Does Carnitine From Red Meat Contribute to Heart Disease Through Intestinal Bacterial Metabolism to TMAO?

Posted on April 10, 2013 by Christopher Masterjohn • 80 Comments

In April of 2011, I posted a rebuttal of a *Nature* paper from Stanley Hazen's group at the Cleveland Clinic arguing that choline from animal foods causes heart disease:

Does Dietary Choline Contribute to Heart Disease?

Their argument was that our intestinal bacterial convert choline to trimethylamine, which our livers then convert to trimethylamine oxide (TMAO), which causes atherosclerosis in mice, and thus, by extension, probably in humans. I pointed out that previous studies have shown that supplements with salts of free choline do in fact generate TMAO, but uncontaminated phosphatidylcholine, the main form of choline found in food, does not. Moreover, choline-rich foods like liver and eggs did not produce more TMAO than a control breakfast, but seafood, which is generally contaminated with some trimethylamine or TMAO, did.

In a new paper in *Nature Medicine*, these authors have expanded their argument to claim that the carnitine in red meat contributes to heart disease through the same pathway. Put on your seat belts, folks, and let's take a look!

The new paper can be found here:

> Koeth RA, Wang Z, Levison BS, Buffa JA, Org E Sheehy BT, Britt EB, Fu X, Wu Y, Li L, Smith JD, Didonato JA, Chen J, Li H, Wu GD, Lewis JD, Warrier M, Brown JM, Krauss RM, Tang WH, Bushman FD, Lusis AJ, Hazen SL. Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013; April 7 [Eub ahead of print].

The press reported on the paper widely, and this *New York Times* article by Gina Kolata gave it a big boost in popularity:

Culprit in Heart Disease Goes Beyond Meat's Fat

In brief, here is the "clean version" of the story. The authors showed that eating a steak increased blood and urine levels of TMAO in five omnivores, whereas the same meal did not have this effect in a vegan. Furthermore, carnitine supplements increased blood TMAO in five omnivores, but not in five vegetarians and vegans. Baseline blood levels of TMAO were also higher in 30 omnivores than in 23 vegetarians and vegans, as were the levels of certain strains of intestinal bacteria.

Antibiotics suppressed TMAO levels in five omnivores, showing the role of intestinal flora in its generation. Plasma concentrations of carnitine and TMAO correlated with atherosclerosis in just under 2,600 humans, and, like they had previously shown for choline, carnitine produced atherosclerosis in female mice genetically engineered to be vulnerable to that disease, but not when the mice were kept germ-free with antibiotics.

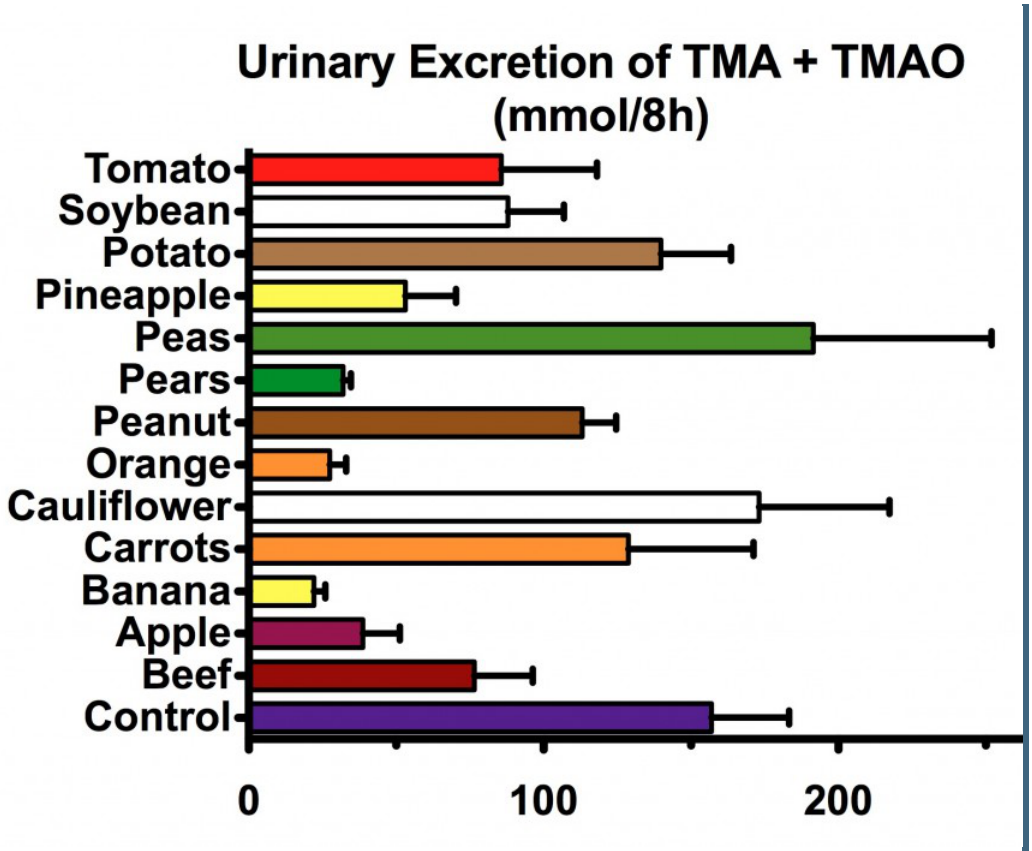
Overall, parts of this study are very well conducted, providing insights into metabolism that should fascinate anyone who loves biochemistry for its own sake and doesn't mind meandering down rabbit holes that have no clear relevance to the health of humans or natural strains of animals. The problems with this study and its portrayal in the media are the often-times incomplete reporting of data in the paper and the wild runaway inferences published all over the press, particularly the conclusion that red meat contributes to heart disease by generating TMAO, and the even stranger notion that we should eat less red meat for this reason. Let's take a look at the less "clean" version of the story.

Why Single Out Red Meat?

First of all, why pick on red meat? As I pointed out in my last post on this topic, lots of foods seem to increase TMAO in humans and red meat does not stand out among them. A 1999 study in six human volunteers evaluated excretion of trimethylamine and TMAO after consumption of a handful of supplements and 46 different foods. For comparison, the new paper in *Nature Medicine* reported data for one food (red meat) fed to two (urine data) or six volunteers (plasma data). Consistent with a 1983 finding from the group of famed choline researcher Steven Zeisel that salts of free choline but not uncontaminated phosphatidylcholine (lecithin) generated trimethylamine, this group found that high-dose choline and carnitine, but not lecithin, generated TMAO. Eight ounces of carnitine-rich foods, however, like red meat, produced no more TMAO than common fruits and vegetables. Seafoods, by contrast, led to large increases in TMAO. Let's take a look at some of this data.

