Barnyard Brouhaha: What About Dairy and Eggs in the Diet?

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Dairy and Eggs

Good sources of protein

Good sources of vitamin B12

Associated with controversy: risk regarding ASCVD risk

- Saturated fat in dairy
- Cholesterol in egg yolks

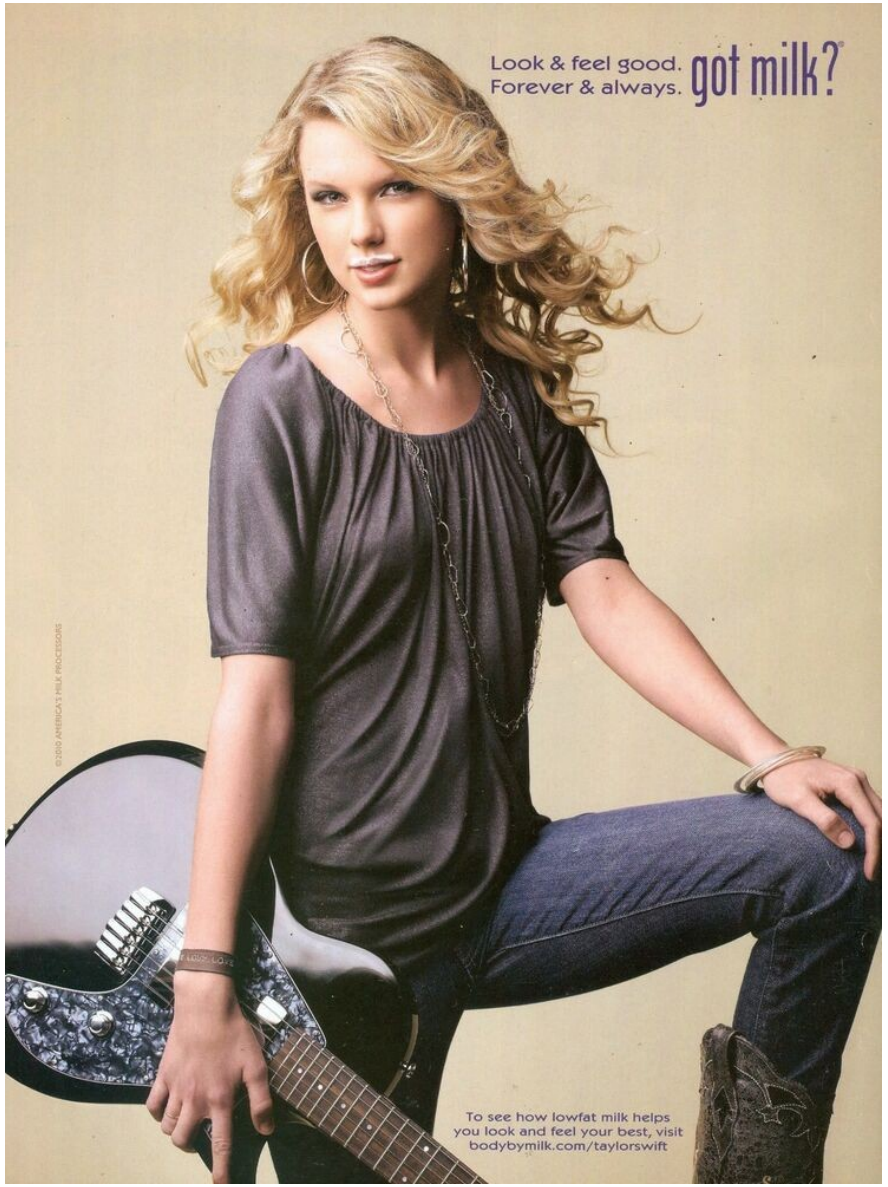
Whole-food, plant-food advocates claim animal proteins possess special risks

Vegans avoid these food sources for various perceived benefits

- Avoiding ethical issues of using animals as food
- Reducing environmental impact due to inefficiencies of resource utilization
- Health risks of animal-sourced food

What do the data say about their effect on health?

got milk?



Iconic advertising ad campaign for dairy products: the milk moustache

Milk: It's for babies

Nursing is Nature's means of providing nutrition for mammalian offspring in early life

Milk sugar, lactose, is an important ingredient in human milk

An enzyme to digest milk was essential

- Lactase breaks lactose into its two primary sugars, glucose and galactose, for absorption

Milk: It's not for grownups

After weaning, lactase production falls off dramatically, i.e., gene is turned off, no longer expressed, as the normal situation

Individuals without lactase typically have unpleasant intestinal symptoms when they consume milk with lactose

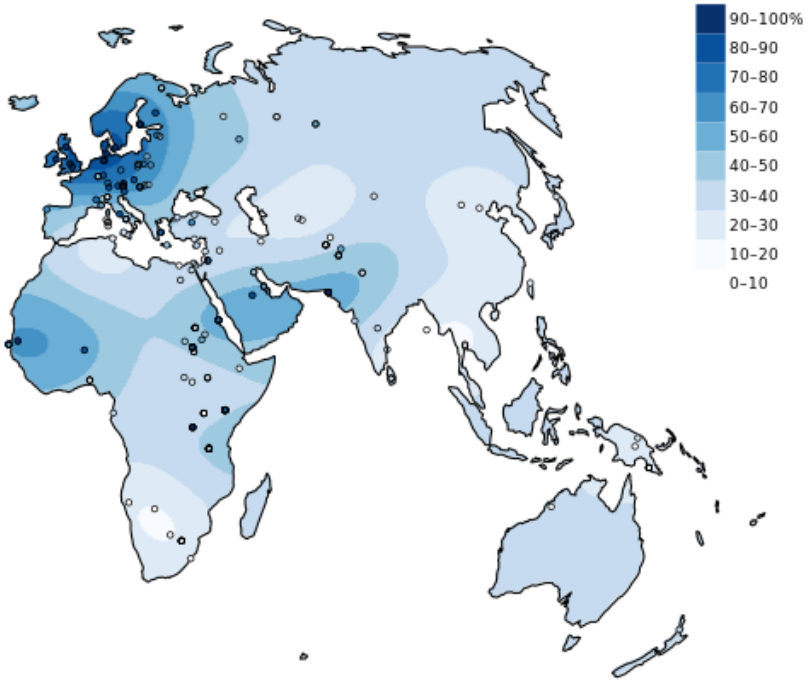
- Dairies can produce lactose-free milk products enzymatically
- One can take lactase supplements to allow lactose digestion

