

Progress in nutrition and CHD – Ten steps forward, nine steps back

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Potential conflicts of interest, 2006-2015

Research contracts:	Nonprofit only (Heart Foundation, Royal Academy of Sciences, ZonMW)
Consulting:	Unpaid only
Employment in industry:	No
Stockholder of a healthcare company:	No
Owner of a healthcare company:	No
Other:	Newspaper columns; royalties from book

The ancient Greeks told us that diet is important



*Hippocrates in
Asclepeion, Kos*

“
**Let food be thy medicine
and medicine be thy food**

Hippocrates
”



Ancient nutritional knowledge was mostly superstition, and people died like flies



Agenda

- The three ages of modern nutrition science
 - Vitamins and minerals
 - Diet, lipids, and heart disease
 - Bioactives and megavitamins
- Epidemiology vs trials: which is right?
- Obesity research requires a paradigm shift
- An experiment on diet and weight gain

The three ages of modern nutrition

1898 – 1948 : Vitamins and minerals

1948 – 1979 : Diet, lipids and heart disease

1979 – 2005 : Bioactives and megadose
vitamins

1898: beriberi is a nutrient deficiency disease



Gerrit Grijns conceived the notion of essential nutrients

Eijkman, NTVG 1928



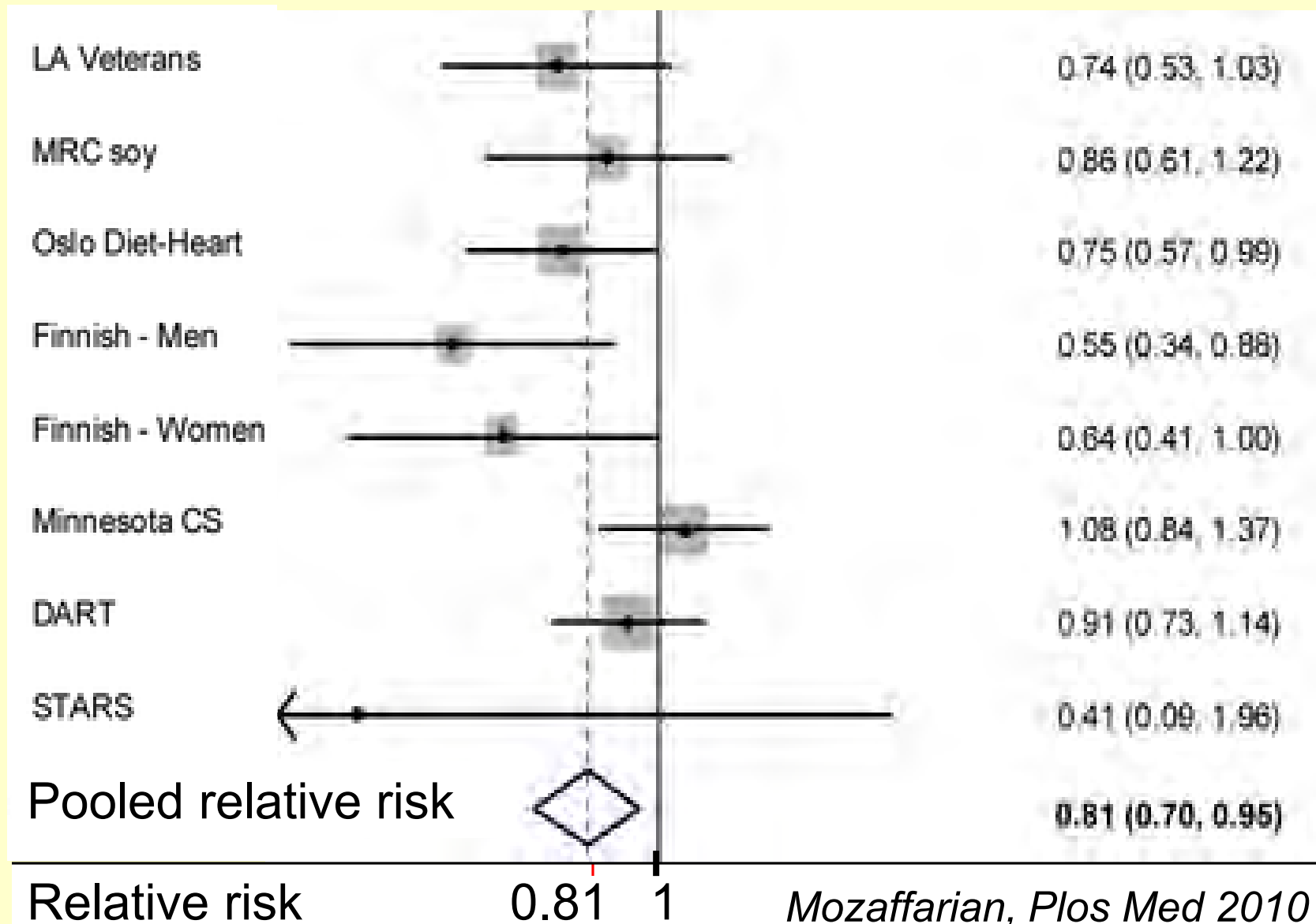
Heart failure due to vitamin B1 deficiency

Ramazzina 2011

1948-1980: what we learned about diet and cardiovascular disease

- Saturated fats, trans fats and dietary cholesterol raise LDL levels and CHD risk
- Abdominal obesity causes heart disease and stroke
- Sodium raises, and potassium lowers blood pressure