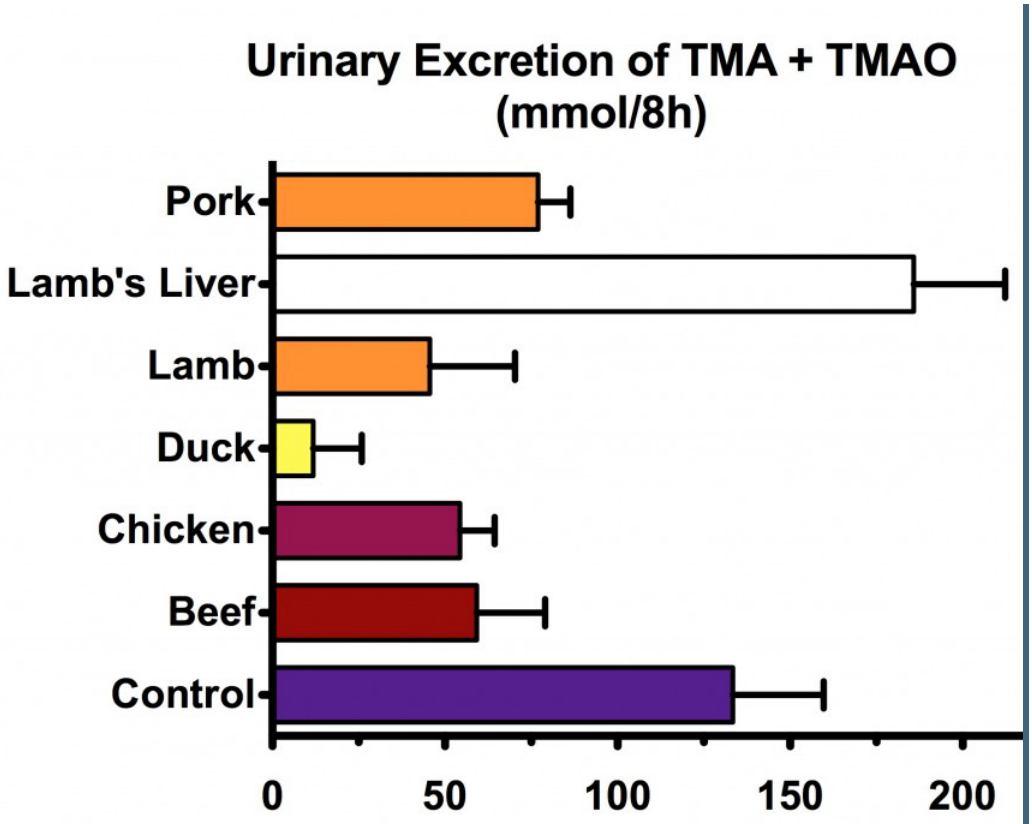
The authors compared eight ounces of 46 foods eaten with a "light breakfast" free of seafood to the "light breakfast" alone, which acted as a control. It would appear from the data that the "light breakfast," which the authors did not describe any further, generated some TMAO. In each graph below, an asterisk indicates a statistically significant difference between the food in question eaten with the breakfast and the control breakfast alone. Lack of statistical significance relative to the control does not mean the food did not generate any TMAO, though statistical significance makes the generation of TMAO more clear. Nevertheless, it should primarily be taken to mean that the food actually stands out relative to other foods as a source of TMAO.*

Here's a comparison between the control, beef, and a variety of fruits and vegetables:

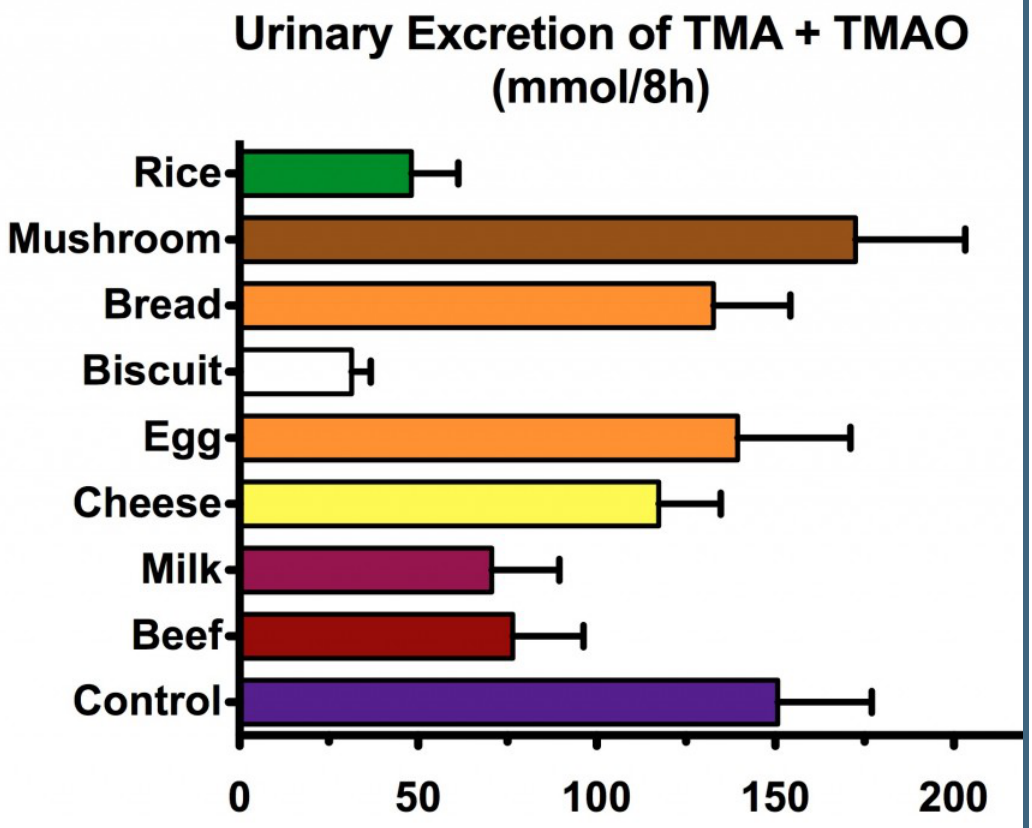


We can see that none of these foods statistically stands out from the control. Looking at the numbers alone, this “light breakfast” alone, along with carrots, cauliflower, peanuts, peas, potatoes, soybeans, and tomatoes generated more trimethylamine and TMAO than beef. In general, we could say that there is no clear evidence that beef produces more or less TMAO than any of the fruits and vegetables tested.

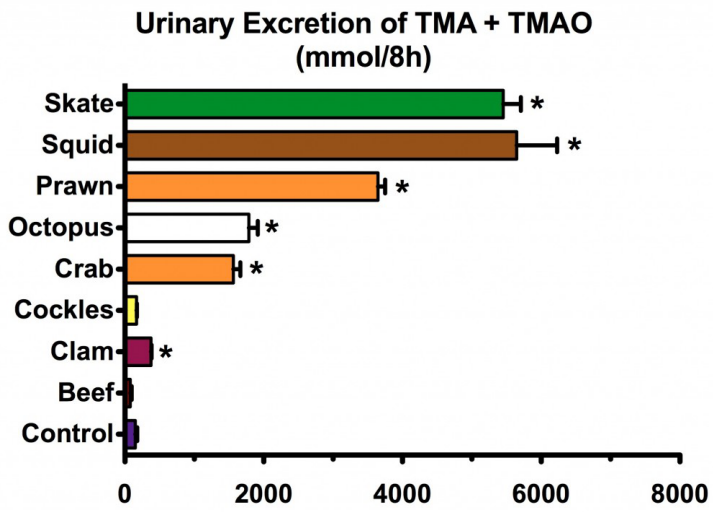
Here we see that none of the meats tested were statistically different from the “light breakfast” control alone (numerically, all of them except lamb liver were lower), and that there is no relation to the “redness” of the meat, with chicken having an almost identical value to beef:



Here we see that mushrooms and an assortment of grain and dairy products are statistically no different from the “light breakfast” control alone, and that bread, mushrooms, cheese and eggs all produced numerically (but not statistically) higher values than beef:

