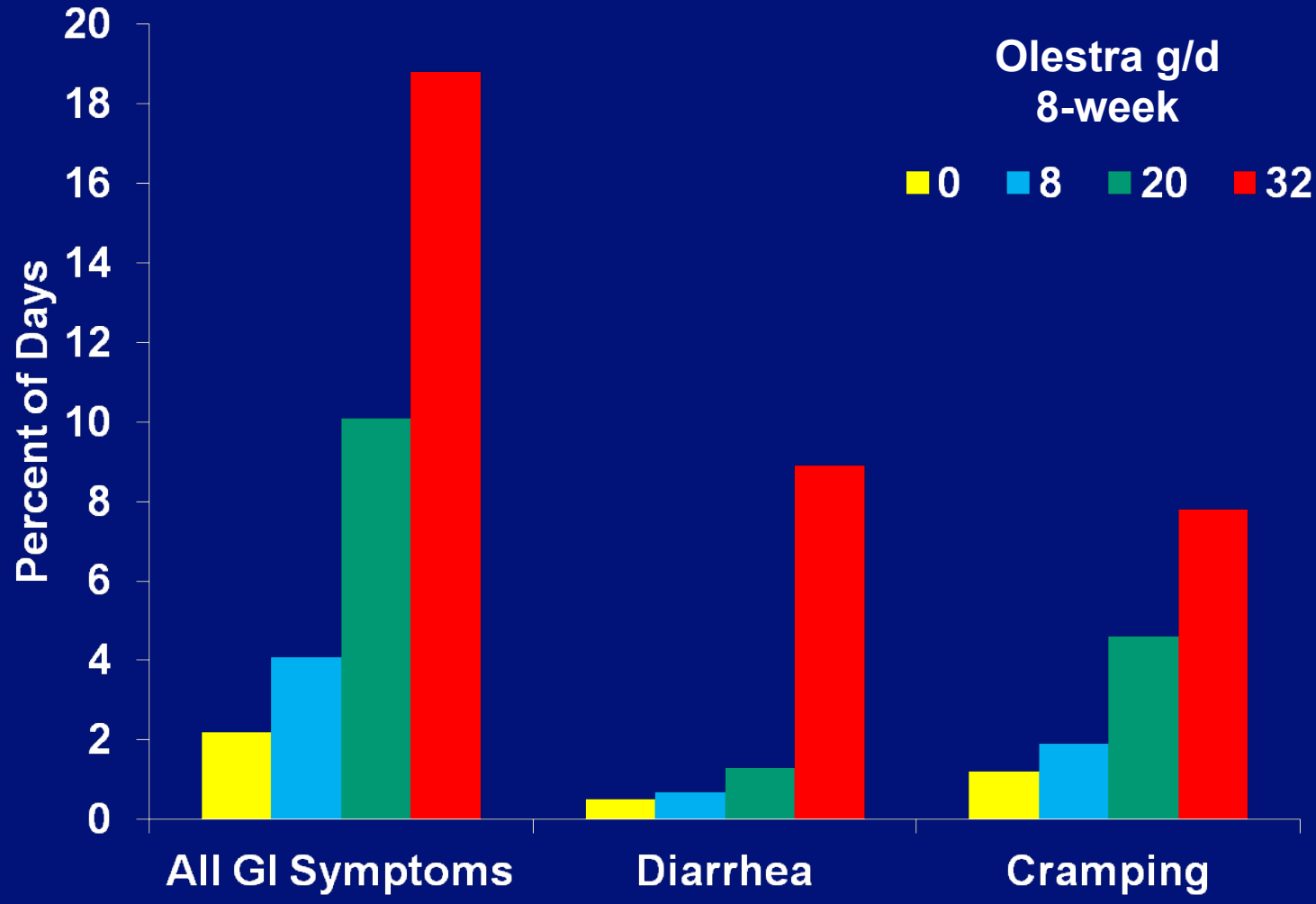
Westrate, Am J Clin Nutr, 1995.