Replacing saturated by polyunsaturated fatty acids reduces CHD in trials



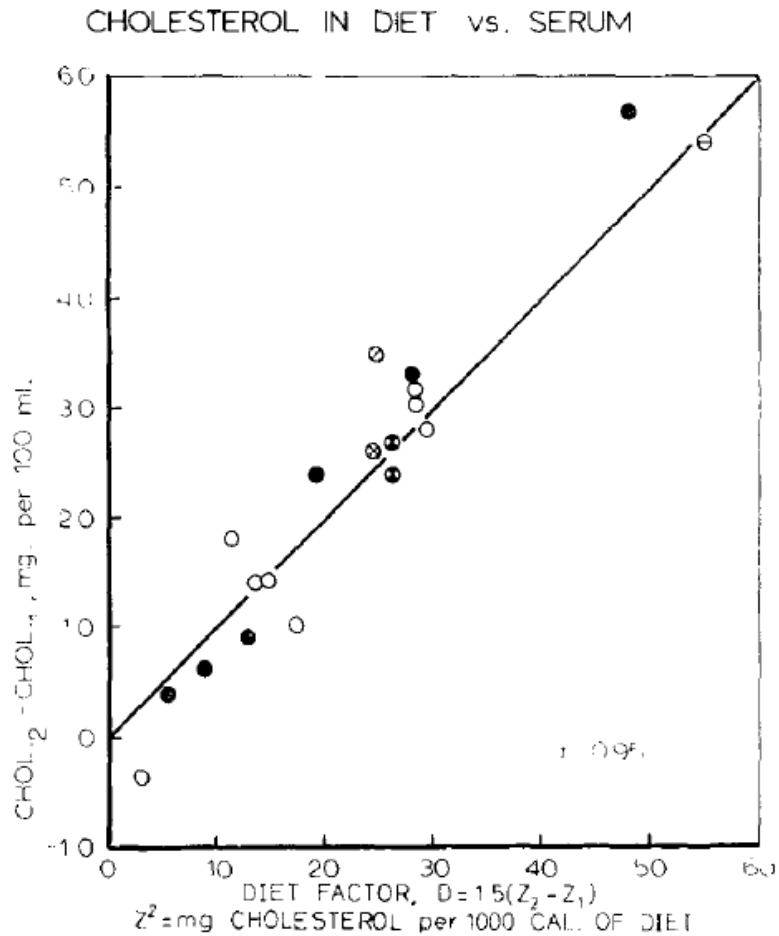
Effect of dietary cholesterol on CHD risk is fading from the collective memory

Draft US Dietary Guidelines 2015:

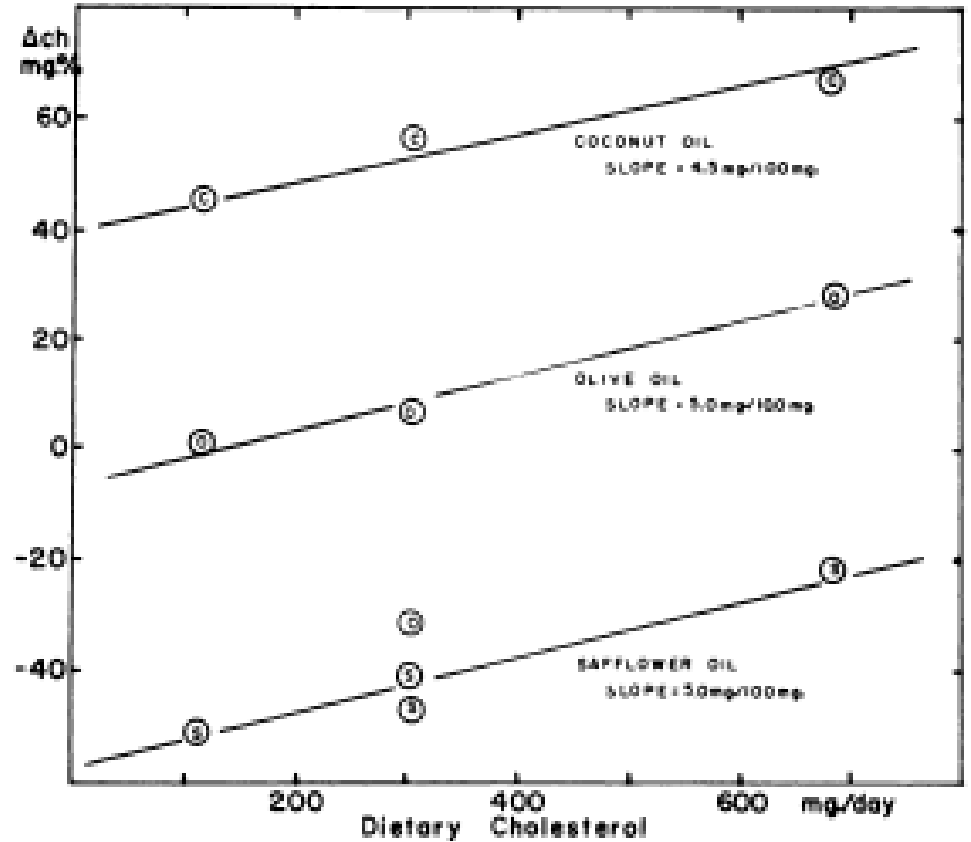
'available evidence shows no appreciable relationship between consumption of dietary cholesterol and serum cholesterol'