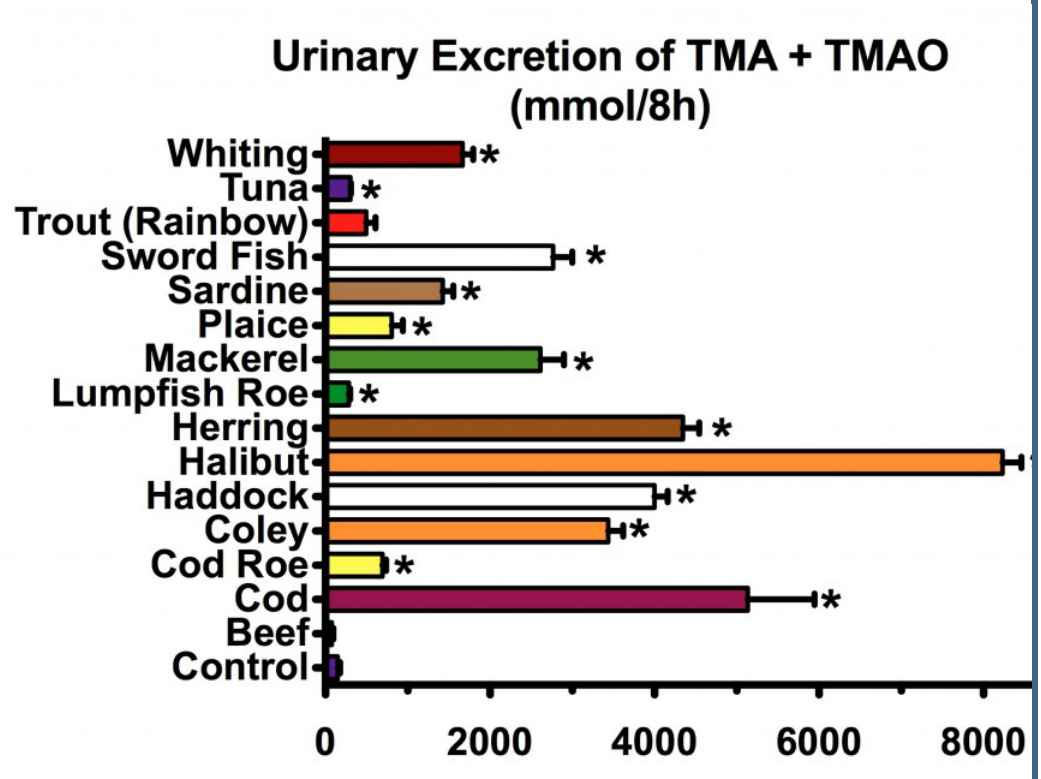


Now here’s the real kicker. What foods ***do*** stand out as supreme sources of TMAO? Seafoods! Let’s take a look at these boneless seafoods first:



Here we see that, unlike beef, all the boneless seafoods (in which I've included invertebrates as well as cartilaginous fish) tested except cockles produced statistically significantly more TMAO than the "light breakfast" control alone. Based on my own statistical test,** all of the seafoods shown in the graph except clams and cockles produced significantly more TMAO than beef.

Now let's take a look at the bony fish:



All the fish except trout produced statistically more TMAO than the "light breakfast" control alone. My own statistical analysis** indicates that all the fish except tuna, trout, plaice, and the two samples of roe produced significantly more TMAO than beef.

The single "representative female omnivore" from the *Nature Medicine* paper excreted similar amounts of TMAO in her urine as the six subjects from the 1999 study after consuming red meat,*** suggesting that, had they measured the response to seafood, the authors of the *Nature Medicine* paper would also have found much greater excretion of TMAO after consumption of seafood than after

consumption of red meat.

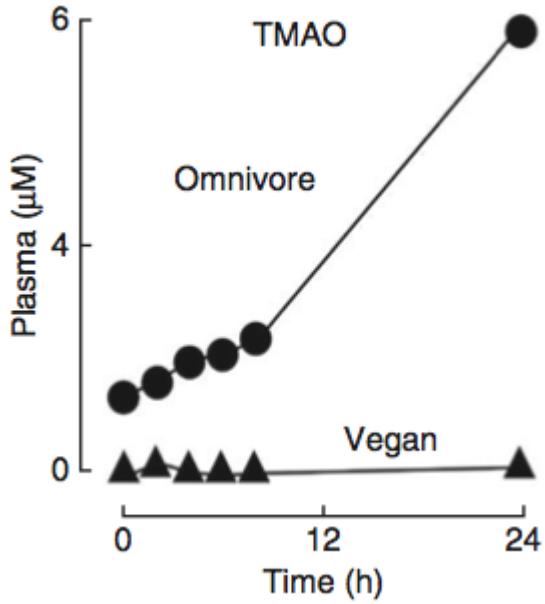
The difference between seafoods and red meat in the 1999 paper is like the difference between night and day. To take the most extreme example, halibut generated over 107 times as much TMAO as red meat. It seems obvious from this study that if any foods should be singled out for the production of TMAO, it should be seafoods. Yet the *Nature Medicine* paper makes no mention of fish and the *New York Times* article only mentions fish to point out that it has less carnitine than red meat (and thus, by inference, will generate less TMAO, though that is clearly not the case, presumably because seafood tends to be contaminated with trimethylamine or TMAO itself; see Tom's comment).

If we are to single out red meat as a source of TMAO, we should be able to identify other foods with which it should be replaced that generate less TMAO. Yet this 1999 study, which had a small sample size but tested an expansive number of foods, found that there basically are no other foods that generate meaningfully less TMAO than red meat.

Do Meat-Eaters Generate More TMAO From Steak Than Vegans?

Do meat-eaters produce more TMAO from steak than vegans? The "clean" version of the story is, as described in the *New York Times*, "the answers were: yes, there was a TMAO burst in the five meat eaters; and no, the vegan did not have it." The data presented in the *Nature Medicine* paper are less clear.

First, as I'll explain in more detail below, no one ate steak alone. They ate steak with 250 milligrams of supplemental carnitine.



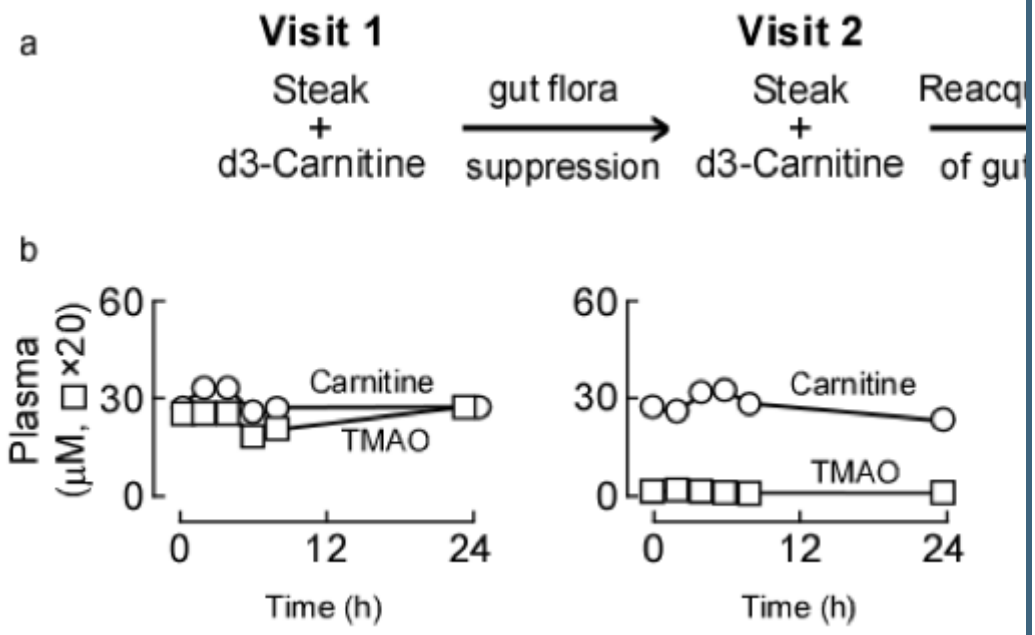
It certainly seems from Figure 2a, shown above, that the single "representative female omnivore" whose data is shown had a greater TMAO increase after consuming steak + carnitine than the one male vegan they were able to convince to eat the same meal. The vegan had no increase and the omnivore's levels roughly tripled. Since the sample size is one per group, the authors did not report a statistical analysis, so we cannot make any comparison between "omnivores" as

a group and “vegans” as a group.

Besides this, this same group has previously shown that the enzyme responsible for converting trimethylamine to TMAO is suppressed by androgens, and its activity is low in males compared to females. Thus, comparing a female omnivore to a male vegan is misleading.

In any case, it’s not so clear once we look at the supplementary figures, or once we read the main text, how “representative” this female omnivore actually was.