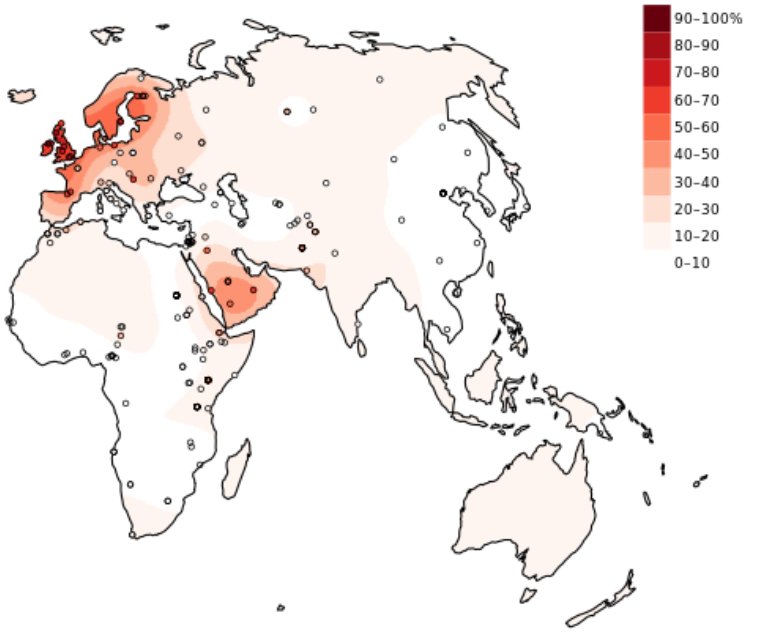
Mutant lactase genes exist that do not get turned off – "hereditary persistence of lactase"

- Mutants are very common in some areas
- This allows the mutant individual to digest lactose into adult life

So-called "lactose intolerance" is not an abnormal condition – it is the default!

Persistence of lactase





Old World lactose tolerance (blue) vs. lactase persistence (red)

Persistence of lactase

Advantages

- Allows populations to use dairy products, and milk in particular, as a food staple

Disadvantages

- Not apparent at first glance, but we'll revisit

Dairy consumption and mortality

Goldbohm *et al*, Am J Clin Nutr, 2011

Netherlands Cohort Study (NLCS)

120,852 men and women

150 item food frequency questionaire

Endpoints: Death from CVD, all causes

10 year followup

16,136 deaths

Results: NLCS

Analysis with respect to:

- All milk products
- Full fat milk, low fat milk
- Fermented milk (yogurt, processed sour milk), non-fermented milk
- Full fat cheese, low fat cheese
- Butter

No meaningful mortality differences in any category, or separately by gender, or by cause of death (CVD, all)

Dairy consumption and CVD

Sonestedt *et al*, Eur J Epi, 2011

Malmö Diet and Cancer Cohort (Sweden)

16,445 (38% men), recruitment 1991-96

Exclusions: Prior dx CVD, diabetes

Followup: 12 years

Endpoints: Dx cardiovascular, dx cerebrovascular

2,520 incident CVD (1,344 CHD, 1,176 CVA)

Results: Malmö

Evaluated by:

- Total dairy
- Milk: full and low fat, fermented and non-fermented
- Cheese: full and low fat
- Butter

Generally, no association between CVD and dairy consumption level, except:

- Lower CVD in women with greater cheese consumption
- Lower CVD in all with greater fermented milk consumption (yogurt, processed sour milk)

Milk Consumption and Mortality: Meta-Analysis

Larsson et al, Nutrients, 2015

367,505 subjects in 13 studies

Outcome: Mortality, all cause ± CVD, cancer

Followup: 4.1-25 years

70,743 deaths

Most adjusted for age, sex, smoking, BMI, alcohol, physical activity, socioeconomic

Few adjusted for other food items

Milk and mortality meta-analysis

Evaluated by fermented and non-fermented

No consistent association between non-fermented or fermented milk consumption and mortality, except:

- Study from Sweden (Michaelsson, 2014) showing statistically significant positive correlation between milk intake and mortality in men (HR 1.10) and women (HR 1.93)
- Study from Japan (Wang, 2015) showing inverse correlation between milk intake and mortality (HR 0.91) in both men and women

Studies were too heterogeneous to combine

Swedish dairy & mortality study

Milk intake and risk of mortality and fractures in women and men: cohort studies

Karl Michaëlsson *professor*[1], Alicja Wolk *professor*[2], Sophie Langenskiöld *senior lecturer*[3], Samar Basu *professor*[3], Eva Warensjö Lemming *researcher*[1 4], Håkan Melhus *professor*[5], Liisa Byberg *associate professor*[1]

BMJ 2014

Swedish dairy & mortality study

Swedish Mammography Cohort

Subjects: 61,433 woman aged 39-74 (mean 53)

Follow-up: 22 years median

Endpoint:

- Total deaths – 15,541 (25%)
- Cardiovascular death – 5,728
- Cancer deaths – 3,283
- Any fracture – 17,252
- Hip fracture – 4,259

RR of mortality vs. milk intake

	Daily milk intake (glasses)			
Mortality	<1	1-2	2-3	3+
Total	1.00	1.21	1.60	1.93
Cardiovascular	1.00	1.16	1.59	1.90
Cancer	1.00	1.07	1.16	1.44