(www.health.gov/dietaryguidelines, part D p. 17)

Dozens of trials showed effect of dietary cholesterol on serum cholesterol trials

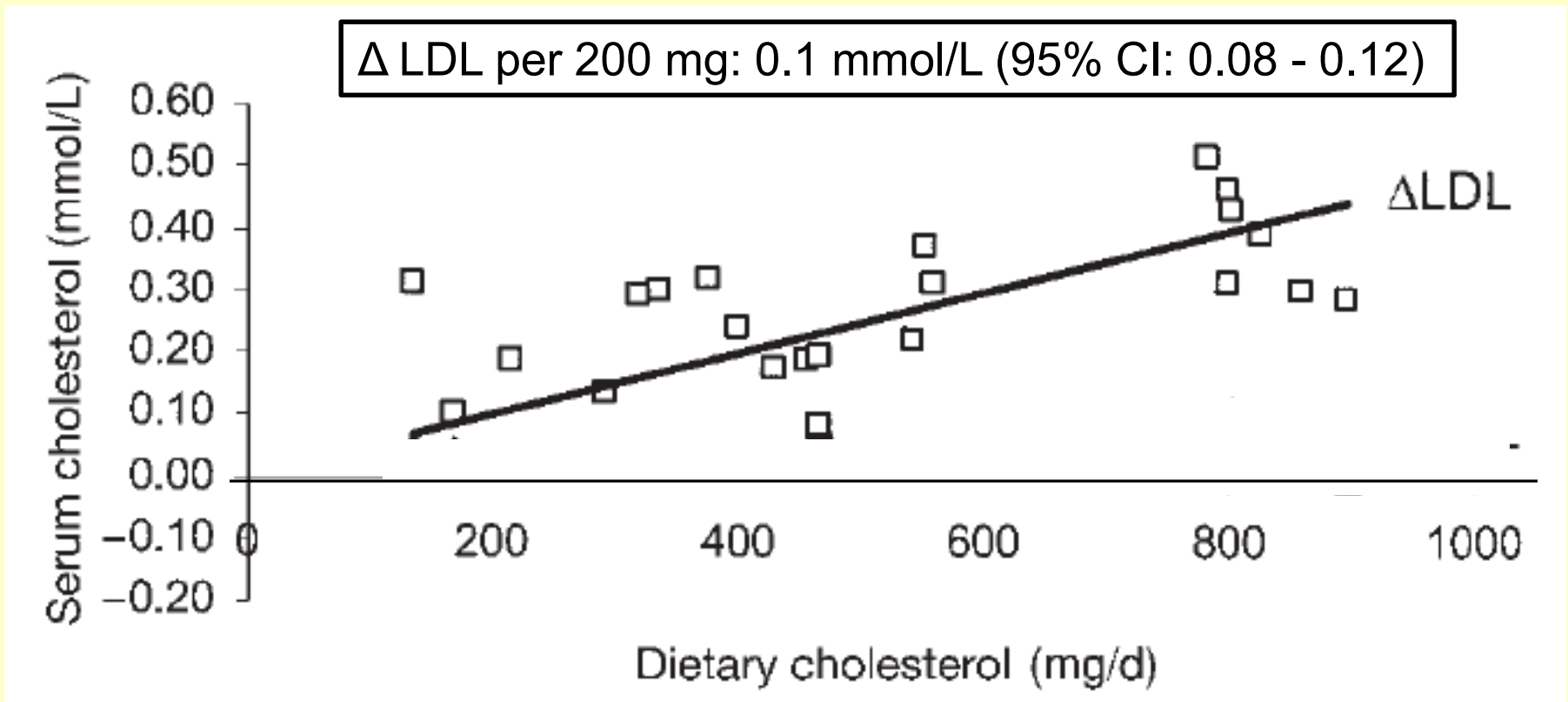


Keys, Metabolism 1965



Hegsted, Am J Clin Nutr 1965

Effect of dietary cholesterol on LDL cholesterol in 17 trials, 1981-2000



Weggemans, Am J Clin Nutr 2001

How could the draft US guidelines ignore the effect of egg cholesterol on LDL?