In Supplementary Figure 5, we find this schematic and data of one person’s three steak + carnitine challenges:



The legend says this is data for “a representative omnivorous subject” (they do not specify the person’s gender). Prior to antibiotic treatment, shown on the left, the TMAO remained flat over 24 hours after consuming a steak and carnitine supplement. We only see an increase after this omnivore was given antibiotics and his or her intestinal flora grew back over a week, shown on the right, and in that case it didn’t even double after the steak, let alone triple as in Figure 2a. Did this subject develop dysbiosis from the course of antibiotics, and is that why TMAO increased after antibiotics but not before antibiotics?

If, prior to antibiotics, this person’s TMAO remained flat after consuming steak + carnitine, while the TMAO of the omnivore shown in Figure 2a nearly tripled, how can they both be “representative”? Is the data in Supplementary Figure 5 from a male, and does this represent a fundamental difference between males and females? Is the data shown in Figure 2a “representative” of a female omnivore before or after she was given antibiotics? If the latter, does the increase simply represent the effects of antibiotic-induced dysbiosis?

As mentioned above and as can be seen in the top of Supplementary Figure 5, moreover, the subjects did not simply consume steak. Along with the steak, the authors fed carnitine labeled with a heavy isotope (d3), which is like a chemical tag that allowed the investigators to trace its metabolism. If they observed labeled TMAO in the blood, this would show that the carnitine was converted to TMAO. Indeed, they showed this in a single “representative female omnivorous subject” in

Figure 1e. But the amount of labeled TMAO in the blood would be tiny compared to the total amount of TMAO. If we are evaluating the plausibility of the hypothesis that TMAO in the blood contributes to heart disease, we care about the total amount of TMAO. The question, then, is whether eating steak leads to a ***meaningful increase in total TMAO.*** Here is what the authors had to say:

> In most subjects examined, despite clear increases in plasma d3-carnitine and d3-TMAO concentrations over time (Fig. 1e), post-prandial changes in endogenous (unlabeled) carnitine and TMAO concentrations were modest (Supplementary Fig. 5), consistent with total body pools of carnitine and TMAO that are relatively very large in relation to the amounts of carnitine ingested and TMAO produced from the carnitine challenge.

It is unclear what "modest" means in this context. Nowhere appear any data for the entire group of omnivores. We just have a "represenatative" graph in Supplementary Figure 5 where the TMAO increase is non-existent, not "modest," prior to antibiotics, and another "representative" graph in Figure 2a where the result is very different. Since both relevant graphs have a sample size of one, there is no statistical analysis. The authors seem to be saying in the above paragraph, however, that, on the whole, the non-existent increase in total TMAO shown in Supplementary Figure 5 is more representative than the large increase shown in Figure 2a.

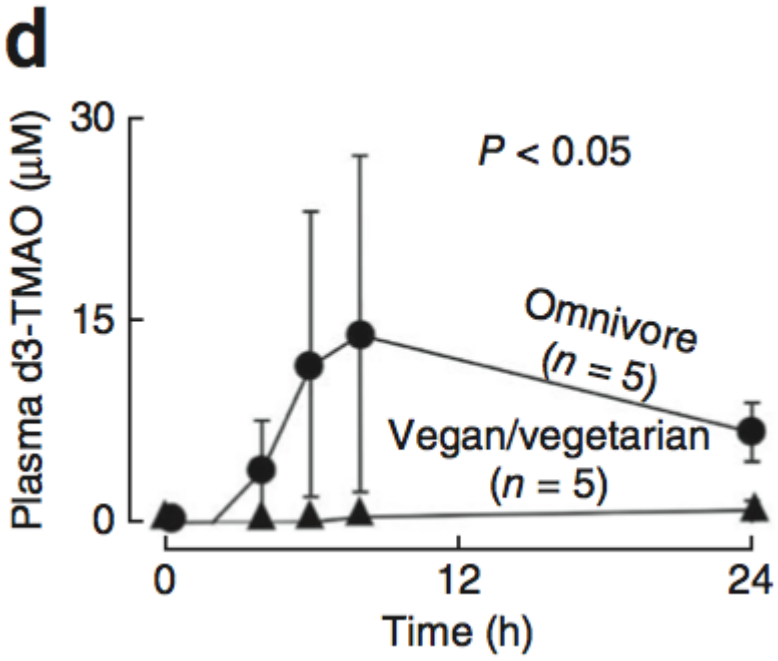
If the labeled TMAO increased after the steak + carnitine challenge but the total pool of TMAO did not, this indicates that carnitine was converted into TMAO, but that the TMAO generated from the carnitine was so small compared to the amount of TMAO already present in the body as to be largely irrelevant.

Finally, we should note that the steak + carnitine challenge provided 180 milligrams of carnitine from meat and 250 milligrams of isotopically labeled carnitine from a supplement. There is no data in this paper showing that TMAO increases in response to steak alone in anyone.

Does Carnitine Increase TMAO More in Meat-Eaters Than in Vegans and Vegetarians?

After these investigators gave five meat-eaters antibiotics to show that suppressing intestinal flora would suppress TMAO, they gave five vegetarians and vegans and five omnivores a labeled carnitine supplement without any steak. It is unclear whether these omnivores are the same omnivores who previously underwent three steak + carnitine challenges, involving the use of antibiotics. In one section of the methods, the omnivores who received antibiotics are described as "additional omnivores," but in another section they seem to be described as a "subset of subjects" who participated in the carnitine alone challenge. If they are the same omnivores, then this experiment is seriously confounded since the investigators never gave any vegetarians antibiotics. In any case, here we encounter a graph that actually includes all ten subjects instead of a "representative" subject from each group:

The most



impressive thing about this graph that should jump out at us is that the standard error bars for the omnivores cover almost the entire vertical axis of the graph. If you are unfamiliar with statistics and wish to get a sense of how dramatic this degree of variation is, one way would be to scroll up to the data I showed for the 1999 study measuring TMAO generation from 46 different foods, where the bars represent the same measure of variation. The variation in that study was quite large for many foods, but not like this. For all we know, the variation could be driven by a single outlier, meaning perhaps only one omnivore's labeled TMAO increased and that of the others remained flat. Or, perhaps it represents a large difference between the male and female subjects. With this level of variation, it seems unlikely that there was a statistically significant increase in TMAO among the omnivores at any specific time point, and the authors give no indication that this was so. When they compared the area under each curve, however, the difference was statistically significant.

While this *may* indicate that meat-eaters as a group generate more TMAO from supplemental carnitine than vegetarians, it is somewhat unclear whether this experiment was confounded by antibiotic treatment, and the authors do not explain whether the result is driven by a single outlier or a fundamental gender difference, neither do they show any results indicating that the *total* amount of TMAO in the blood (instead of just isotopically labeled TMAO) increased.

Do Omnivores Have Higher TMAO Than Vegetarians and Vegans Because of Meat-Induced Changes in Intestinal Bacteria?

Among 23 vegans and vegetarians and 30 omnivores, the authors reported differences in intestinal bacteria that they tied to blood levels of TMAO in the absence of a steak or carnitine challenge. The most dramatic difference seen was a roughly three-fold greater level of TMAO in the blood of four subjects with "enterotype 2," with bacterial DNA from *Prevotella* species dominating their feces, when compared to 49 subjects with "enterotype 1," with bacterial DNA from *Bacteroides* species dominating their feces. As the authors note in the discussion, enterotype 2 had previously been associated with "low animal-fat and protein

consumption," but three out of four subjects with this enterotype in the current study were omnivores.

Although the largest difference was seen between those with enterotypes 1 and 2, TMAO levels were nevertheless 45 percent higher among the meat-eaters than among the vegans and vegetarians. There were also significant differences in specific strains of intestinal bacteria between the dietary groups that could hypothetically account for this difference.

While it is possible that intestinal flora accounts for the difference, it is disappointing that the authors did not consider other possibilities, such as differences in the activity of the enzyme that converts trimethylamine to TMAO. For example, vitamin B2 is the main cofactor for the enzyme, and vegans are three times as likely to be deficient in vitamin B2 as vegetarians and omnivores.