All-cause mortality was nearly double in those consuming 3 or more glasses of milk a day

Drinking just 2-3 glasses a day was associated with a 60% increase in overall mortality

Cardiovascular mortality was the most prominently affected, but cancer mortality was also significantly increased with increasing milk consumption

RR of fractures vs. milk intake

	Daily milk intake (glasses)			
Fractures	<1	1-2	2-3	3+
Any	1.00	1.07	1.16	1.16
Hip	1.00	1.19	1.55	1.60

Fractures increased with numbers of glasses of milk a day

Hip fractures were significantly increased with increasing milk consumption, contrary to expectation

- Vitamin D and calcium were thought to be helpful in preventing fractures

RR of mortality vs. cheese intake

	Daily cheese intake (grams)			
Mortality	<20	20-39	40-59	60+
Total	1.00	0.70	0.75	0.68
Cardiovascular	1.00	0.69	0.74	0.61
Cancer	1.00	0.89	0.84	0.96*

All-cause mortality was 32% lower in those eating 60 gm (2 oz) or more a day

Cardiovascular mortality was the most prominently associated with cheese consumption, but cancer mortality was not

Other fermented dairy products – yogurt and soured milk – had weak and inconsistent beneficial associations with mortality

$P < 0.05$ except * - not significant

RR of fractures vs. cheese intake

	Daily cheese intake (grams)			
Fractures	<20	20-39	40-59	60+
Any	1.00	0.86	0.92	0.85
Hip	1.00	0.69	0.81	0.57

Hip fractures were 43% lower in those eating 60 gm (2 oz) or more a day!

Other fermented dairy – yogurt and soured milk – had weak and inconsistent relationships to fractures

Dairy, mortality and fractures

Drinking milk was associated with increased mortality, especially cardiovascular disease, and increased hip fractures

Eating cheese was associated with decreased mortality, especially CVD, and decreased hip fractures

How to explain !?!

Death, fractures and dairy

Milk and cheese have opposite effects on both fractures and cardiovascular mortality

- Milk adverse, cheese beneficial

Milk and cheese have essentially the same profile of fats

- Substantial amounts of saturated fatty acids
- It's probably not the fat

Milk has lactose, cheese has little to none

- A possible candidate for cardiovascular and bone effects

Lactose, glucose and galactose

Milk sugar, lactose, a disaccharide, is split into glucose and galactose during digestion by lactase

Glucose enters normal glucose cycle

Galactose must be converted to glucose for use

- A special pathway quickly does the job – normally
- What if that pathway is not working, or gets overwhelmed?

Galactose effects

Galactose given to laboratory animals is a model for accelerated aging due to oxidative stress and chronic inflammation

Galactose reacts with proteins to produce advanced glycation end products (AGEs) that are implicated in systemic inflammation, which is a contributing factor in developing atherosclerosis

- Similar to mechanism by which chronically elevated blood glucose in diabetics leads to severe blood vessel damage

Genetic disorders in humans with missing or ineffective enzymes in the pathway for converting galactose to glucose result in high levels of galactose

Known as *galactosemia*, this situation can result in severe disease, with permanent organ damage and even death, in infants

Lactose, blood vessels and bones

Oxidative stress marker levels 8-iso-PGF2a in the Swedish women were increased with increasing milk intake

Researchers hypothesized that excess galactose levels from milk consumption led to excessive AGEs, which then led to accelerated atherosclerosis and bone deterioration

Caveat

The present study is the first, and only, study that, to our knowledge, shows a strong direct relationship of milk and mortality and inverse relationship of cheese and mortality

- Ditto for bone fracture correlations – increasing fracture with increasing milk

It will certainly inform future studies to further elucidate these relationships

Its results should be considered tentative until they are replicated

Milk and protein

Milk has abundant protein

Main milk proteins

- Casein: Main protein in cheese, yogurt
- Lactalbumin: Main protein in whey – liquid left over from cheese and other cultured products

Milk is a complete protein source – supplies all essential amino acids

Milk and protein

6 oz of milk has 6 gm of protein

1 oz of cheese has 7 gm of protein

6 oz of yogurt has 7-10 gm of protein

6 oz of Greek yogurt has 17 gm of protein

More protein is good, right?

Animal protein and health

Amino acids – the building blocks of proteins - are essential to the growing and developing child and adolescent

Growing evidence suggests that the mature adult animal should reduce the amount of protein consumed, especially that from animal sources

- This was discussed in detail in the Meat lecture

Increasing dietary protein stimulates IIS and mTOR

Insulin / insulin-like growth factor (IGF)-1 signaling (IIS)

Mechanistic target of rapamycin (mTOR)