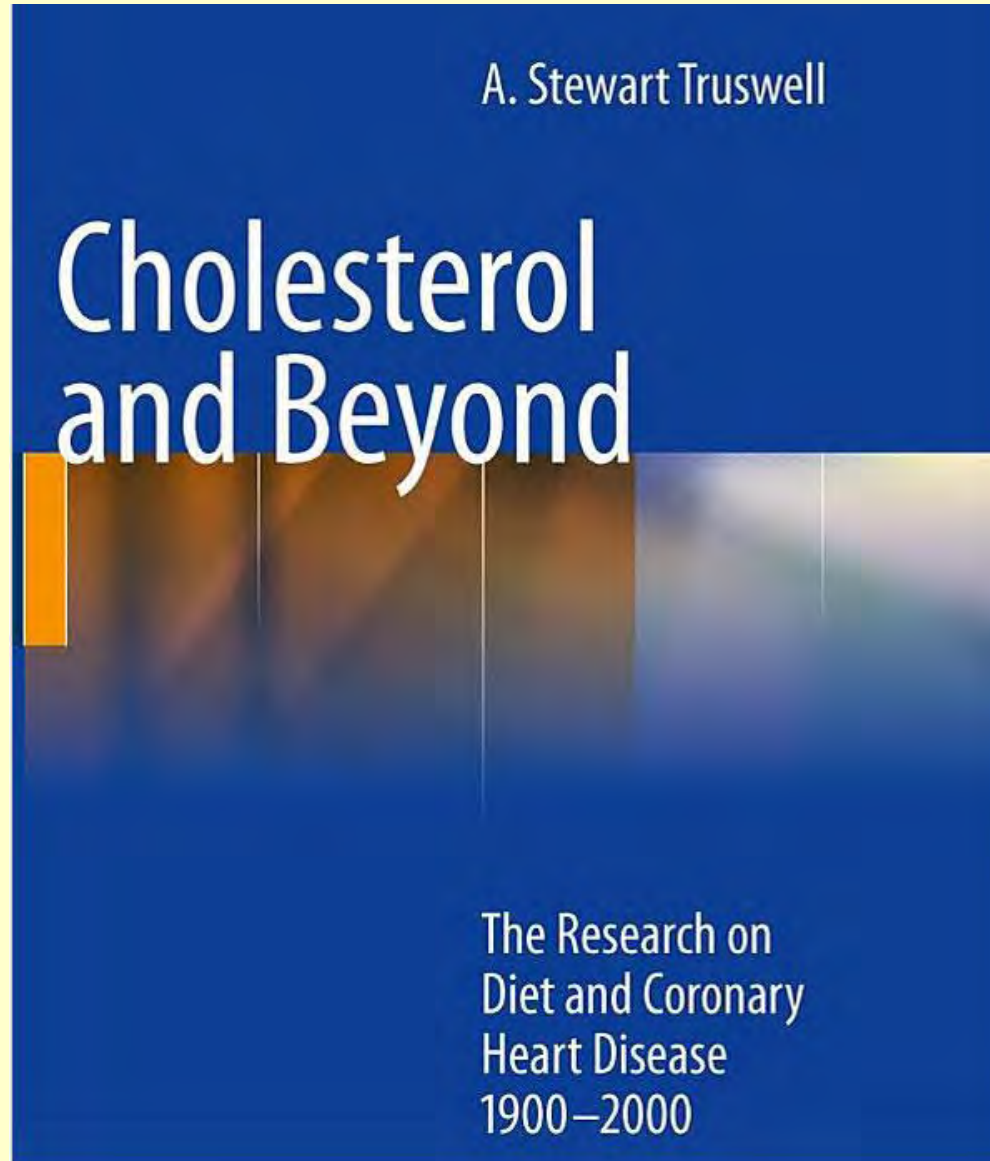
They ignored the 20th century!

*'The evidence review date range was
1998 to 2009'*

Eckel et al, AHA/ACC, Circulation 2014

*If you limit publications to 1998-2009,
available evidence shows no appreciable relationship
between consumption of vitamin B1 and beriberi*

If you want to know about diet and CVD, read Truswell's book



The three ages of modern nutrition

1898 – 1984 : vitamins and minerals

1948 – 1980 : Diet, lipids and heart disease

1979 – 2005 : Bioactives and megadose vitamins

Two main methods in nutrition research

Observational epidemiology



Real people, real foods, real disease, long term



Confounding

Randomized Clinical Trials



Prove causality



Sick people, high doses, too short

1980-2005: Epidemiology finds exciting new effects of diet on CVD

- Antioxidants
- High-dose vitamins
- Polyphenols and other bioactives
- Selenium
- Fish oil
- Fruits and vegetables
- Alcohol

New effects of diet on CVD do not hold up in randomized clinical trials: an overview


BMJ

BMJ 2013;346:f10 doi: 10.1136/bmj.f10 (Published 18 January 2013)