To support their hypothesis that the difference in intestinal bacterial metabolism of carnitine can be induced by meat consumption, the investigators fed mice 1.3 percent carnitine in drinking water and showed that this altered intestinal flora and led to a ten-fold increase in the TMAO yield in response to a force-fed carnitine challenge. Before we take this as supporting evidence that people who eat meat have higher TMAO than vegans and vegetarians because of meat-induced changes in intestinal flora, we should consider a couple of caveats.

Suppose each mouse drinks about 5 milliliters of water per day. This would provide 65 milligrams of carnitine per day, more than a third of what could be obtained from eating an eight-ounce steak. Adjusting for body weight, this is like a human eating a thousand steaks per day. This is beyond the capacity of even the most die-hard meat-lovers.

Moreover, the bacterial species that showed up in greater concentrations in carnitine-fed mice and correlated with TMAO levels had no correspondence to those found in meat-eating humans. The authors put it this way:

> Notably, a direct comparison of taxa associated with plasma TMAO concentrations in humans versus in mice failed to identify common taxa. These results are consistent with prior reports that microbes identified from the distal gut of the mouse represent genera that are typically not detected in humans.

For both of these reasons, the carnitine-fed mice provide little in the way of justification for viewing the differences in intestinal flora between vegetarians and omnivores as a result of consumption or abstention from meat.

While antibiotics wipe out TMAO levels in humans and mice, showing that intestinal bacteria are necessary for its formation, the authors provide no clear evidence that the specific differences in intestinal bacteria between vegetarians and vegans on the one hand and meat-eaters on the other cause the observed difference in TMAO levels.

It is unclear whether the 45 percent higher TMAO levels in meat-eaters represents something that we should regard as "unhealthy." As I pointed out above, for all we know it could be due to riboflavin (vitamin B2) deficiency among the vegans. If we

suppose for the sake of argument, however, that it does represent something unhealthy, there is no reason to connect it to the consumption of meat. As Chris Kresser pointed out in his critique of the *Nature Medicine* paper, most comparisons between vegetarians and omnivores are confounded by substantial lifestyle differences between these two groups. They are also confounded by dietary differences that have nothing to do with meat, such as the consumption of fruits and vegetables. While the possibility that long-term meat-eating itself increases TMAO levels remains a legitimate hypothesis to be investigated, equal investigation should be given to alternative hypotheses focusing on other dietary and lifestyle factors that differ between vegetarians and omnivores.

Does TMAO Cause Heart Disease?

Female C56BL/6J mice genetically engineered to be missing *ApoE*, an important protein involved in lipoprotein metabolism, developed twice as much atherosclerosis when fed a thousand steaks a day worth of carnitine. This and supplementary studies feeding mice TMAO suggested that TMAO derived from dietary carnitine may suppress the removal of cholesterol from the immune cells that populate atherosclerotic plaques. As proof of principle, these studies may have some value, but their relevance is questionable. Such an exorbitant amount of carnitine is surely irrelevant to human meat intake. The mice, moreover, are among the most vulnerable. They presumably used females because males convert trimethylamine to TMAO at a lower rate. *ApoE* knockout mice not only lack a critical protein that humans have, but the C56BL/6J background strain of mice, as I've written about before, has a deletion in a gene related to B vitamin and glutathione metabolism that prevents the mice from recycling glutathione in the presence of oxidative stress.

Can such a result be observed in male mice, in mice without these genetic defects, and in mice fed attainable quantities of carnitine? Without knowing the answers even to these preliminary questions, it seems unreasonable to consider these experiments relevant to human health at this stage of the game.

The authors also investigated the relationship between plasma carnitine levels and heart disease in just under 2600 humans undergoing elective cardiac evaluation. Males had higher carnitine levels than females. In the lowest quartile of carnitine status, only 54 percent of subjects were male. In the highest quartile, 80 percent were male. Those who had the highest carnitine levels were more likely to smoke (77 percent) than those who had the lowest (61 percent). The majority of the subjects were on ACE inhibitors, beta-blockers, statins, and aspirin. Those with higher carnitine levels had a greater likelihood of having cardiovascular disease, peripheral artery disease, and cardiovascular disease. Statistical adjustment for traditional cardiovascular risk factors attenuated the associations. We can imagine that if it were possible to identify all of the confounding factors, further statistical adjustment would further reduce and perhaps eliminate the association.

The authors provide no evidence that the variation of plasma carnitine in these subjects primarily reflects variations in dietary carnitine intake, and there is no particular reason to assume this. To offer one counter-example, in guinea pigs, one of the few experimental animals that have a dietary vitamin C requirement like humans do, vitamin C deficiency leads to a loss of carnitine from muscle and

an increase in plasma carnitine. Vitamin C probably protects against heart disease by preventing lipoprotein oxidation in the blood and by promoting collagen synthesis in arterial plaques, which protects them from rupture. Perhaps plasma carnitine is an inverse marker of vitamin C status.

In a separate analysis, blood levels of carnitine appeared to associate with cardiovascular events only in the presence of high blood levels of TMAO. This is consistent with the authors' hypothesis that carnitine contributes to cardiovascular disease through its conversion to TMAO, but it could be consistent with a number of other hypotheses as well. Perhaps blood levels of TMAO reflect intestinal dysbiosis, variations in the activity of the enzyme that converts trimethylamine to TMAO (as I wrote in my last post on this topic, activity of the enzyme could reflect drug exposure, genetically determined drug efficacy, iron overload, ethnicity, or other factors), or perhaps TMAO increases in heart disease to play important physiological roles such as protein stabilization.

This study provides a foundation for future studies to investigate whether TMAO can be used as an independent predictor of heart disease risk and whether TMAO and carnitine status can be used as markers of clinically relevant metabolic changes, but it hardly provides us with a basis for believing that carnitine from fewer than a thousand steaks per day causes heart disease through its conversion to TMAO.

The Bottom Line

The bottom line here is that the popular interpretation of this study as an indictment of red meat makes no sense. Even if physiological levels of TMAO contribute to heart disease in humans (which is a big "if" at this point) and even if red meat were to raise TMAO substantially more than most other foods (which appears to be false), it wouldn't in any way whatsoever follow that eating red meat causes heart disease. The biological effects of a food cannot possibly be reduced to ***one*** of the biological effects of ***one*** of the food's components. Believing such a thing would require believing not only that the particular component has no other relevant biological effects, but that there are no relevant biological effects of any of the other tens of thousands of components of that food.

As Chris Kresser pointed out today, the balance of epidemiological evidence fails to show an association between fresh, unprocessed red meat and heart disease. Numerous studies, including randomized trials, have suggested that carnitine supplementation improves outcomes in patients with cardiovascular disease. Carnitine thus may be a generally heart-protective nutrient. The authors acknowledge these studies in their discussion but suggest that carnitine may have conflicting effects, especially when used orally rather than intravenously as in some studies, since the oral route allows exposure to intestinal bacteria.

If the carnitine in red meat were promoting atherosclerosis through its conversion to TMAO, however, then red meat should be no more dangerous than potatoes and carrots and the real killer should be seafood. How likely is this to be true? Prospective studies correlate fish consumption with a reduced risk of heart disease mortality. Some Pacific Island groups that eat seafood regularly, such as the Kitavans, appear to be free of heart disease. Randomized trials have tended to

focus on fish oils rather than whole fish. Those testing advice to eat more fish are ambivalent, but they don't seem to suggest that eating whole fish increases the risk of heart disease.

The elucidation of nutritional pathways and biochemistry in this paper is interesting, but it shouldn't serve as a reason to avoid red meat.

Read more about the author, Chris Masterjohn, here.

Acknowledgments

Thanks to Chris Kresser, Stephan Guyenet, Ned Kock, and Peter Attia for discussing some of the points made in this post.