Only Co-Consumption of Olestra with Food Reduces Serum Vitamins



Schlagheck, J Nutr 1997

Olestra Increases Frequency of Gastrointestinal Symptoms



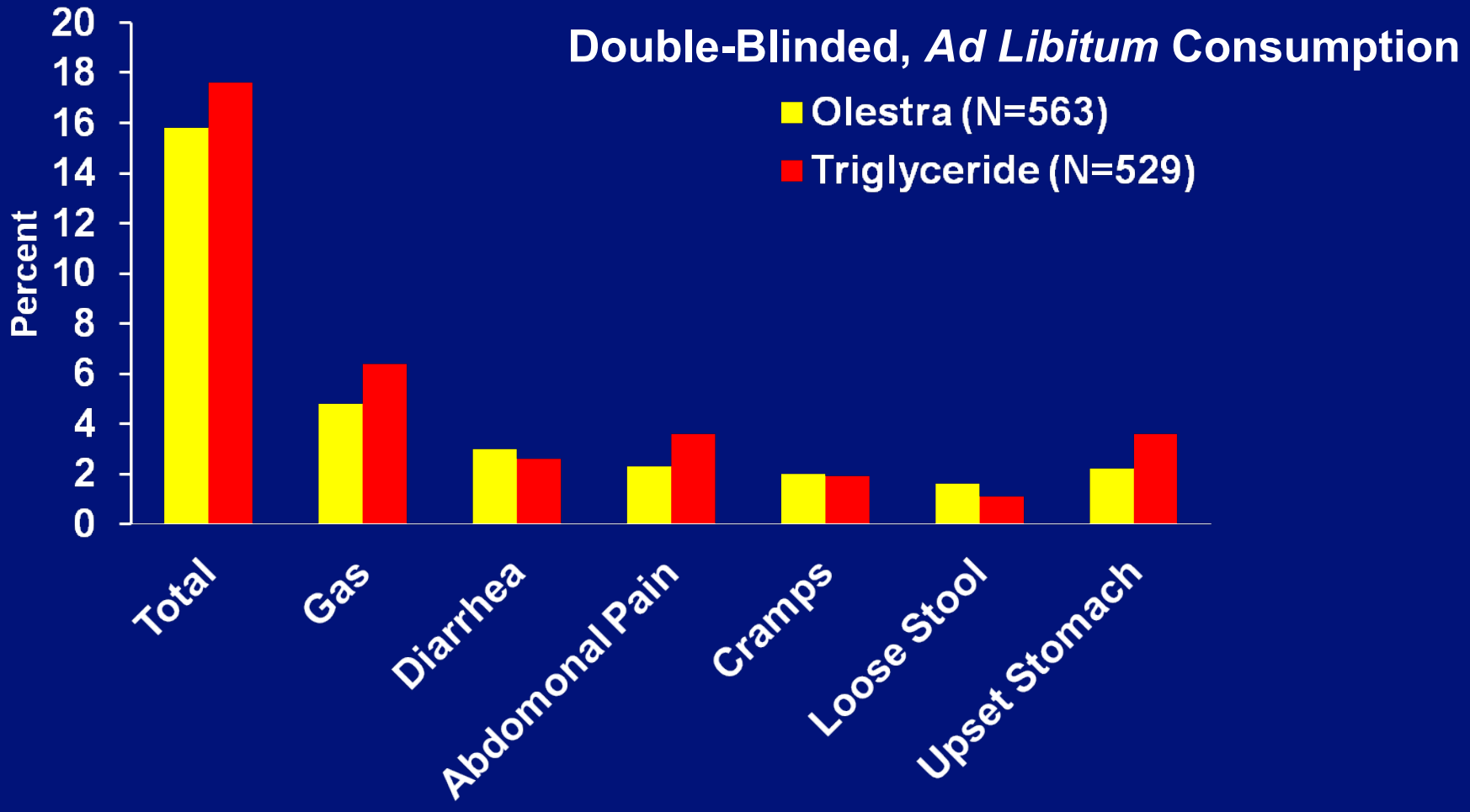
Schlagheck, J Nutr 1997

Procter and Gamble Promised to Monitor

1. Olestra intake
2. Changes in food consumption patterns
3. Changes in nutritional status

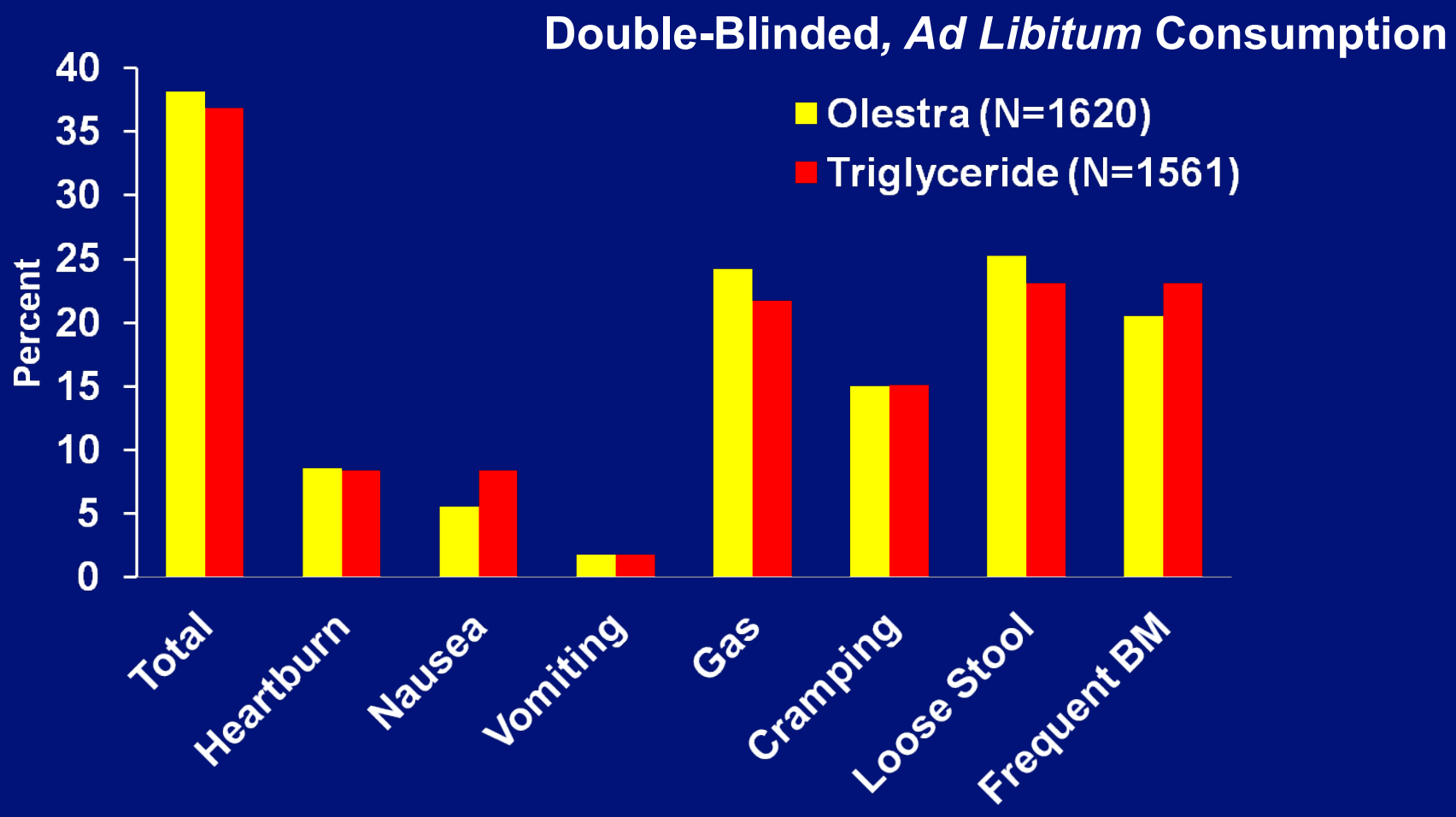
Gastrointestinal symptoms were evaluated in randomized clinical trials

No Difference in Gastrointestinal Symptoms Olestra vs. Triglyceride Chips at Single Occasion



Cheskin et al, JAMA, 1998

No Difference in Gastrointestinal Symptoms Olestra vs. Triglyceride Chips for 6-Weeks



Sandler et al, Ann Intern Med, 1999

Three Specific Aims

1. Monitor adoption and patterns of use in the US population

2. Assess associations between introduction of olestra-containing foods and serum micronutrients in the US population (80% to detect 10% reduction)

3. Assess associations of long-term, heavy olestra consumption with changes in serum micronutrients (80% to detect 10% reduction

Aim 1. Monitor Adoption and Use

DESIGN

- Random digit dial telephone surveys
  (Express mail letter with $10 bill enclosed)
- Baseline survey completed before introduction of olestra-containing foods
- Repeated surveys Years 1, 2 and 3

Aim 2. Olestra and Serum Micronutrients in U.S. Population

DESIGN

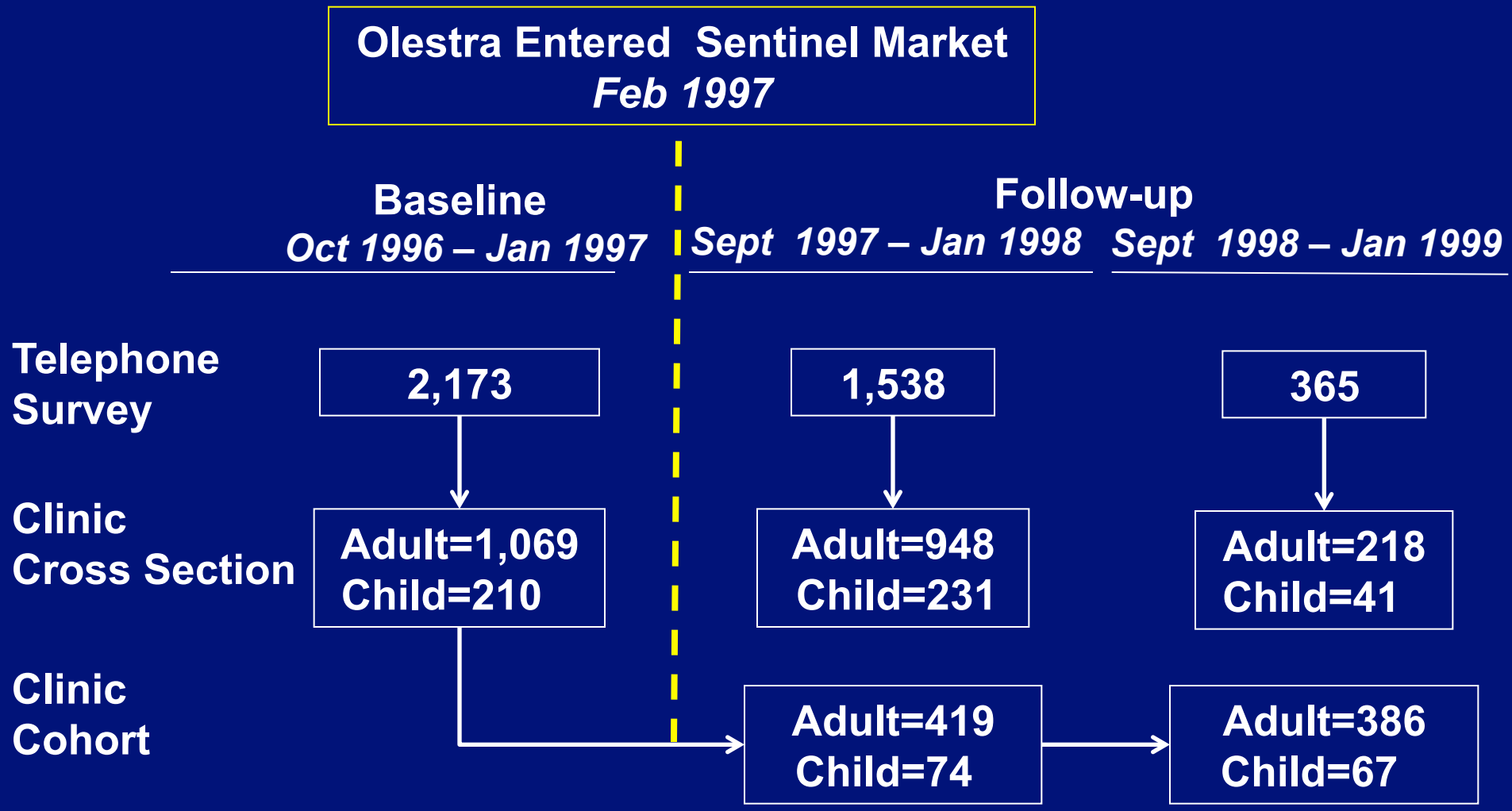
- Telephone-survey participants invited to clinic ($100 individual, $200 with child)
- Baseline completed before introduction of olestra-containing foods
- Repeated cross-sectional samples Years 1, 2 and 3