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RESEARCH

Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials

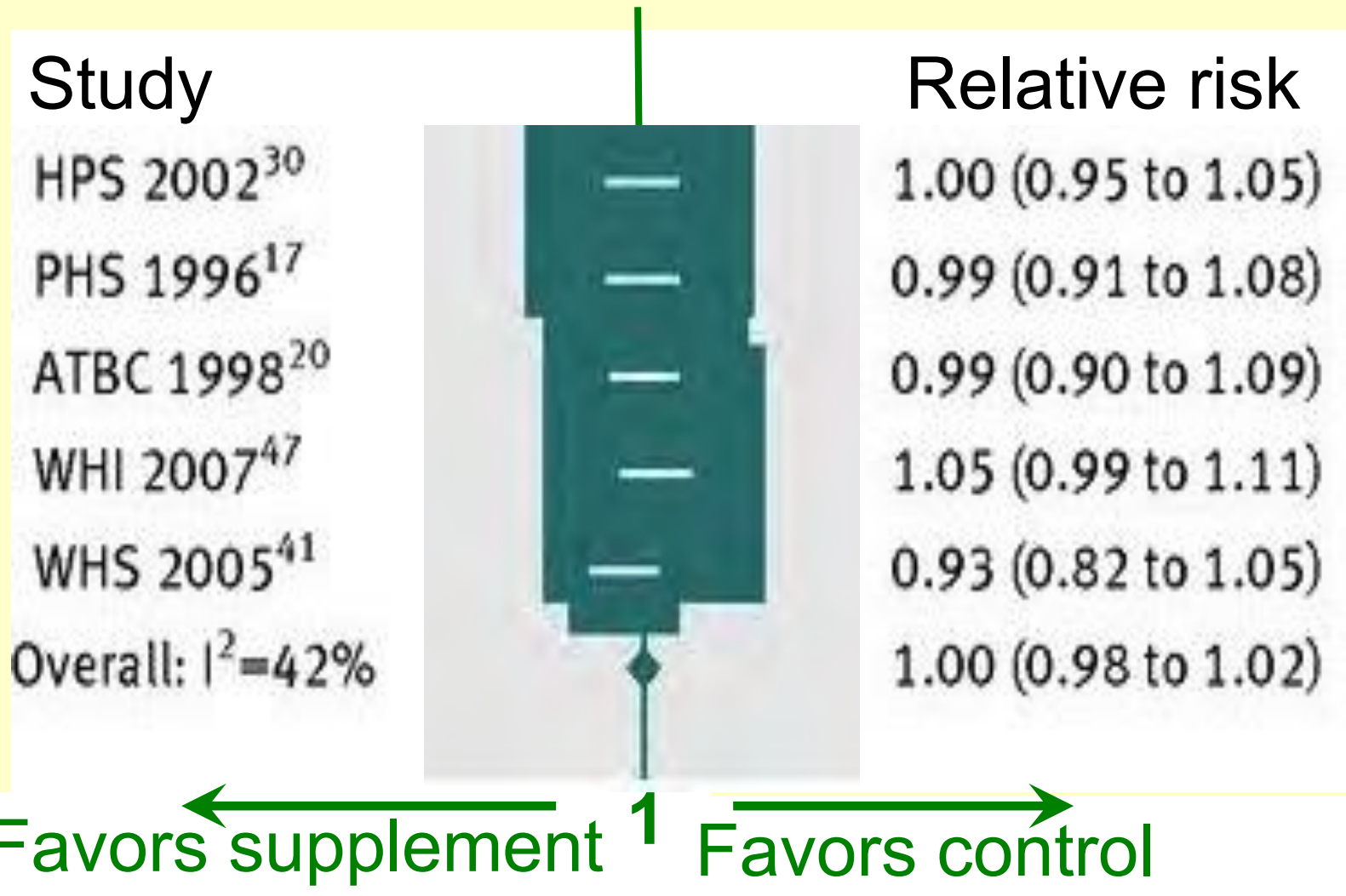
 OPEN ACCESS

Seung-Kwon Myung *senior scientist*^{1,2}, Woong Ju *associate professor*³, Belong Cho *professor*¹, Seung-Won Oh *assistant professor*⁴, Sang Min Park *associate professor*¹, Bon-Kwon Koo *associate professor*⁵, Byung-Joo Park *professor*⁶, for the Korean Meta-Analysis (KORMA) Study Group

RCT's on dietary supplements

- 50 trials
- 294 478 participants, 49-82 years old
- Duration 6 months to twelve years
- No effect on cardiovascular outcomes of vitamin A, vitamin B₆, vitamin B₁₂, folic acid, vitamin C, vitamin D, vitamin E, beta-carotene or selenium

Vitamins, antioxidants and CVD: Efficacy in the five largest trials



Do fish fatty acids protect from CVD?

Epidemiology: Yes, trials: No

- Consistent benefit in observational studies
Zheng, Public Health Nutrition 2012
- Little or no benefit in trials
Rizos, JAMA 2012

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Why the discrepancy between trials and epidemiology?

- Shortcomings of trials?
 - Too short
 - High-risk subjects
 - Many subjects already receive optimal medication
- Shortcomings of epidemiology?
 - Residual and unmeasured confounding

Do the objections against trials of vitamins and CVD hold up?

Objection	Rebuttal
Trials too short	What works in CVD prevention usually works within five years
Trial populations too sick	Not that sick; most trials were primary prevention
Current drugs leave no room for improvement	Preventive treatments for CVD add up. That is why patients get so many pills!

CVD epidemiology's problem: residual or unmeasured confounding



Educated, lean, nonsmoking, exercise, the right doctor, good neighborhood, healthy job, nuts, fish, broccoli, moderate alcohol, yoghurt, wholewheat bread, vitamin-du-jour, healthy at age 70



Little schooling, obese, smokes, 6 h of TV per day, wrong doctor, poor neighborhood, factory job, no alcohol, pork chops, french fries, cola, white bread, no vitamins, ill at age 60

What are residual and unmeasured confounding?

- *Residual confounding:*
Imprecise measurement of a factor which correlates with diet.
Example: heavy smokers eat less vegetables than light smokers
- *Unmeasured confounding:*
Unmeasured factor that correlates with diet.
Example: the kind of people who prefer pork chops to fish may be the kind who forget to take their statin.

Can statistics establish the effect of each factor separately?



Statistical adjustment is supposed to pry entangled factors apart. But it doesn't!