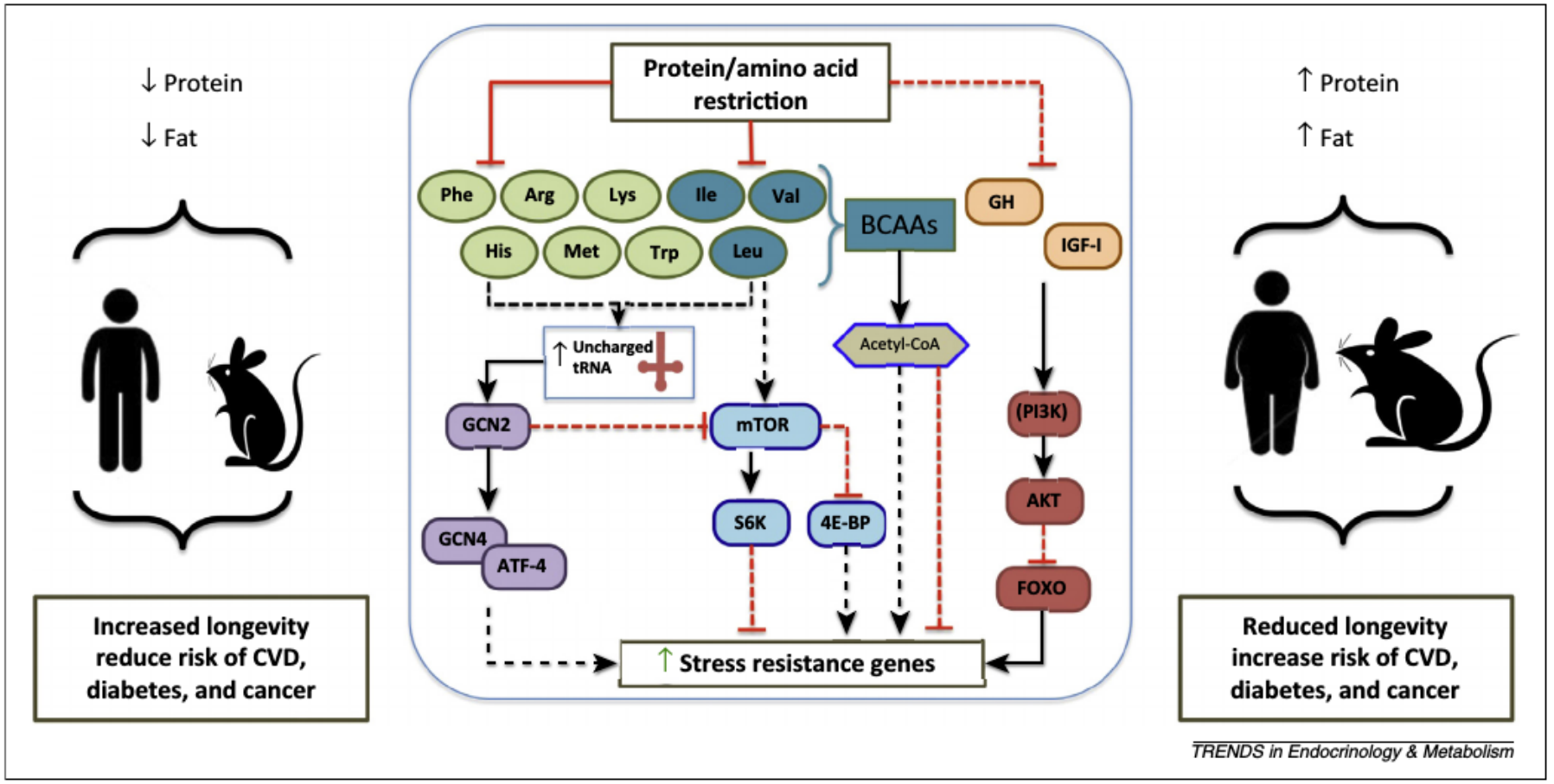
IIS and mTOR are activated by increasing dietary protein

- Certain amino acids are more potent activators – those in animal proteins

IIS and mTOR activation triggers processes that promote glucose intolerance, inflammation, oxidation and cancer initiation / progression

IIS and mTOR activation associated with shortened lifespan and increased chronic diseases in multiple species

Metabolic effects of dietary protein



Conclusions: Dairy

Evidence does not support concern that saturated fat content of dairy products is associated with excessive risk of CVD

The neutral risk of dairy in most studies suggests that it is a reasonable replacement, providing protein and energy, for choices that have negative consequences (processed meat), but not to the extent that it eliminates choices with even lower risk (nuts, fiber)

The finding of strikingly increased mortality and hip fractures with increasing milk consumption in the Swedish study raise concerns

- Limitation of milk intake seems prudent for the time being

By contrast, lower mortality and hip fractures observed with increasing cheese intake suggest that its consumption is relatively safe and perhaps even beneficial

The prominence of protein in dairy products should be kept in mind

Recommendations: Dairy

Cheese can be a valuable part of the diet, providing protein, energy (fat), vitamin D, and calcium

- Good replacement for red meat
- But not to the exclusion of plant protein sources, such as nuts, grains and beans

Yogurt can also be a valuable food

- Weight loss over time is associated with greater yogurt consumption
- Good substitute for milk with cereal
- Watch out for yogurt with added sugars

Milk should be consumed cautiously in adults until further studies clarify its risk-benefit balance

- Lactose-free milk is not sugar-free; lactose has been converted to glucose and galactose by enzyme treatment, which are absorbed individually
- Plant-based "milk" (almond, soy) have no data to shed light on their risks or benefits

Dairy products are a good source of vitamin D, protein and energy for the child and adolescent

- There is no data to suggest harm from galactose in children, though has not been studied to my knowledge
- Surprisingly, low-fat or skim milk is associated with greater weight gain compared to full-fat

Eggs: The other breakfast dilemma

Eggs have had a roller-coaster ride in their image

- Concerns over contribution to heart disease
- However, they are very popular as the anchor of breakfast for many people
- Good source of protein, choline