Aim 3. Long-Term, Heavy Olestra Consumption and Serum Micronutrients

DESIGN

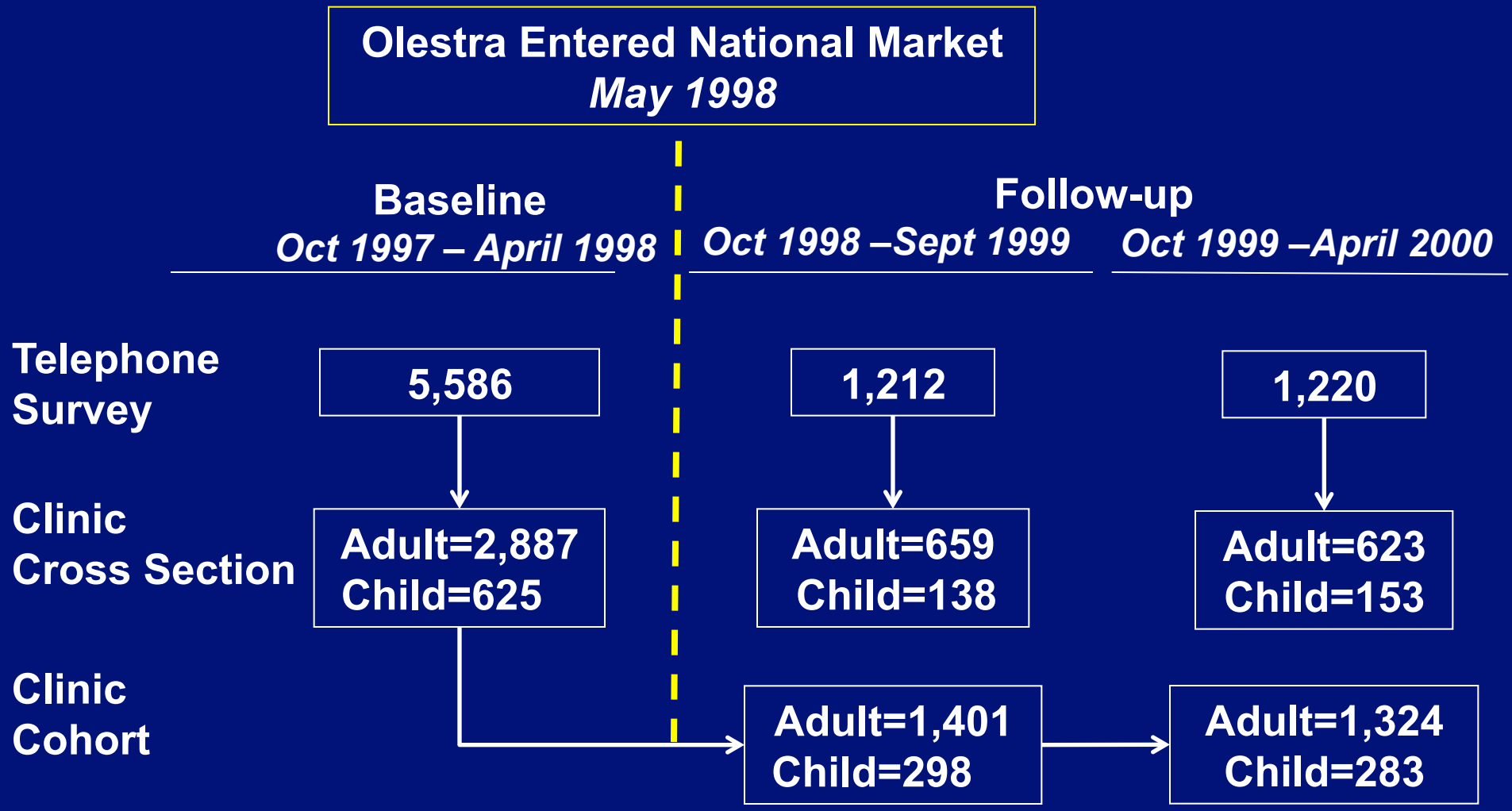
- Baseline clinic cross-section participants followed every 4 months by phone for olestra use
- Olestra users (80%) and non-users (20%) invited to repeat clinic visits Years 1, 2 and 3
  ($100 individual, $200 with child)

Sentinal* Site Design



*Indianapolis. IN

National* Site Design



*San Diego CA; Minneapolis MN; Baltimore MD

Aim 1. Monitor Adoption and Use

CONTENT

1. Diet-related psychosocial constructs
2. Usual consumption of savory snacks, fruits and vegetables over past month
3. Savory snack, fruit and vegetable consumption over past 24-hours
4. Demographic characteristics

Aim 1. Monitor Adoption and Use

METHODS

- "Usual" food consumption in past month
  - *Standard 5-item fruit and vegetable questionnaire*
  - *Developed "snack" questionnaire*

- Food consumption in past 24-hours
  - *Developed and validated "focused" 24-hr dietary recall*
  - *At each eating occasion, assessed specific types and amounts of savory snacks, fruits and vegetables, and foods made with high-carotenoid ingredients*