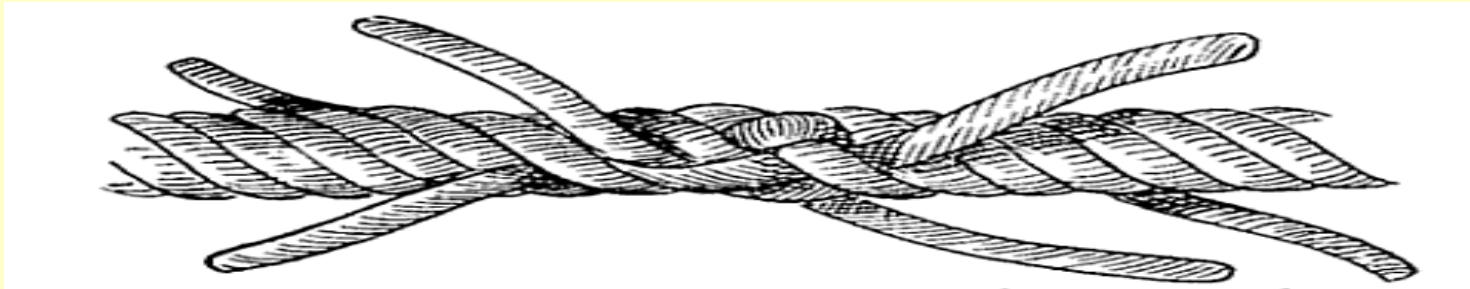
Mathematicians know how fallible
statistical control and adjustment are

**“Risk Factors, Confounding, and the
Illusion of Statistical Control”**

Christenfeld & Greenland, Psychosom Med 2004

*“statistical control” is nothing more than a
highly fallible process filled with judgment
calls that often go unnoticed in practice.*

The problem with CVD epidemiology

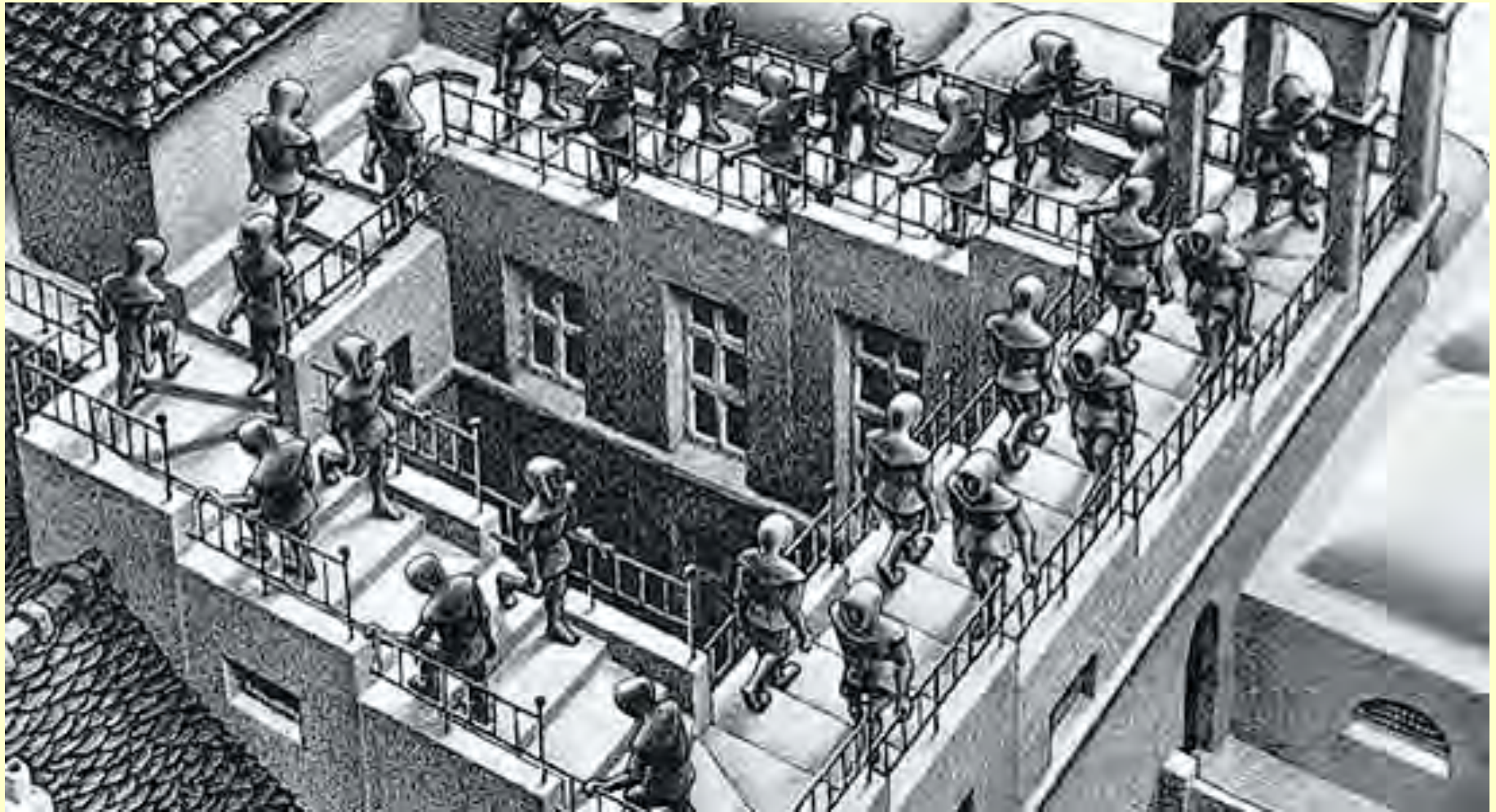


- Even after extensive statistical adjustment, effects of diet on risk of 30% – 50% may in reality reflect effects of confounders

Bioactives, megadose vitamins and CVD: summary

Antioxidants (beta-carotene, vitamin C, vitamin E)	Do not work
Vitamin D	Probably does not work
Bioactives (polyphenols, resveratrol, catechins)	Doubtful
Fish oil and omega-3	Uncertain
Folic acid, B-vitamins	Still some hope (<i>Huo, JAMA 2015</i>)

Nutrition science and CVD: lots of steps but getting nowhere?