Eggs and cardiovascular disease

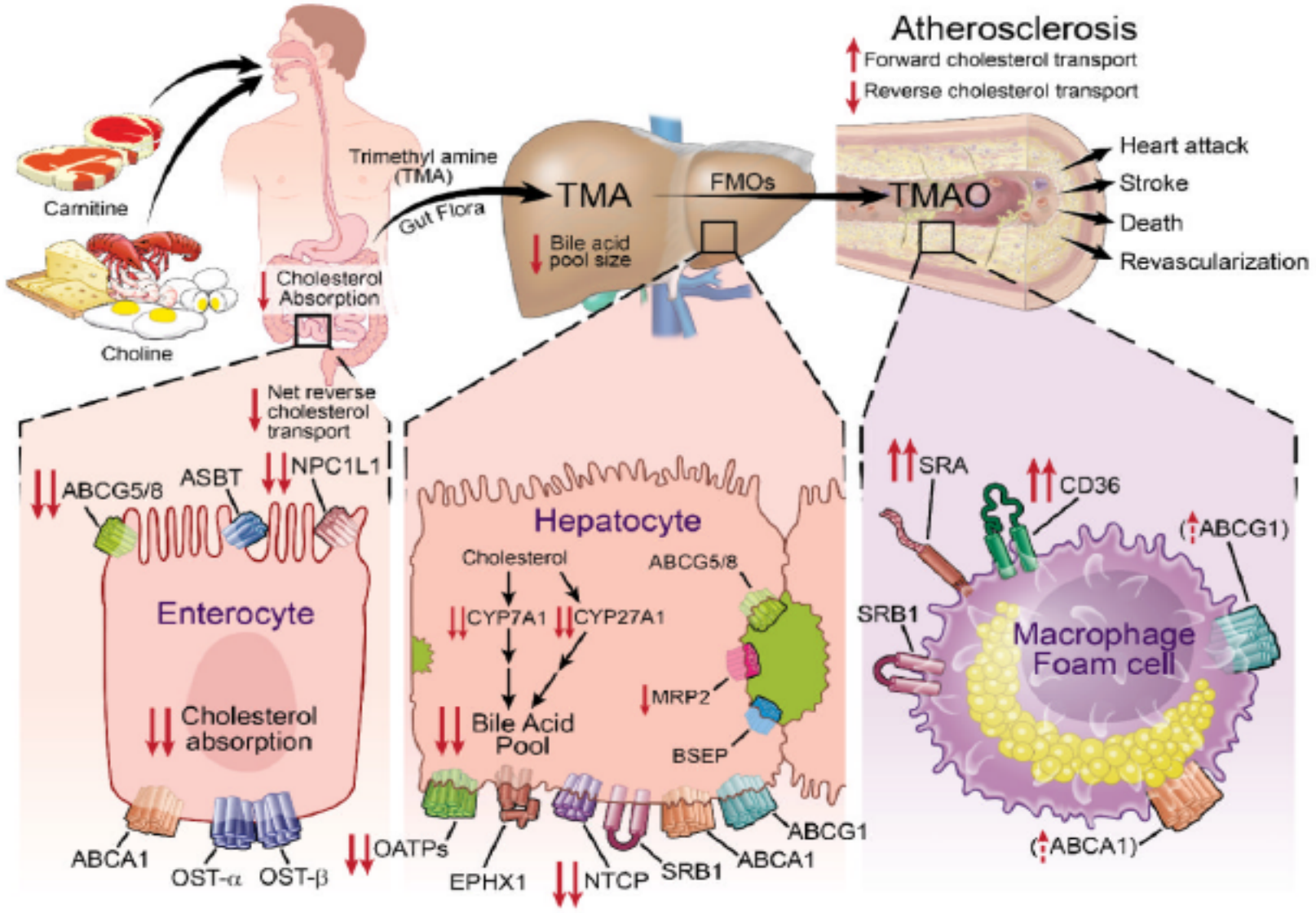
Earlier studies implicated cholesterol in egg yolks as possible contributors to ASCVD

Current thinking rejects dietary cholesterol as a significant contributor to disease

On the other hand, we must now consider choline (as phosphatidyl choline, lecithin) as a potential source of risk

- Remember TMAO from the meat lecture?
- Choline – abundant in egg yolks – is a major precursor to TMA production by certain bacteria in the gut microbiome

TMAO & ASCVD


Atherosclerosis
Forward cholesterol transport
Reverse cholesterol transport
Heart attack
Stroke
Death
Revascularization
Carnitine
Choline
Trimethyl amine (TMA)
Gut Flora
TMA
FMOs
TMAO
Bile acid pool size
Cholesterol Absorption
Net reverse cholesterol transport
ABCG5/8
ASBT
NPC1L1
Enterocyte
Cholesterol absorption
ABCA1
OST-α
OST-β
Hepatocyte
Cholesterol
CYP7A1
CYP27A1
Bile Acid Pool
ABCG5/8
MRP2
BSEP
OATPs
EPHX1
NTCP
SRB1
ABCA1
ABCG1
SRA
CD36
ABCG1
SRB1
Macrophage Foam cell
ABCA1

TMAO and egg consumption

Effect of egg ingestion on trimethylamine-*N*-oxide production in humans: a randomized, controlled, dose-response study[1–4]

Carolyn A Miller, Karen D Corbin, Kerry-Ann da Costa, Shucha Zhang, Xueqing Zhao, Joseph A Galanko, Tondra Blevins, Brian J Bennett, Annalouise O'Connor, and Steven H Zeisel