Aim 1. Monitor Adoption and Use

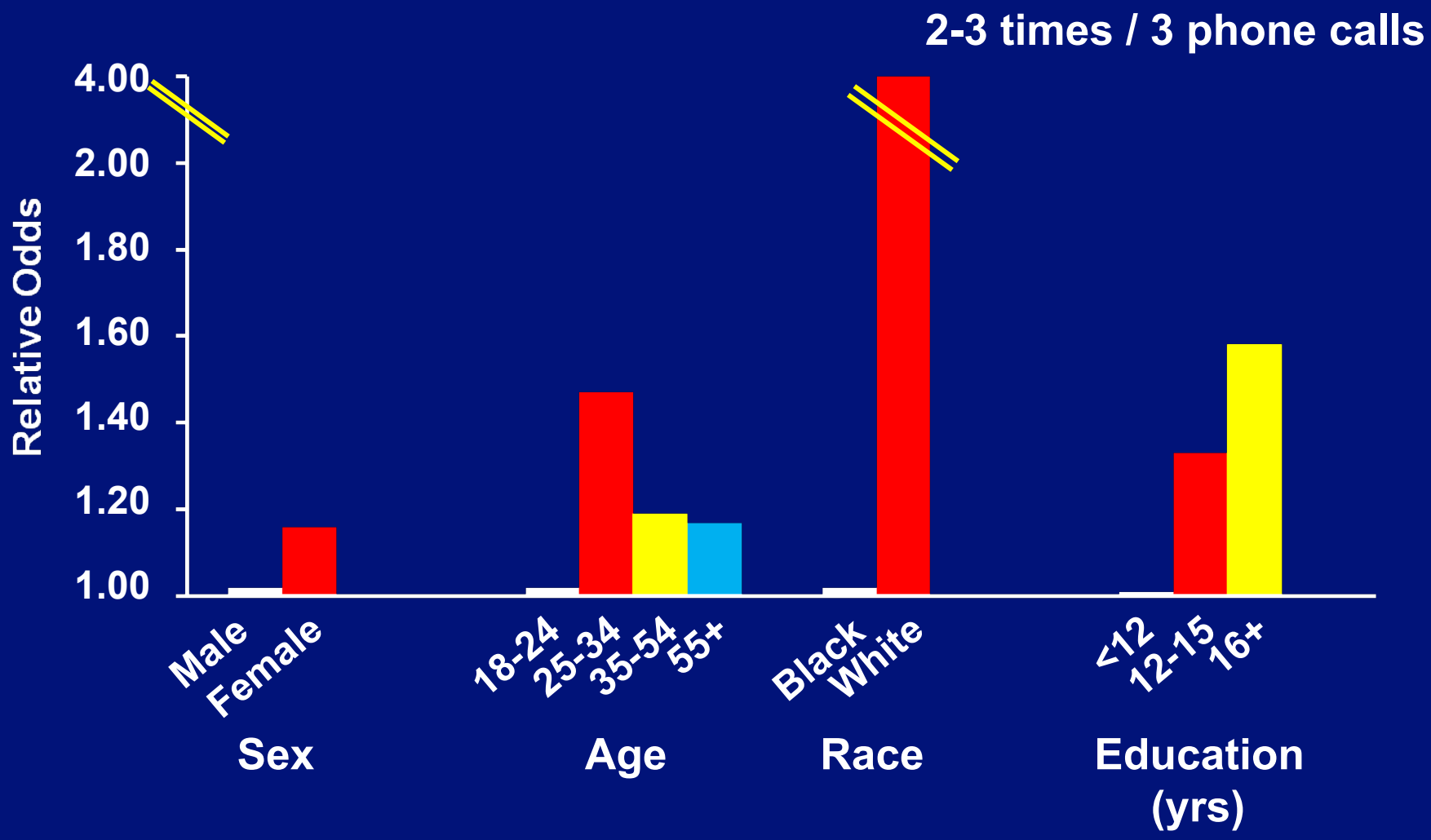
ANALYSES

- Each observation weighted for sampling probability and population age/sex distribution
- Total and age/sex specific distributions of consumption of savory snacks
- Associations of demographic characteristics and psychosocial constructs with snack and fruit and vegetable consumption
- Frequency of co-consumption of high-carotenoid and olestra-containing foods

Olestra Consumption was Very Low

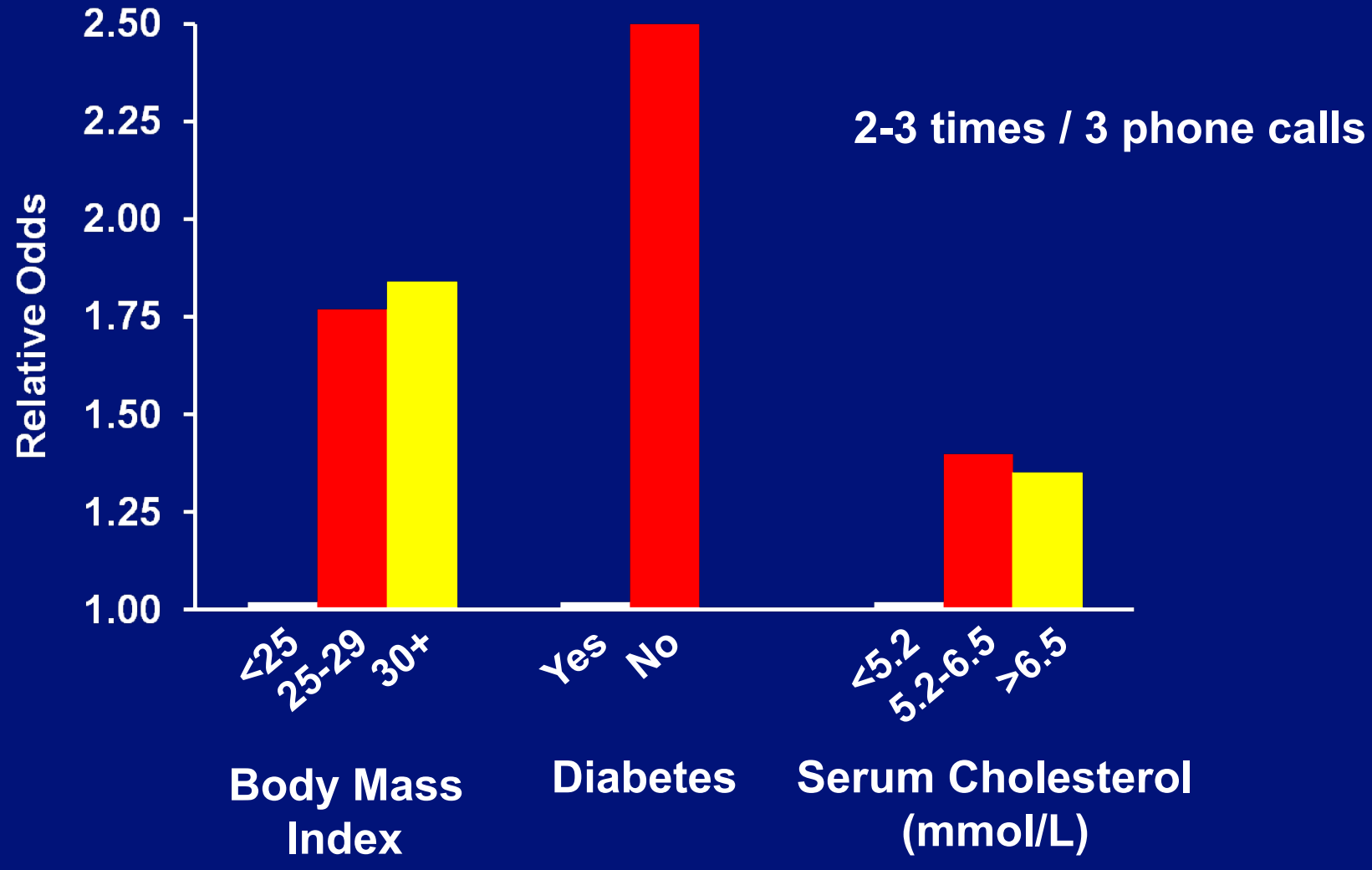
Snack Type	Mean (svgs/m)	Eating ≥ 1/m (%)	Mean among Eaters (svgs/m)	90%tile (svgs/m)	95%tile (svgs/m)
Total	10.9	95.2	13.0	39.0	53.3
Regular Fat	3.8	75.1	6.0	29.2	40.1
Reduced, Fat Non-Fat	4.1	79.7	6.3	23.9	30.6
Olestra	0.3	15.5	3.6	10.8	14.4
Olestra (g/d)	0.1		1.1	4.0	5.8

Olestra Consumption Differs by Demographic Characteristics



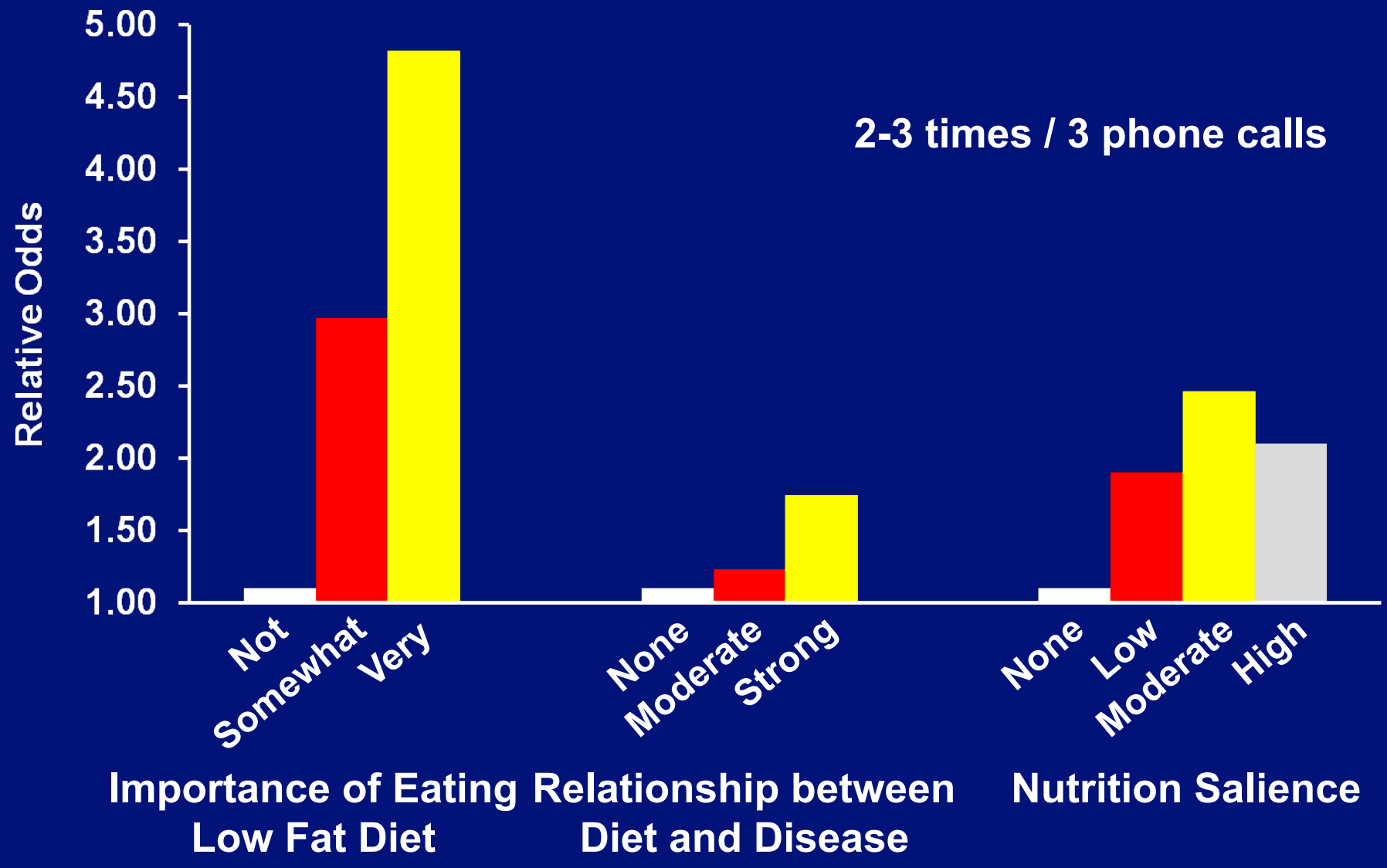
Neumark-Stainer, et. al., J Am Diet Assoc, 2000