Notes

* Of course it would be better if we could see these foods and the control breakfast compared to a control of pure water or something that should be similarly ineffective at generating TMAO. A certain proportion of the TMAO excreted in the urine could perhaps be due to endogenous trimethylamine precursors circulated through the gastrointestinal tract. Nevertheless, this should be similar across foods. Additionally, the authors did not specify the mix of foods in the "light breakfast." Thus, it is unclear how much TMAO for each item comes from the light breakfast and how much from the food being tested. The only certain thing is that those foods yielding statistically greater TMAO excretion generated more TMAO than the control and the other foods tested.

** One-way ANOVA using Dunnet's post-test to compare all values to beef and adjust for multiple comparisons, using Graphpad Prism 5.

*** Did these subjects generate substantially less TMAO from red meat than the subjects in the new *Nature Medicine* paper? It would seem not. The *Nature Medicine* paper reports urinary TMAO excretion in different units, and it reports TMAO alone rather than the sum of it and its precursor, trimethylamine. Nevertheless, according to my calculations, the "representative female omnivore" excreted a little under 212 micromoles/8 hours, whereas the average excretion after eight ounces of beef in the 1999 study was 76.5 micromoles/8 hours, indicating perhaps slightly higher but more or less similar generation of TMAO after red meat between the studies, especially considering the variation in responses in the 1999 study (SD 48.5) and compared to seafood. The modestly larger amount reported in the *Nature Medicine* could easily be explained by the extra 250 milligrams of supplemental carnitine provided, and perhaps by the use of TMA + TMAO rather than TMAO alone.

Assuming the average person clears about 1 mg creatinine into their urine per minute (480 mg/min) and 113.12 g/mol creatinine (thus 480 mg/1000 mg/g and divided by the molar mass, multipled by 1000 to convert mol to mmol, yielding an average excretion of 4.24 mmol creatinine in 8 hours), I calculate that just under 50 mmol TMAO/mol creatinine, as shown in Fig 2b of the *Nature Medicine* paper converts to 212 umol/8 h (50 mmol TMAO/mol creatinine * 1 mol creatinine/1000 mmol creatinine *4.24 mmol creatinine/8 hours * 1000 umol/TMAO/mol TMAO).

Christopher Masterjohn

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80 Responses to *Does Carnitine From Red Meat Contribute to Heart Disease Through Intestinal Bacterial Metabolism to TMAO?*

Frank Foster alias beefeater says:
April 10, 2013 at 7:30 pm

A great rebuttal of the danger of partial truths being used to create controversy and fear by anti red meat factions.
The evidence, when considered as a whole, is irrefutable that red meat, today represented by grass/greens fattened beef is extremely healthy. Not only is it the modern equivalent of wild ruminant big game our ancestors consumed throughout our evolution, but if eaten daily, suitably fattened, gives long healthy life. It is a functional food with Omega 3's in balance and equal to cod fish, plus the added advantage of other essential nutrients such as CLA and fat soluble vitamins A,D,E, and K. Science indicates we developed our brains from eating it long before learning to fish.
To deny its goodness is to deny all history, now increasingly supported by balanced scientific enquiry.

Reply

Angie says:
April 11, 2013 at 7:04 pm

Totally agree! Grassfed beef is the only way to go.

Reply

David I says:
April 26, 2013 at 1:38 pm

"Science indicates we developed our brains from eating it long before learning to fish."

Highly debatable. Some authorities suspect the distant ancestors of humans may have been littoral dwellers, along the edge of the sea or lakes. In this case, although they may not have "fished" in the sense that Hemingway did, their animal protein and fat intake may have been from shellfish and crustaceans–and possibly grubs and insects as well.

In any case, we don't know enough to make blanket statements. All we really know is that our distant ancestors were extremely versatile omnivores, and that it is silly to condemn any of the foods they were likely to have eaten.

Reply

vaclav nikdo says:
May 18, 2013 at 3:07 pm

We are always comparing ourselves to our ancestors of the remote past in terms of the diet we should follow. This is good but it only can be taken so far. We are trying to find a diet that helps us maintain a healthly life into our 80's and beyond. These ancestors didn't live much past 30. Before 30 most of us can eat all kinds of junk and feel fit. I think looking at how our biochemistry developed around food sources is great, but evolution doesn't care if we develop deseases in our later years, we have already passed our genes on, they are real focus of biological evolution. What we are looking for, in my opinion, is a diet that takes us beyond what biological evolution has created. Some focus on early diets is educational but it has limits in directing us toward a goal for which is there is little precident in nature, to go beyond our evelolutionary blueprint.

Reply

Chris Masterjohn says:
May 18, 2013 at 11:16 pm

Sorry I initially read your comment in a different interface and thought you were replying to the article rather than the above

comment, so I left a comment that didn't make much sense, which I'm deleting now.

Chris

Reply

Polo says:
June 12, 2013 at 7:29 am

I'm not sure that there is no evolutionary advantage to old people being around. They carry knowledge and techniques which they transfer, they have experience, and they are more prudent, keeping people social and civilized, and crime lower:) Communities with old people possibly allowed younger people to eat better, stay healthier, and reach reproduction age.

Reply

Heather says:
June 25, 2013 at 12:09 pm

No they didn't live until 30 and then drop dead. It's an average age. You are comparing the hostility of two environments. In 1900 the average lifespan was 40. Infant mortality dropped and the average lifespan increased.

Reply

George @ the High Fat Hep C Diet says:
April 10, 2013 at 8:19 pm

Excellent post Chris. Especially the points about gender and TMA>TMAO. The idea of looking for toxic bacterial metabolites (or at least eliminating them as causes of disease) is a good one (shades of Elie Metcnikoff) but someone appears to have hijacked this study and ridden off to Crazytown.

"An analyte with identical molecular weight and retention time to
l-carnitine was not in the top tier of analytes that met the stringent

P value cutoff for association with CVD. However, a hypothesis-driven
examination of the data using less stringent criteria (no adjustment for
multiple testing) revealed an analyte with the appropriate molecular
weight and retention time for l-carnitine that was associated with cardiovascular event risk (P = 0.04)."

A vegan ate a steak? No wonder this story was big news. I hope he's OK.

Reply

Robert Klosa says:
April 10, 2013 at 8:38 pm

Reading your commentary after the original paper felt like the reveal at the end of a mystery novel . Somehow all the clues where there but darned if I could see them… Thanks for connecting the dots.

Reply

Steven says:
April 10, 2013 at 9:27 pm

Excellent analysis Chris. The real question is of course: 'will supplemental carnitine increase CVD?'. Without an RCT its unknown but seeing as there are many studies which find benefits of carnitine after a CV event, it's unlikely that carnitine promotes carnitine.

There are other instances of carnitine being therapeutic. The combination of carnitine and alpha-lipoic acid increases mitochondrial biogenesis and reduces the symptoms of neurodegenerative diseases.

Seeing as mitochondrial function is probably an important part of CVD, and carnitine improves outcomes following CV events and increases mitochondrial biogenesis (with ALA), my hypothesis would be that carnitine is therapeutic for CVD.

Reply

Rob says:
April 11, 2013 at 12:37 am

Thanks for all of the time you put in to these articles, Chris.

Reply

Dimezzano says:
April 11, 2013 at 4:46 am

what about “The China Study ?”

Reply

Frank Foster alias beefeater says:
April 11, 2013 at 3:49 pm

China study keeps coming up amongst our converted vegan now beef eating customers who, convert for health challenge reasons. I even wasted time checking it out this red herring only to discover the same quantum leaps of interpretation as in the Cleveland study.
Please Google rebuttals to it and dig down into, what becomes biased interpretation of partial truths. I thought all with open minds now give it the negligible weight it deserves.

Reply

Leaf Eating Carnivore says:
April 11, 2013 at 4:04 pm

Go read Denise Minger’s excellent dissections of this really stinky dead mouse.

The studies were generally so bad that (even before I found her analyses) I ripped up the book and threw it away – a lifetime first for me.

And I’m not even a biochemist.