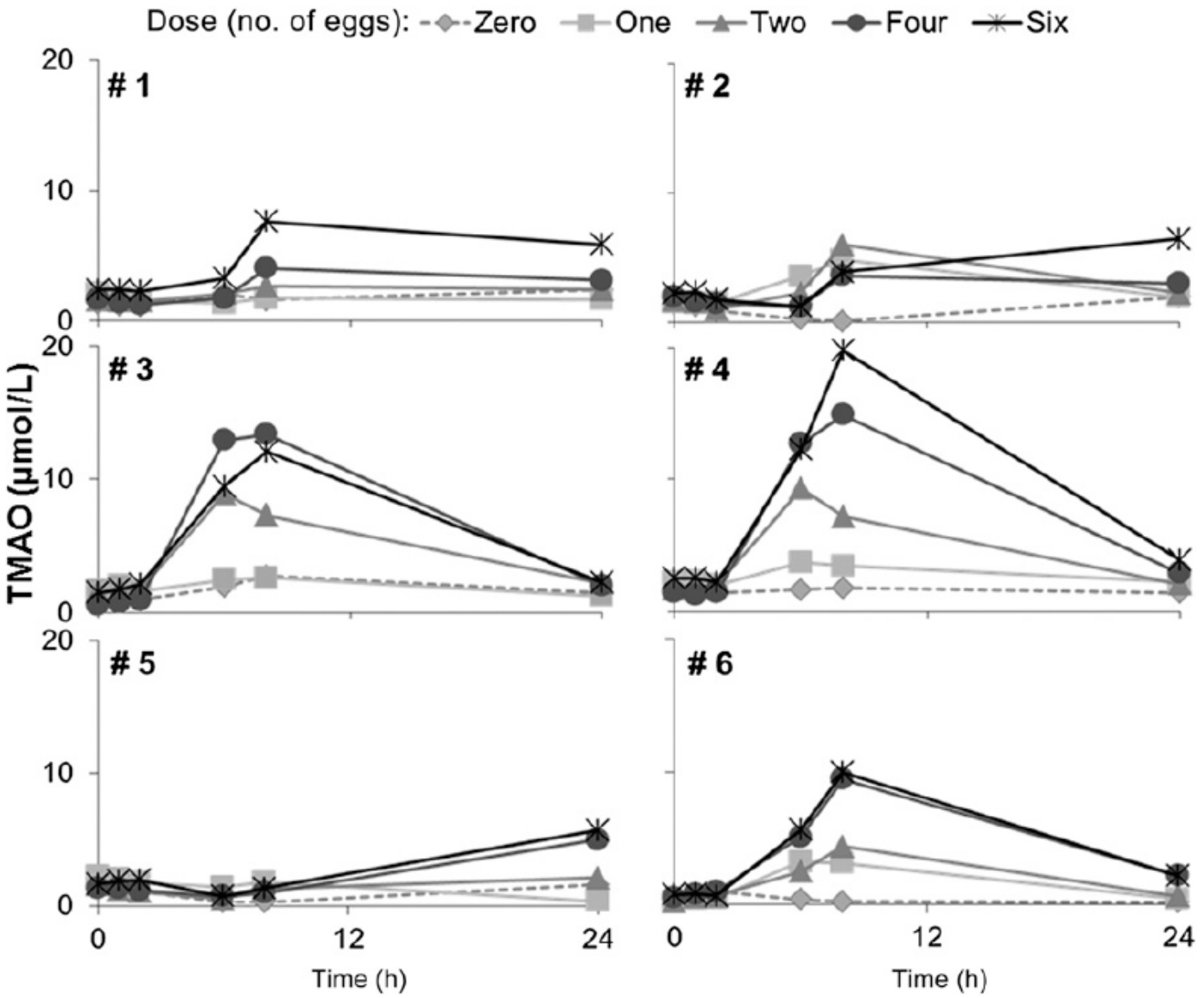
Am. Journal of Clinical Nutrition 2014

TMAO and egg consumption

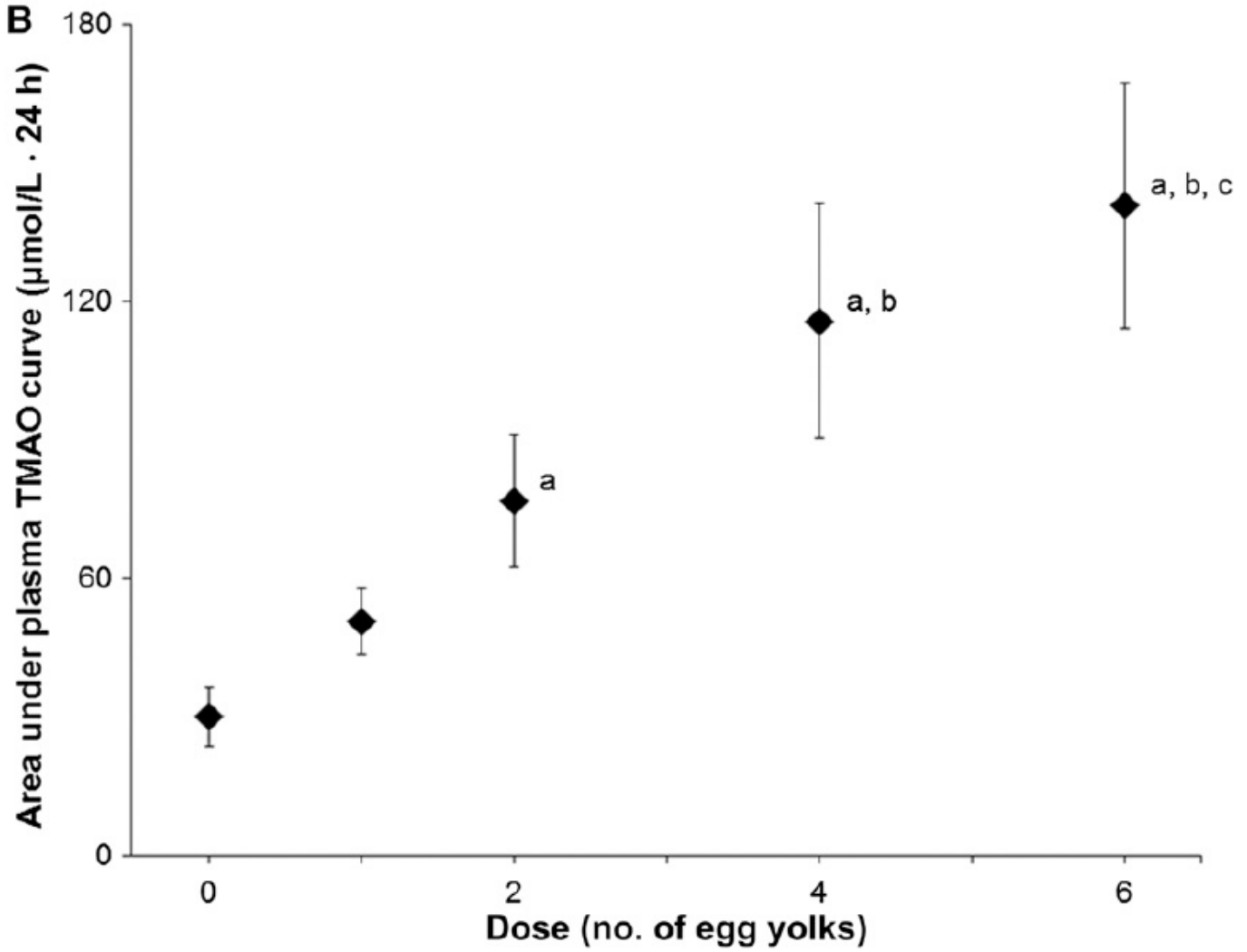
TMAO blood levels were studied in six healthy volunteers