Olestra Consumption Differs by Health Conditions



Neumark-Stainer, et. al., J Am Diet Assoc, 2000

Olestra Consumption Differs by Diet Beliefs

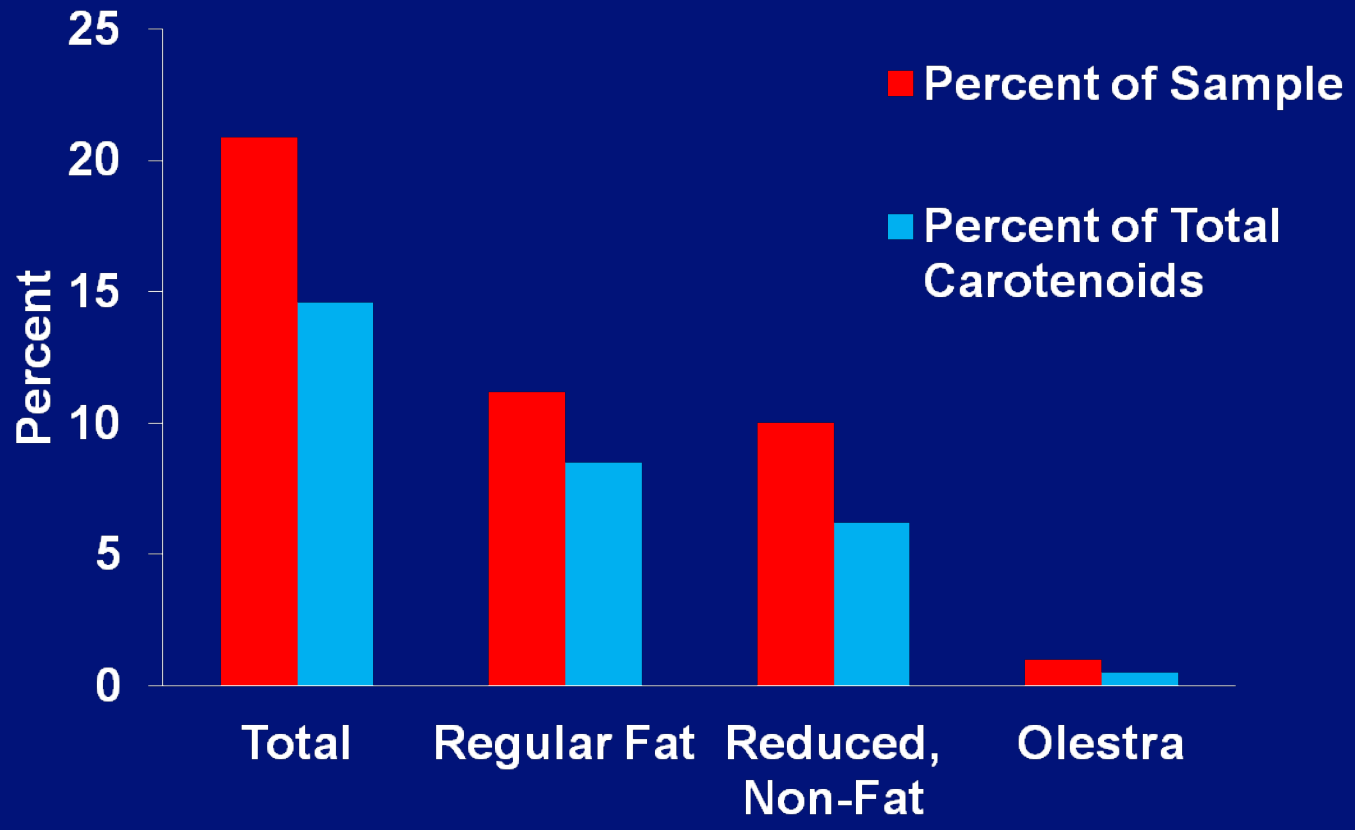


Neumark-Stainer, et. al., J Am Diet Assoc, 2000

Consumption of Savory Snacks with High-Carotenoid Foods is Rare

Meal	Eating	Fruit or Vegetable	High-Carotenoid Fruit or Vegetable	Savory Snack	Savory Snack with Fruit or Vegetable	Savory Snack with High-Carotenoid Fruit or Vegetable
	(%)	(%)	(%)	(%)	(%)	(%)
Breakfast	69.9	68.9	2.8			
Mid-Morning	23.2	40.5	4.6	35.6	11.8	1.1
Lunch	79.3	61.5	38.6	23.6	14.6	9.8
Mid-Afternoon	35.2	40.5	4.1	36.2	12.2	1.2
Dinner	92.4	73.2	42.8	13.3	8.8	4.8
Late Night	41.0	35.1	2.7	24.2	7.9	1.1

Very Little Carotenoid "At –Risk" of Poor Absorption



Aim 2. Olestra and Serum Micronutrients in U.S. Population

METHODS

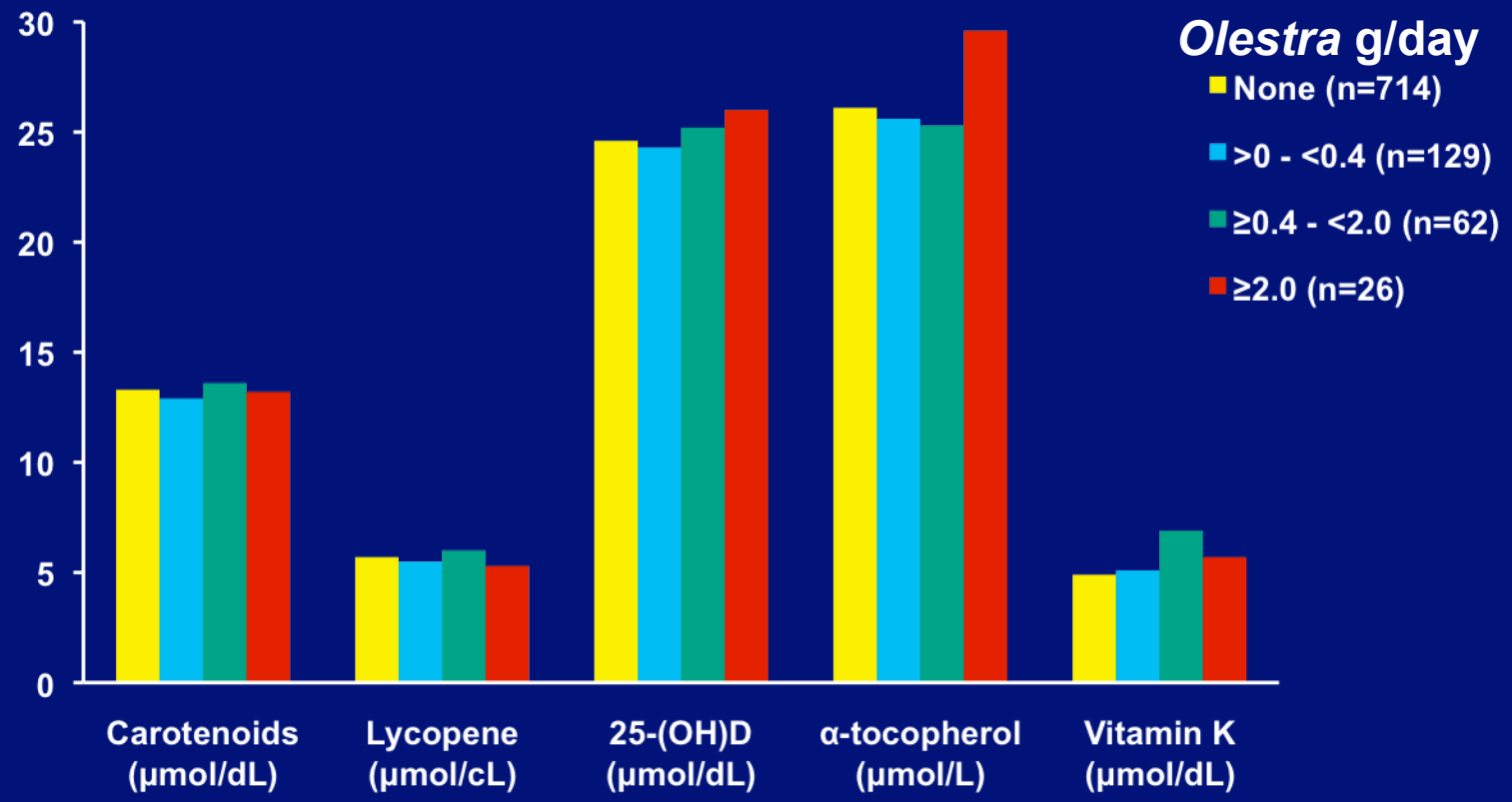
- 1 ½ hour clinic visit
- Fasting blood draw for serum micronutrients and carotenoids
- Diet (FFQ, Snack Foods and Focused Recall)
  Supplement use
  Dietary micronutrients and carotenoids
  Sun exposure, physical activity
  BMI, smoking, etc.