'Ascending and Descending'. Maurits Escher, 1960

From nutrients to food patterns

- *'There MUST be something to broccoli'*
- *'Unique interactions of multiple vitamins and bioactives'*
- *We need to look at foods and food patterns, not at molecules*
- These are untestable ad-hoc hypotheses, but still there is a paradigm shift in the air...

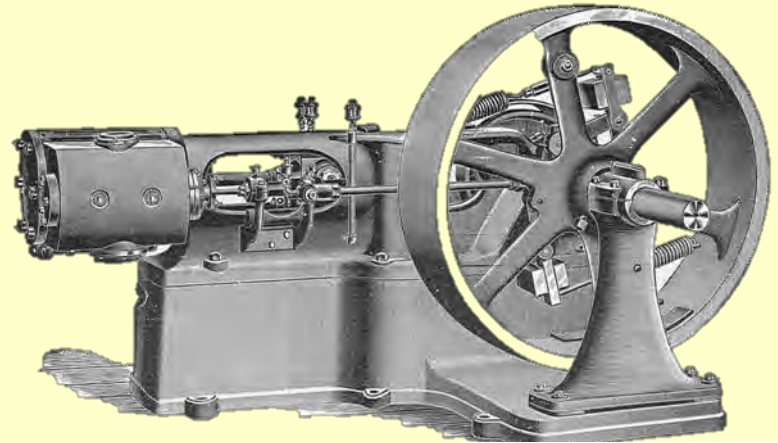


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A paradigm shift: nutrition research → obesity research

- Classical nutrition was like steam engine science: solid and unambiguous



$$\Delta S_H = Q_H/T_H \quad \Delta S_C = Q_C/T_C$$

- Obesity science is like global warming: so many variables, so little certainty



Is sugar fattening?

- Classical nutrition:

NO

sugar = glucose + fructose = bread + fruit

- Trendy nutrition:

YES, it is the main villain

- Dr Katan's Sweet & Easy diet:

Lose weight on sugar!

Dr Katan's Sweet & Easy diet: Eat all the sugar you want and still lose 1 kg per week



- Always carry sugar
- Sprinkle it liberally on ALL your food and drinks



'Fattening' is not determined by properties of molecules, substances or foods

Are French fries fattening?

Not if you eat them with knife
and fork at an expensive
restaurant



Can science handle all these determinants of weight gain?

- Appetite
- Convenience
- Portion sizes
- Prices, taxes
- Trendiness
- Social pressure
- Urban design



Obesity science seems easy, but it is hard, like Mozart's sonatas

*'The sonatas of Mozart are too easy for
children, and too difficult for artists.'*

Attributed to Artur Schnabel



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Obesity research is doable: an experiment on sugary drinks



The double-blind randomized trial in kids: Sugar-free versus sugar-sweetened drinks and body weight

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Sugar-free or Sugar-Sweetened Beverages and Body Weight in Children

Janne C. de Ruyter, M.Sc., Margreet R. Olthof, Ph.D., Jacob C. Seidell, Ph.D.,
and Martijn B. Katan, Ph.D.

De Ruyter, NEJM 2012

Study design

Before trial

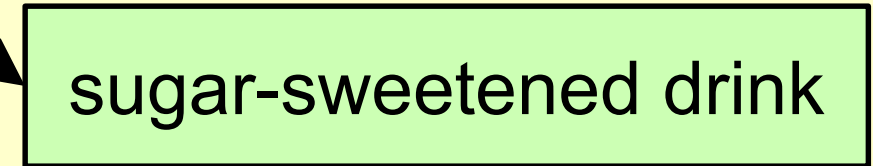
0 mo

18 mo

641 kids, aged 5-11
All habitually brought a sugary drink to school

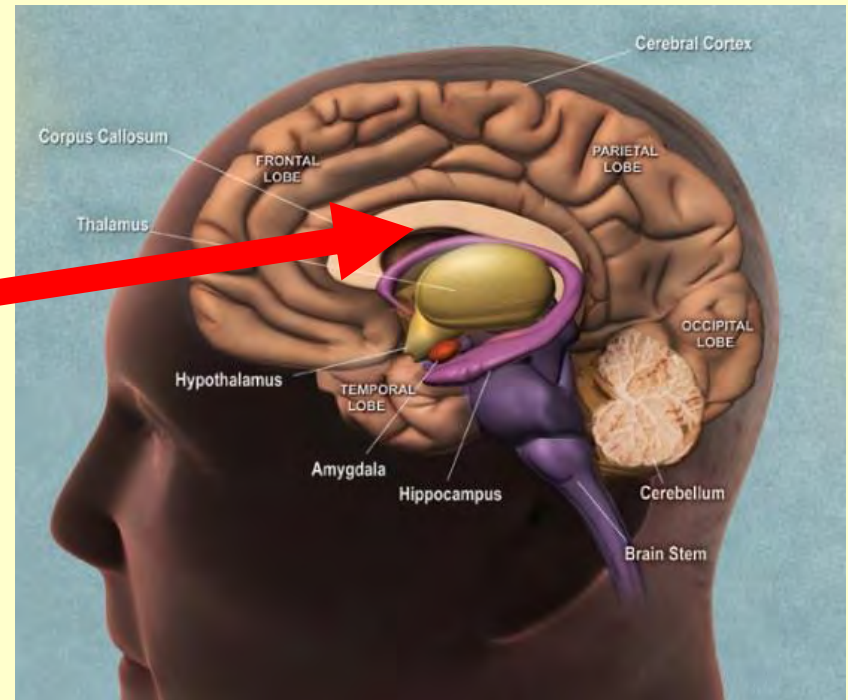
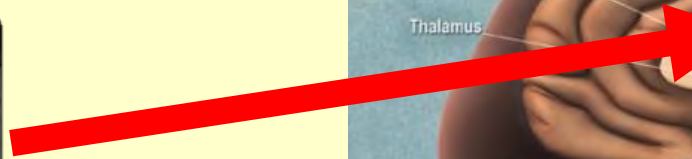
sugar-free drink