- Each fed 0, 1, 2, 4 and 6 egg yolks on different days
- Separated by washout
- Area under curve (AUC) of repeated measurements of TMAO
- AUC vs. # of egg yolks

TMAO and egg consumption



TMAO and egg consumption



TMAO and egg consumption

Six subjects had a baseline level of TMAO corresponding to a steady level of about 1 umol

One egg increased that, but not statistically significantly, to 2 umol

Two eggs increased the average level to 3, with considerable inter-subject variation, significantly different from baseline

Four eggs increased the level to 5, above the cut point associated with increased risk of CHD (Cleveland Clinic)

TMAO and egg consumption

Response was highly variable among the six subjects; three with little response, three with rather dramatic responses (>10 with 4 or more eggs)

The TMAO response is due to choline in the yolk; eating egg whites should not be a concern

On the other hand, these responses give me concern about habitual consumption of two or more whole eggs daily, and the risk it could entail of promoting atherosclerosis

Egg consumption and CVD

Larsson, Am J Clin Nutr 2015

37,766 men (Cohort of Swedish Men)

32,805 women (Swedish Mammography Cohort)

Followup: 13 years

Cardiovascular events: 7,331 men, 5,266 women

Outcomes: Onset of heart failure (HF), myocardial infarction (MI), ischemic stroke (ICVA), hemorrhagic stroke (HCVA)

Results: Eggs and CVD in Sweden

No association between level of egg consumption and rate of MI, HF, or CVA, except:

- Men consuming 1 or more eggs per day had increased risk of HF (RR 1.30, CI 1.01-1.67)

Egg consumption and coronary artery calcification

Choi et al, Atherosclerosis, 2015

23,417 asymptomatic w/o CVD or elevated cholesterol undergoing health screening

Coronary artery calcifications (CAC) are associated with risk for subsequent MI

CAC present in 11% of screened subjects

Asked about # eggs consumed / day

Egg intake and *CAC*

7+ eggs / week vs. < 1 egg / week

- RR *CAC* 1.80 (*CI* 1.14-2.83)

Increase in RR per egg / day:

- 1.54

CAC – egg association enhanced by low vegetable intake, higher BMI

CVD & diabetes risk in relation to egg consumption

Shin et al, Am J Clin Nutr, 2013

22 cohorts in 15 studies

Considerable heterogeneity among studies

Outcomes: Dx of CVD, dx of diabetes, death

Egg consumption & mortality

11,845 deaths in 103,202 subjects followed for average 15.3 years

No association between level of egg consumption and all-cause mortality

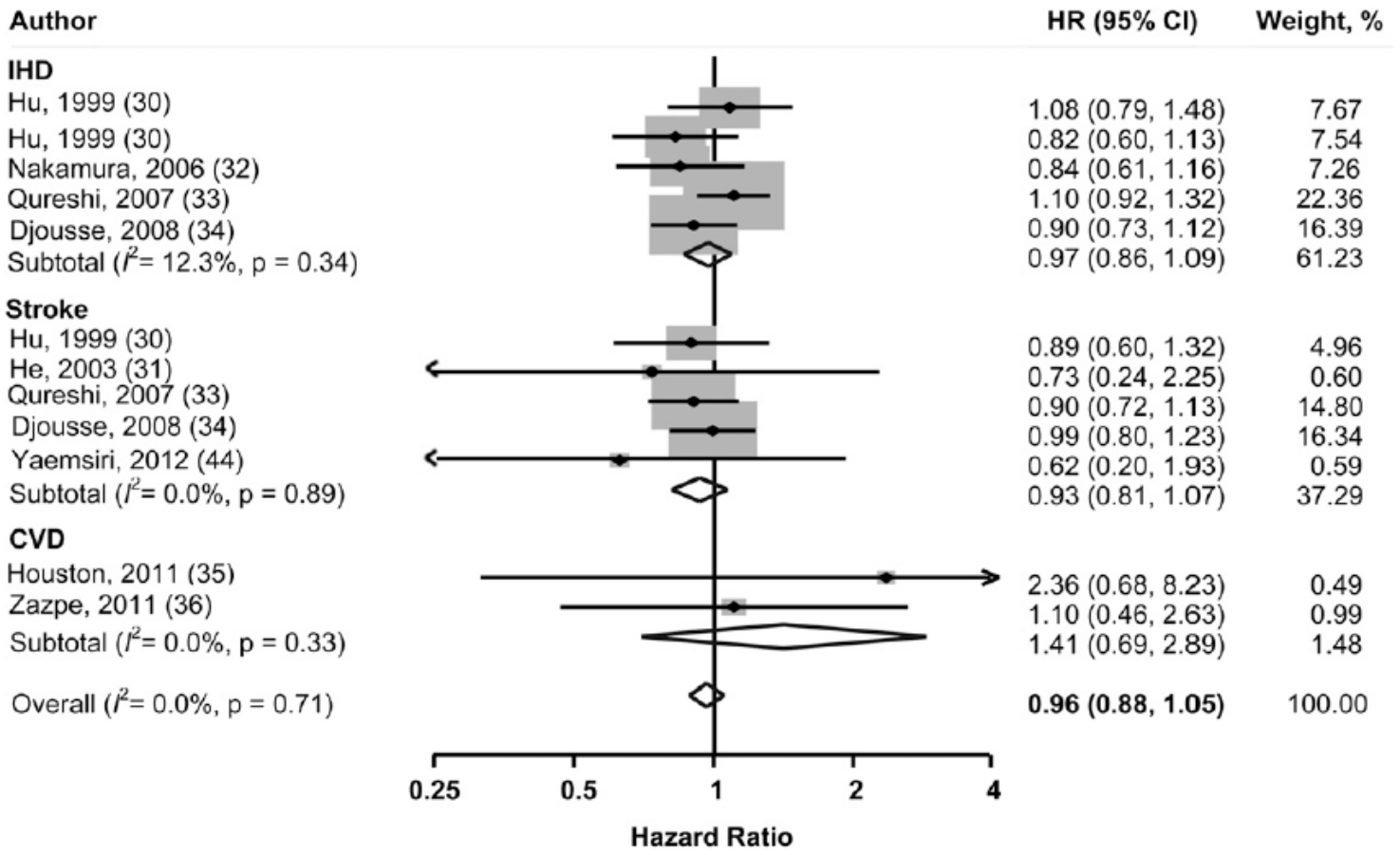
No association between level of egg consumption and cardiovascular deaths