Aim 2. Olestra and Serum Micronutrients in U.S. Population

ANALYSES

- Each observation weighted for sampling probability and population age/sex distribution
- Using baseline data, fit models predicting Vit E, D and K and carotenoids from diet, supplements and covariates
- Using Year 1 data, replicate baseline models with the addition of olestra consumption

Olestra was Not Associated with Population-Level Serum Micronutrients



Thornquist *et al*, J Nutr, 2000, Sentinel Site, n=931

Aim 3. Long-Term, Heavy Olestra Consumption and Serum Micronutrients

METHODS

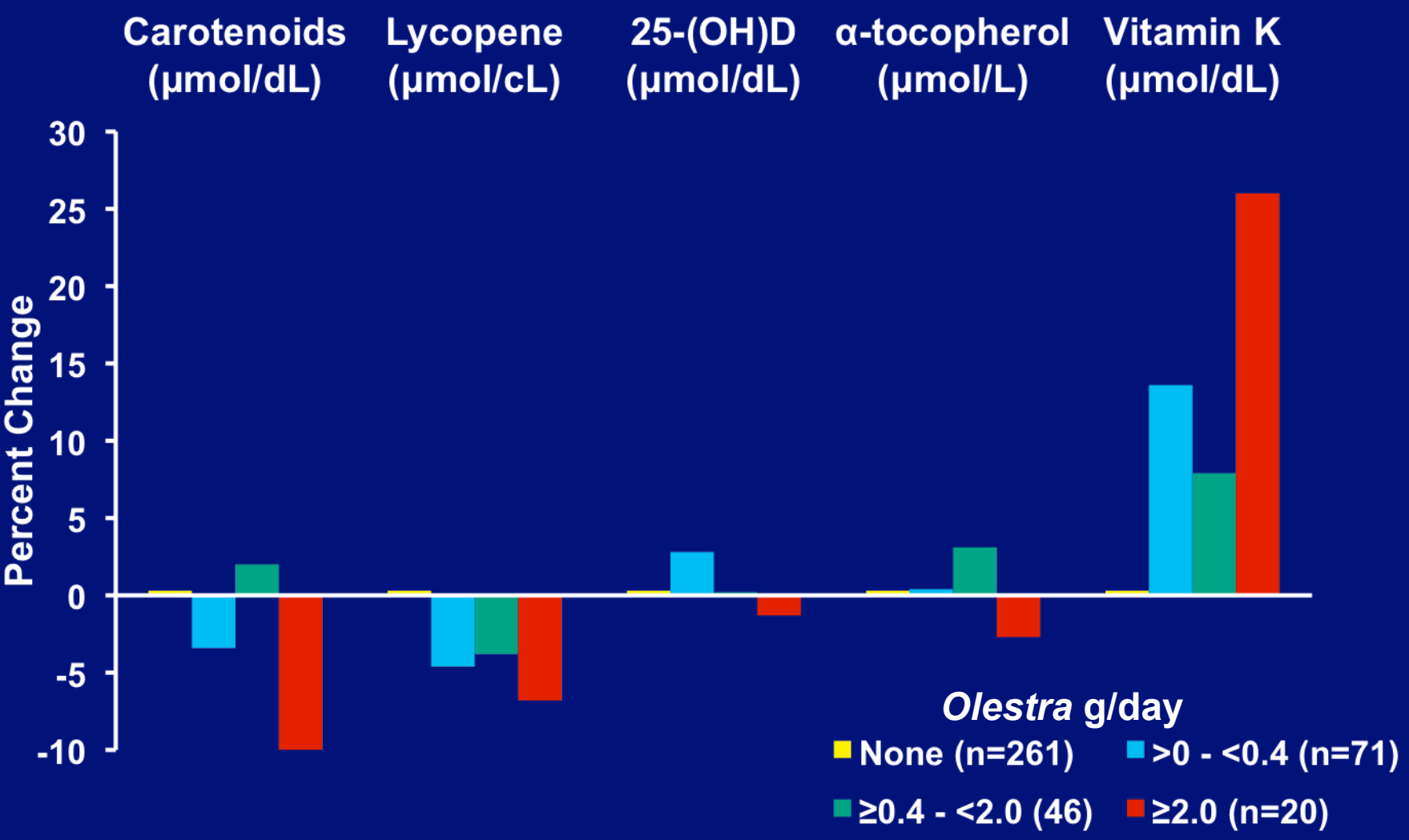
- 1 ½ hour clinic visit
- Fasting blood draw for serum micronutrients and carotenoids
- Diet (FFQ, Snack Foods and Focused Recall)
  Supplement use
  Dietary micronutrients and carotenoids
  Sun exposure, physical activity
  BMI, smoking, etc.