sugar-sweetened drink



Why double-blind?

- Get rid of cognitive and behavioral effects
- Investigate biologic mechanisms only



Double-blind design required indistinguishable beverages

- Designed by us
- Sugar vs artificial sweeteners, 220 000 cans each
- Sugar and sugar-free same look and taste



104 kcal



0 kcal

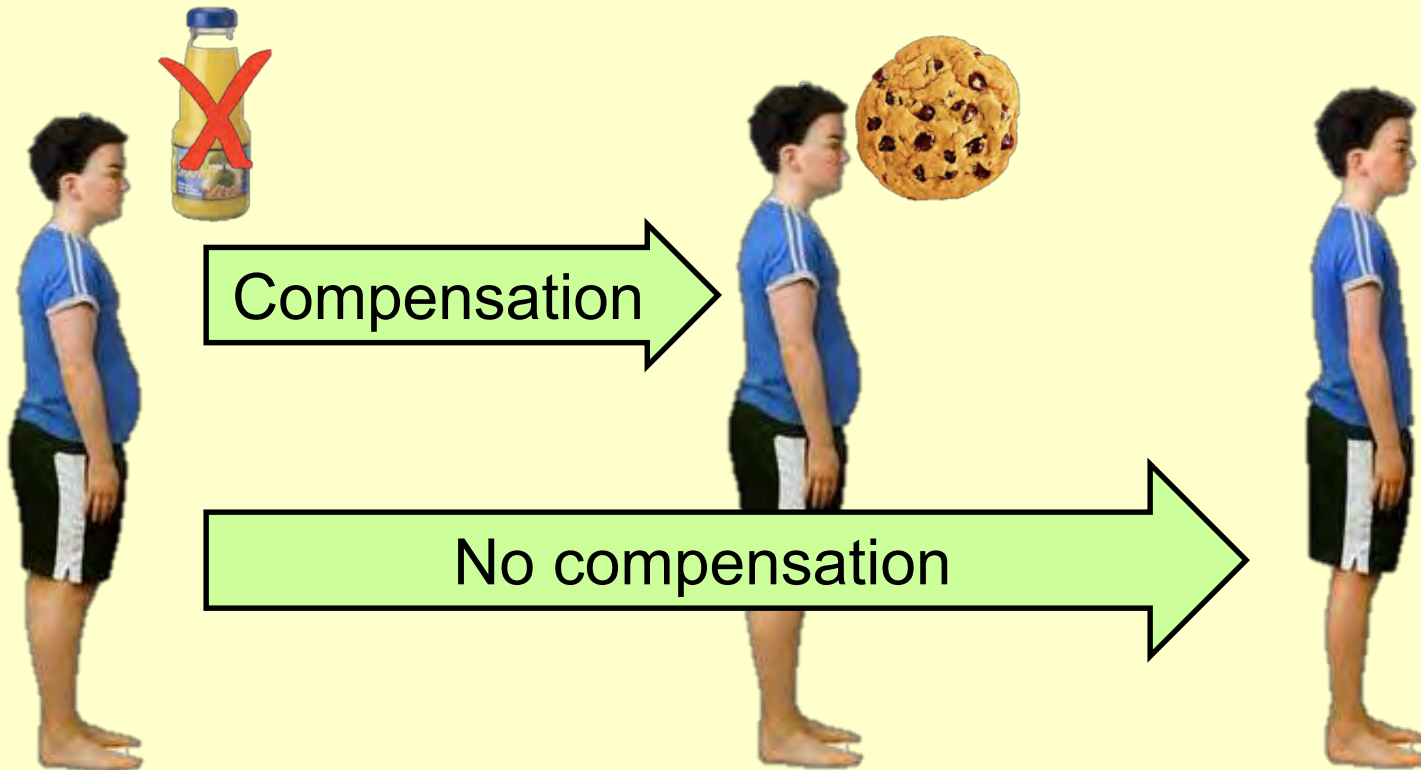
Study drink replaced habitual sugary morning drink. Otherwise kids were free to eat as they liked.



Central question:

Do children *compensate* for the covert removal of sugar?

Does removal of sugar from beverages *increase* intake of other beverages and foods?



Results

- Sugar-free group gained 1 kg less weight
- Most of the difference was fat tissue

Conclusion

Substituting sugar-containing with noncaloric beverages reduced weight and fat gain in normal-weight children