Egg consumption & diabetes

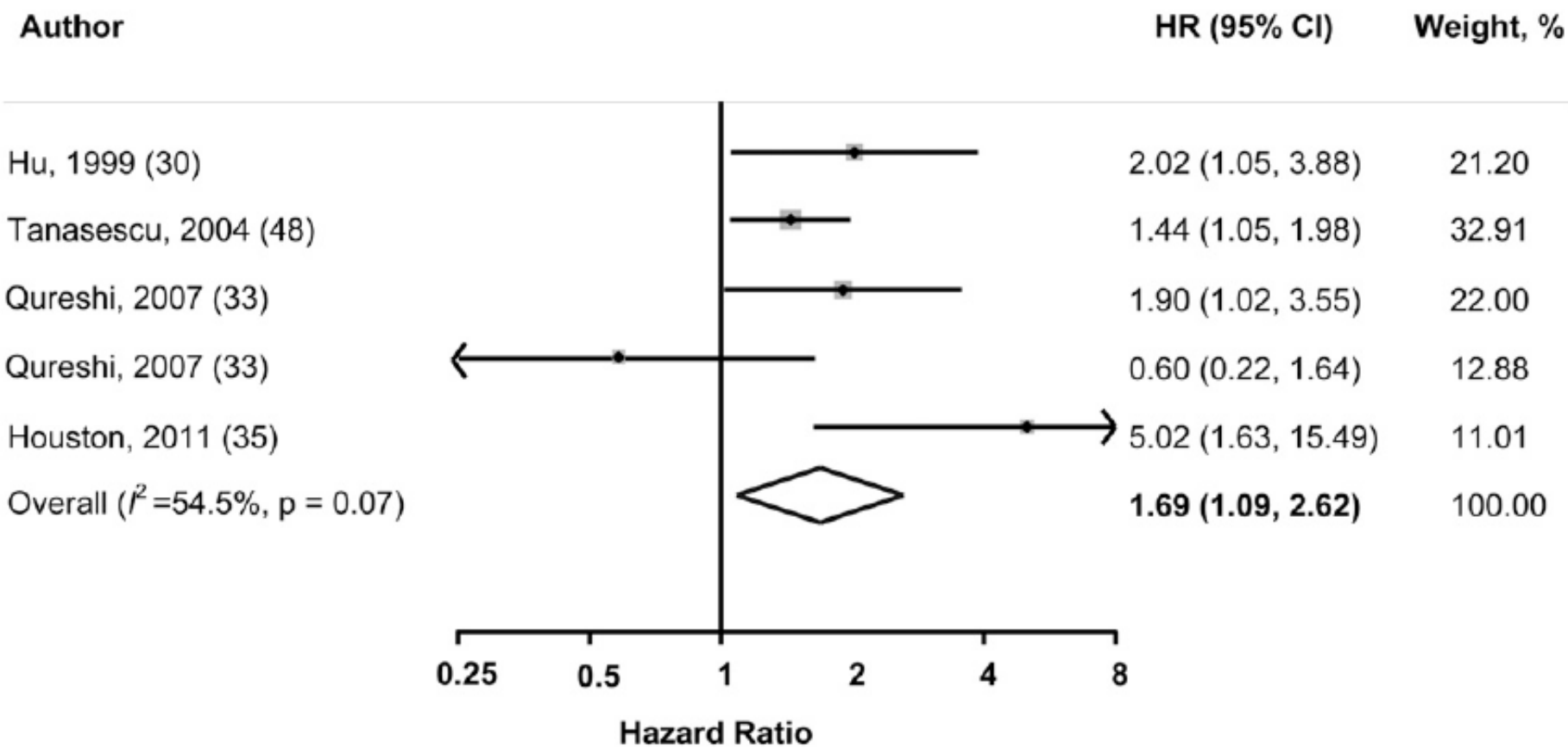
Diabetes diagnosed in 4,889 of 69,297 subjects over 14.8 years followup

Diabetes risk for highest vs. lowest quantile of egg consumption: RR 1.42 (CI 1.09, 1.86)

CVD risk vs. egg consumption



CVD risk in diabetics vs. egg consumption



Conclusions: Eggs, CVD & diabetes

Egg consumption thus far not associated with increased risk of diagnosed CVD, IHD, CVA, stroke in observational studies

Egg consumption not associated with increased risk of mortality (overall or CVD-specific)

However...

Eating 1+ / day on average associated with 42% increase in risk of diabetes

Diabetics eating 1+ / day on average had 69% increase in CVD

Reproducible rise in blood TMAO after consuming egg yolks raises concerns that regular egg consumption might contribute to cardiovascular disease

Recommendations: Eggs & health

Egg yolks are rich in choline

- Gut microbiome converts choline to TMA, and TMA becomes TMAO, which promotes ASCVD
- A feeding study confirmed the appearance of significantly increased amount of blood TMAO after two eggs

Modest egg intake (up to a couple per week) is probably beneficial, at worst neutral

Regular consumption of eggs (more than one daily on average) should be viewed with concern