Aim 3. Long-Term, Heavy Olestra Consumption and Serum Micronutrients

ANALYSES

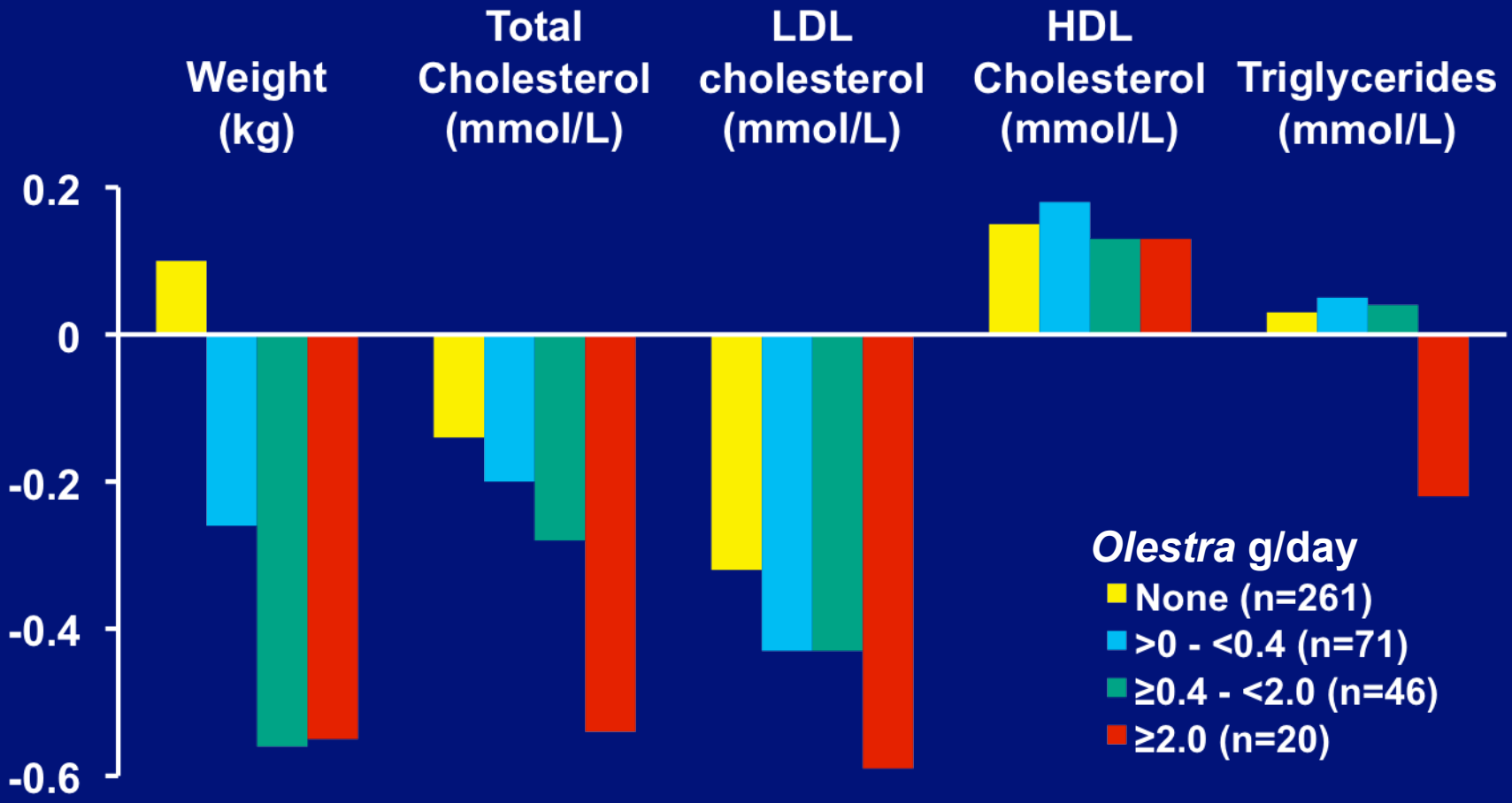
- Fit models predicting change in Vit E, D and K and carotenoids associated with Olestra consumption

Olestra was Not Associated with Changes in Serum Micronutrients



Thornquist *et al*, J Nutr, 2000, Sentinel Site, n=398

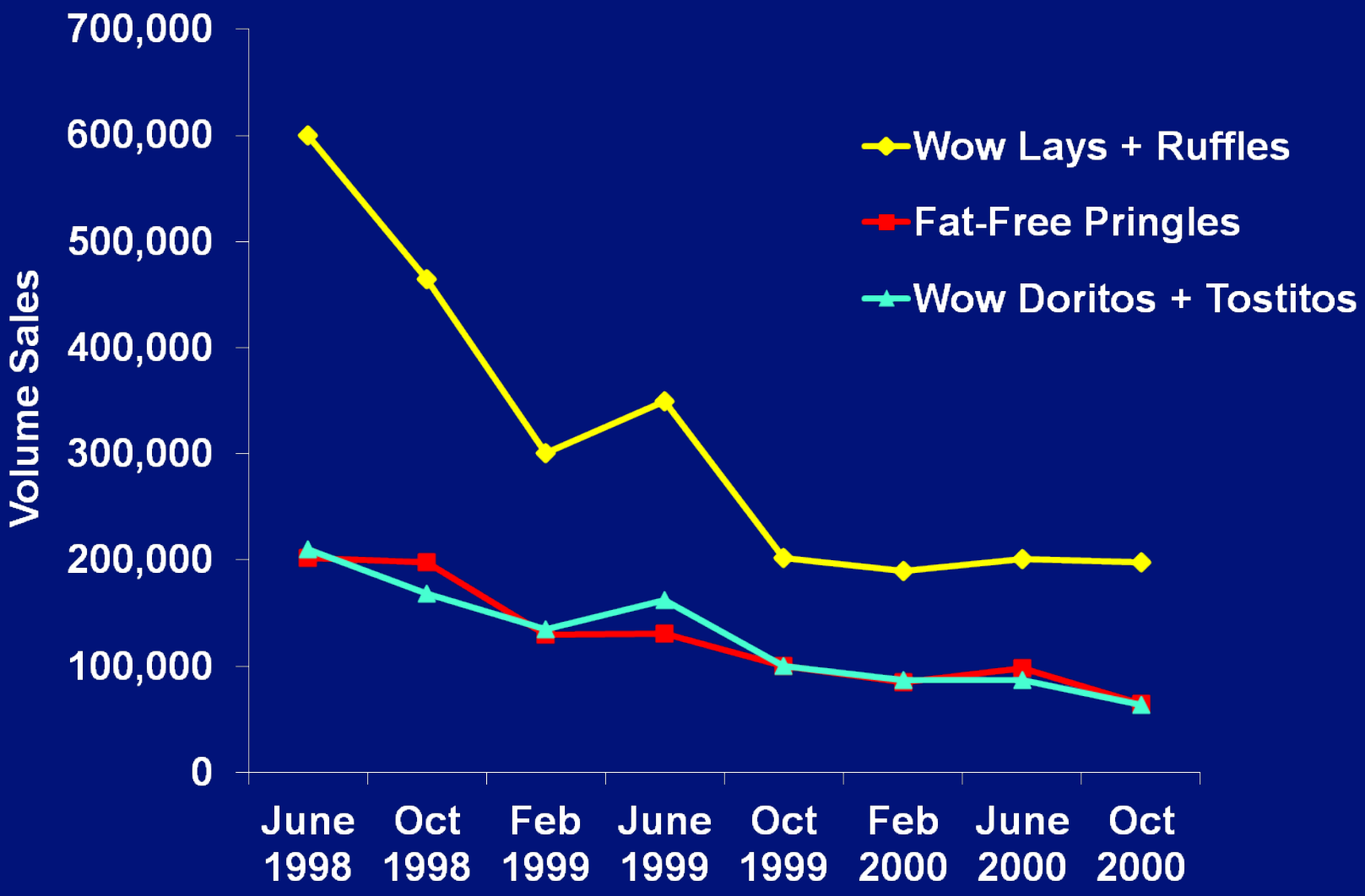
Olestra was Associated with Weight Loss and Reduced Serum Lipids



Patterson et. et. al., Arch Intern Med 2000, Sentinel Site, n=326

Based on Sentinel Site Results, FDA Continued Approval in 1999

Olestra Sales were Poor



Proctor and Gamble Ended Post-Marketing Surveillance Activities Abruptly in April of 2000