Reply

Tim says:
April 11, 2013 at 6:13 am

Thank you very much Chris, for this supreme work of deconstructive diligence. It really has a sobering effect on ones to give any bias to a study depending on the journal it is pulished in…

I have just one question left unanswered: if and I repeat, if LMAO would have any effect on atherosclerosis in wild-type

humans :D, there would be much more reason to be concerned about carnitine and coline salt supplements than about red meat (excluding fish which I consider absolved by epidemiologcal evidence).

As I have no access to the 1999 study, could you give the excretion levels for the supplements administered in that study too? I would like to see how they compare to the foods you have shown in the diagrams.

Reply

Chris Masterjohn says:
April 11, 2013 at 10:41 am

Hi Tim,

It's tough to say because the methodology and reporting was somewhat different in the 1999 study between the supplements and the foods. There were three trials per person with 24-h urine collection for the supplements and one trial per person with 8-h urine collection for the foods. They reported that ~30% of a 15 mmol supplement was converted to TMA+TMAO over 24 h. If excretion in urine is constant over 24 h, this yields 1500 umol/8 h, which is comparable to some of the lighter seafoods. However, the dose is very large (~2.4 g, about 13 servings of steak).

Chris

Reply

Tim says:
April 12, 2013 at 4:55 am

Hi Chris,

thanks for giving those numbers. It's interesting that even such a large dose of pure carnitine doesn't seem to cause more LMAO excretion than fish does.

I guess the only possible loophole for the authors' hypothesis that elevated TMAO promotes atherosclerosis could be found in the time domain – if dietary LMAO would be rapidly excreted in contrast to

endogenously produced LMAO from carnitine or choline. Thus the gut bacteria would create some “slow-release” TMA over a long period of time, resulting in chronically elevated TMAO levels, while oraly ingested TMA(O) would cause only a rapid spike in blood levels. I don’t know if this loophole-hypothesis makes any sense though.

Reply

Tim says:
April 12, 2013 at 5:07 am

PS. Some short in my orthographic neurons apparently caused me to write TMA(O) instead of LMA(o)

Reply

Chris Masterjohn says:
April 12, 2013 at 9:41 am

The 1999 paper I cited “assumed” that 50% of TMAO is metabolized by gut bacteria to TMA and reoxidized to TMAO in the liver, so probably in both cases TMA is being generated. They didn’t have quantitative data on that though. Anyway, it seems pretty implausible to me that the TMAO is going to have a different half-life in the plasma depending on where it comes from. If it does, that does not salvage their hypothesis. It’s a different one. Thanks for your comments!

Chris

Reply

Tom says:
April 11, 2013 at 9:33 am

Well done – a well-written and considered article. My only

quibble with it, and your previous, related one on choline, is your comment that seafood "…is generally contaminated with some trimethylamine….". In fact, fresh saltwater fish do not contain much, if any, TMA. However, they do contain large amounts of TMAO that they use as an organic osmolyte. In caught fish this is rapidly reduced by bugs to TMA – hence the need to keep fish chilled. When fresh fish is eaten the TMAO can be reduced back to TMA by some classes of gut microbes that use TMAO as a terminal electron acceptor in anerobic respiration.

Also, I'm not sure that the male-female difference in TMA-(FMO3)->TMAO is observed in other species other than mice (probably making the mouse a poor model for these experiments). Male mice lack FMO3 in the liver as they excrete TMA as a 'chemosignal' (see PMID:23177478). Rats don't show this sexual dimorphism.

Reply

Chris Masterjohn says:
April 11, 2013 at 10:51 am

Hi Tom,

Thanks for the clarification. Could you provide a reference for that? I'll edit my post accordingly.

Hazen co-authored a paper I linked to that found that mRNA expression of hepatic FMO3 is reduced in males. It doesn't look like they confirmed it with protein expression or activity, but it seems consistent with their more extensive mouse data.

Chris

Reply

Tim says:
April 12, 2013 at 4:39 am

The muscle of marine fish contains between 0.1 and 1% TMAO, depending on the species and on the depth of its habitat. As Tom said, old fish smells like old fish because the TMAO degrades to TMA. This doctor thesis covers the subject in great detail (beware – hughe PDF!)

Reply

Chris Masterjohn says:
April 12, 2013 at 9:41 am

Thanks!

Reply

Tom says:
April 12, 2013 at 11:22 am

Paul Yancey knows all there is to know about marine organisms and 'osmolytes'. See his references here…

http://people.whitman.edu/~yancey/

I also think this an interesting paper with respect to TMA/TAMO.

http://www.sciencedirect.com/science/article/

Reply

Jeff says:
April 11, 2013 at 11:48 am

i had scribbled a post last night – tracking on some of the same things you highlight – although i'm more focused on the microbial issues. will post 2day. had a quickQ: on the 1.3% carnitine supplement in the mice, you mentioned that it was administered in water. i had been looked throughtout the article and supplement info to try and estimate dosage as well – but could not find a reference to water – only that the chow was spiked. thanks, jeff

Reply

Chris Masterjohn says:
April 11, 2013 at 12:03 pm

Hi Jeff,

It's after the references in the main pdf (confusing and hard to find, I know).

Chris

Reply

Jeff says:
April 11, 2013 at 12:11 pm

ah. muchas gracias!

Reply

Jeff says:
April 11, 2013 at 12:14 pm

i guess i'm still wondering, is the 1.3% 'of the water' or 'of the diet'?

Reply

Chris Masterjohn says:
April 11, 2013 at 1:56 pm

Of the water. It says it in the methods.

Reply

Kenny says:
April 11, 2013 at 4:09 pm

Chris, can you tell us the magnitude of the supposed increased risk of CVD, PAD, and CAD?

I looked Figure 4's Forest plots of odds ratios and couldn't understand it.

Can the increased relative or absolute risk be quantified?

Reply

Chris Masterjohn says:
April 11, 2013 at 4:54 pm

An odds ratio of 2 means twice as likely. An odds ratio of 1 means no difference in likelihood. If the error bars cross the vertical dotted line extending from one, it means the difference is not statistically significant.

Chris

Reply

Richard David Feinman says:
April 11, 2013 at 5:23 pm

Thanks for this great review. I would normally dismiss this out of hand, especially given it's informercial title, but, as you say, "parts of this study are very well conducted, providing insights into metabolism that should fascinate anyone who loves biochemistry" although I never thought of it as "meandering down rabbit holes." Well, maybe that means Wonderland. You saved us all a lot of time.

One thing on the figure labeled d is that the errors are worse than you say. It might be worth pointing out that all the figures in the paper, like so many in the literature report SEM (standard error of the mean) which, for readers who are not familiar is a way to determine statistical significance but can drastically visually obscure the real spread in the data. Much better (I think should always be used) is the standard deviation, SD. To convert the SEM to SD you multiply by the square root of n which in this case is about 2.2 so the terrible spread in error in the figure is even worse.

In the end, there's something sad about all this. This was a lot of work and well designed with some sound logic but by trying to make the point about heart disease they gave it a phenomenological character along the lines of somebody's description of high-school science fair projects: "I poured salt on it and it died. "

Reply

Chris Masterjohn says:
April 11, 2013 at 5:35 pm

Hi Dr. Feinman,

I see your point that standard error bars make the variation look smaller than would standard deviation bars, but I don't agree that SD should always be used. In my opinion, SEM was appropriate here because the purpose was not to provide general descriptor of a set of data but rather to provide the basis for comparing one group to another. SEM is the measure of statistical precision used for that purpose. So, in my opinion, SD should be used when the purpose is simply to describe the spread of the data and SEM should be used when the purpose is to compare one group to another. It's a way of tying the graphical depiction to the intended statistical test and the P value reported.

I definitely agree that this good work ruined by the agenda promoted.

Chris

Reply

Richard David Feinman says:
April 11, 2013 at 10:59 pm

SEM is correct for demonstrating that the groups are statistically different and that should be done. The purpose of a figure is to transmit information to the reader and SEM obscures that.