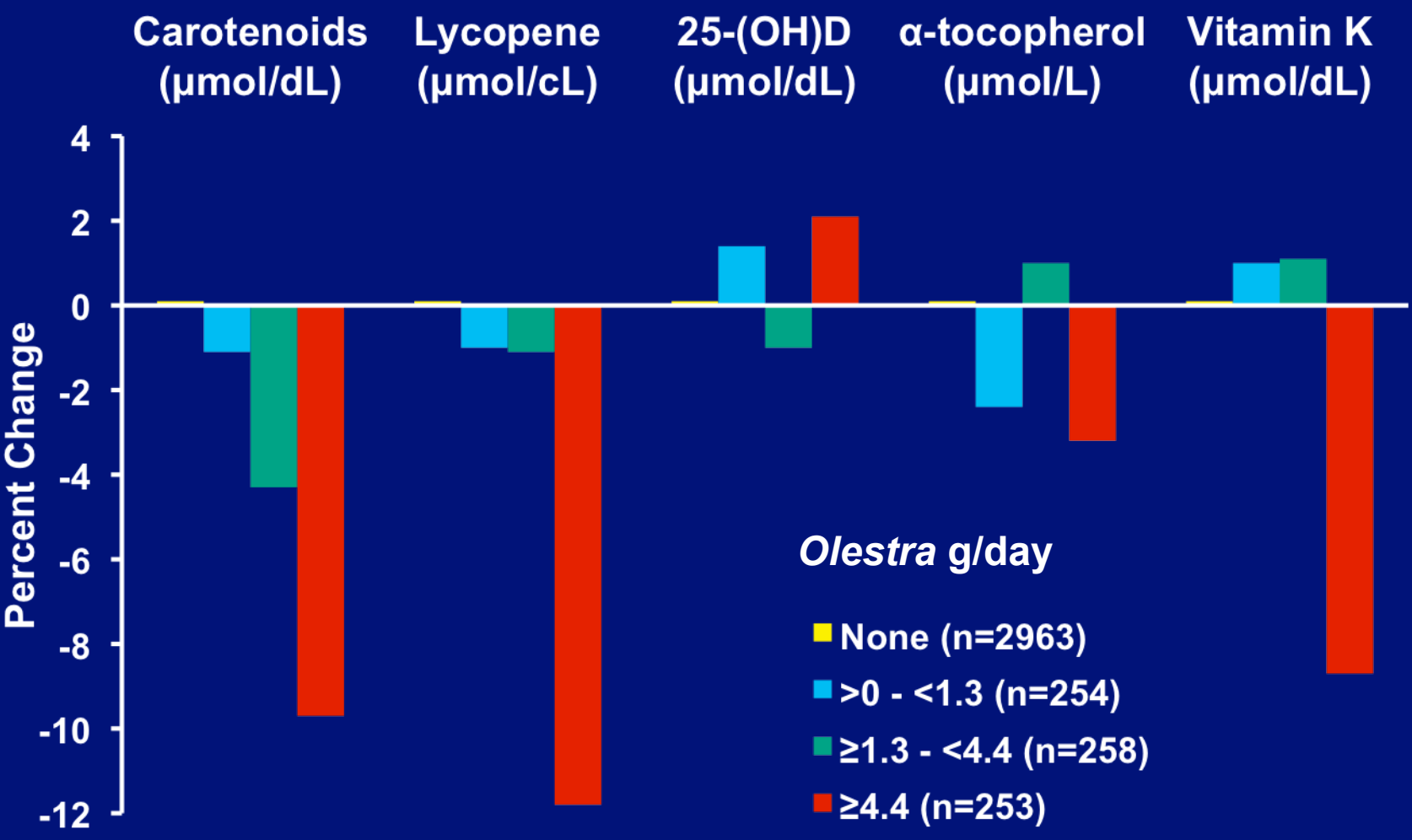
Sentinel site closed at end of Year 2

National sites closed mid way through Year 2

Funding for all activities ended

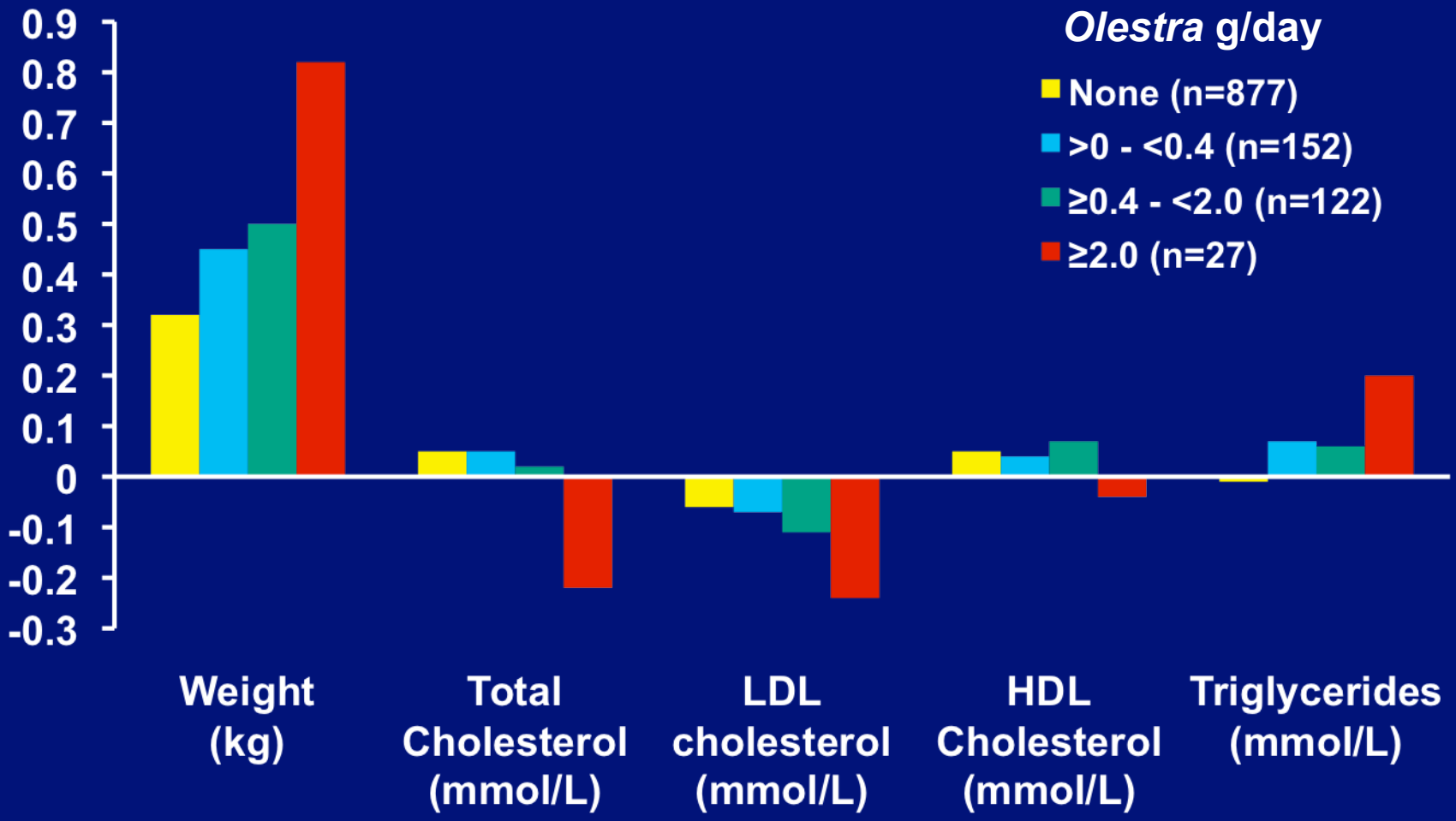
Publication of results delayed until 2006

Olestra was Associated with Small Changes in Serum Micronutrients



Neuhouser et al, Am J Clin Nutr, 2006, National Sites, n=2,535

Olestra was Not Associated with Weight Loss and Reduced Serum Lipids



Satia-Abouta et. al., Nutrition, 2003, National Sites, n=1,178

Post-Marketing Surveillance was Expensive

Budget in US Dollars				
1997	1998	1999	2000	Total
8,172,420	6,389,784	6,377,996	6,229,151	27,169,351

Scientific Challenges in Olestra Post-Marketing Surveillance

- Complex research design and protocols
- Blinding
- Low exposure
- High participant burden
- High costs
- Measurement:
  - Micronutrient and carotenoid intake
  - Snack food
  - Co-consumption of olestra and carotenoids
- Analysis using data from incomplete study

Lesions for GM Post-Marketing Surveillance

- Design
  - Hypothesis driven
    - *Criterion for statistical test*
  - Accurate exposure assessment
    - *Notoriously difficult*
  - Well-defined, unbiased, feasible outcomes
    - *Cannot detect chronic disease risk*
  - Adequately powered
    - *Detect biologically meaningful effect*

- Funding
  - Industry
  - Government
  - Foundation/NGO

Lesions for GM Post-Marketing Surveillance

- Regulatory
  - Data collection and analysis not standardized
    - *Exclusion based on influence statistic*
  - Interpretation subject to judgment
    - *Dose-response, threshold, non-linear*
  - Data documentation and verification unrealistic
    - *Cannot meet FDA requirements based on drugs*
  - Analyses well outside of agency expertise
    - *Covariates, parameterization of statistical model*

Lesions for GM Post-Marketing Surveillance

- Distortion of Research Findings
  - Anecdote
    - *"I took one bite and had headaches and diarrhea for 3 days"*
  - Attribution bias
    - *Common symptoms attributed to salient exposure*
  - Ideology
    - *Natural and organic*
  - Media
    - *Sensational sells*

- Limitations of Observational Epidemiology
  - Reproducibility
  - Generalizability
  - Measurement error
  - Bias and confounding