But really, what's wrong with showing the data points? Any statistical measure reduces information. If you check out Basu (Lustig's paper in PlosOne), he shows all the data points. In the comments with link to annotated figure, I point out that this allows you to see how much variability there is and how inappropriate the conclusion is. That may be why people resort to group statistics.

Reply

Sean P. says:
April 11, 2013 at 5:46 pm

Out of curiosity, why did you choose to use a linear dose conversion when adjusting for body weight between mice and humans when trying to determine the human equivalent dose of carnitine used in this study? Shouldn't you use an allometric scaling conversion? So the mouse dose would be 3,250mg/kg carnitine (assuming 20g mice and 65mg carnitine dose) which would only be 263.5mg/kg in humans (HED = 3,250(mg/kg) x 3 (mouse Km) / 37 (human Km)). For a 70kg adult human that would be 18,446mg of carnitine per day or 80 half-pound steaks per day (at 454mg carnitine per pound of steak) instead of a "thousand steaks per day."

Still, the caritine dose is ridiculously high and no human can even come remotely close to consuming anywhere near this much, but i think the distinction/correction is still important (80 vs 1000 is a pretty big difference).

Reply

Chris Masterjohn says:
April 11, 2013 at 8:43 pm

Hi Sean,

I chose it mainly because it was simple. I don't think it's really "correct," but I don't think it's possible to make a "correct" conversion without understanding the mechanism better and quantifying the relevant variables in humans compared to mice. There are a lot of ways to make the correction. Another could be calorically. The ideal would be based on the pharmakokinetics of the relevant metabolites, but we don't have that information in enough detail to my knowledge.

In any case, I'm familiar with the concept of allometry, but I don't understand your calculation at all. Where do the 3 and 37 come from? What is being measured in kilometers?

Chris

Reply

Chris Masterjohn says:
April 11, 2013 at 8:57 pm

I ran the calculation through this calculator with a recommended mouse-to-human exponent of 0.8, and I got a little over 40 steaks:

http://home.fuse.net/clymer/minor/allometry.html

But I still don't understand the principle here. It makes no sense to me that the pharmacokinetics of all compounds could possibly have the same ratio between humans and mice, or could possibly be directly and primarily related to some anatomical factor. Particularly in this case, where the active component is supposed to be an enzymatic metabolite of a microbial metabolite.

Chris

Reply

Sean P. says:
April 11, 2013 at 10:13 pm

Km in this case refers to the conversion factor for converting mg/kg dose to mg/m^2 dose. Km is equal to the body weight of the species divided by its body surface area. In this case, mice have a BW of .02kg with a BSA of .0066m^2 which gives a Km value of 3; humans have a BW of 60kg and a BSA of 1.6m^2 which gives a Km value of 37. You then divide the 3 (mouse Km) by 37 (human Km) to get the appropriate conversion ratio, which is 1/12 or roughly .08. Using allometric scaling is typically more accurate than using isometric scaling since BSA correlates well across several mammalian species with several parameters of biology, including oxygen utilization, caloric expenditure, basal metabolism, blood volume, circulating plasma proteins, and renal function. See "Dose translation from animal to human studies revisited": http://www.ncbi.nlm.nih.gov/pubmed/17942 and "Animal Models in Toxicology" page 839-849 http://books.google.com/books?id=Rno1rYxR264C&lpg=PA844&pg=PA839#v=

It's obviously not "perfect" but this method of scaling is a good starting point without having additional data points.

Either way, 60 steaks or 1000, no one is ever going to get close to consuming this much carnitine.

Reply

Chris Masterjohn says:
April 11, 2013 at 10:26 pm

Thanks Sean. I'll put an edit in the article linking to your comment. Since neither are going to be perfect (and I'm really not confident in one or the other), I'll

reference both. For what it's worth, based on my data in rats, it seems like isometric scaling is more appropriate to compare the dose of vitamin D and its effect on 25(OH)D levels.

Chris

Reply

Nathan McCorkle says:
April 11, 2013 at 7:17 pm

Thanks for the great teardown and background. My one criticism/opinion is that your 'clean' version was a bit long-winded and watered down. I read most of the article afterwards because the 'clean' version wasn't convincing. I was convinced by the end, so I guess I'm just saying you can improve your writing style a bit. More facts, less opinion in the 'abstract' section would have allowed me to skim to the interesting details faster, etc.

Thanks again!

Reply

Chris Masterjohn says:
April 11, 2013 at 8:46 pm

Hi Nathan,

Thank you for your comment. I don't really understand it though. What was watered down about the "clean" version? What details should I have left out? You read my article or the Nature Medicine paper? You were convinced by what? My post or the Nature Medicine paper? I don't know what you mean by "opinion in the 'abstract' section."

Thanks,
Chris

Reply

Nathan McCorkle says:
April 24, 2013 at 3:25 pm

Hi Chris, I guess generally I just felt the

section before ‘Why Single Out Red Meat’ (the intro section) could have acted more like a journal article abstract. Facts I found quite important were not in that section, these are the facts I found most impressive/telling of the ‘research feel’ of the paper. Things like ‘To take the most extreme example, halibut generated over 107 times as much TMAO as red meat.’ and ‘Adjusting for body weight, this is like a human eating a thousand steaks per day. This is beyond the capacity of even the most die-hard meat-lovers.’

This one is quite informative too:
“While it is possible that intestinal flora accounts for the difference, it is disappointing that the authors did not consider other possibilities, such as differences in the activity of the enzyme that converts trimethylamine to TMAO. For example, vitamin B2 is the main cofactor for the enzyme, and vegans are three times as likely to be deficient in vitamin B2 as vegetarians and omnivores.”

These are the points I’ve been mentioning to people when they mention the Nature article.

Reply

Andy says:
April 12, 2013 at 12:59 pm

Another great post along with Mr. Kresser’s.

It would be wonderful if mainstream media would widely publish a review of this study along the lines of what you have done. Sadly though, since your review is not have a “black and white” outcome, it is not interesting or simple enough to generate interest in the general public. Not to mention it doesn’t demonize red meat, and what else is our society good at if it is not inaccurately chasing any and all reasons to prove that red meat is bad for us.

Love the posts!

Reply

John William Camery says:
April 12, 2013 at 7:19 pm

Studies show that humans that consume certain types of fish do not get heart disease, while humans that consume red meat do. No amount of testing on animals or humans can change that observation. Perhaps there are some synergistic effects involved, but that does not change the bottom line. Eat like people who die a particular way and if you live long enough you will die from that cause, too.

Reply

Chris Masterjohn says:
April 12, 2013 at 11:10 pm

Hi John,

Thank you for your comment, but I don't think you understand how science works, and I don't think you're familiar with the present observations either. There are no studies showing that people who eat certain types of fish don't get heart disease. Of course there are studies showing that people who get red meat die of heart disease. That is because people who eat anything often die of heart disease. You seem to be confusing statistical correlations with absolutes. There are studies that, on the balance, show that people who eat fish are less likely to die of heart disease than people who don't (or who have a negligible intake), but that is very different from showing that anyone who eats fish does not get heart disease. Regardless, it's a basic rule of science that correlation doesn't show causation. It's just a false statement that because "people who do x are more likely to die of y, you should not do x or else you will die of y." Shoe size strongly correlates with reading skill, especially among children, but you're not going to read better by buying bigger shoes, for example.

Chris

Reply

Fred Hahn says:

April 13, 2013 at 11:08 am

Chris this link is not working:

http://www.westonaprice.org/www.ncbi.nlm.nih.gov/pubmed/1(

Nice job BTW.

Reply

Chris Masterjohn says:
April 13, 2013 at 2:35 pm

I fixed it. Thanks Fred!

Chris

Reply

Sean P. says:
April 13, 2013 at 10:21 pm

Have you seen the recently published study, "Supplementation with High Doses of Vitamin D to Subjects without Vitamin D Deficiency May Have Negative Effects: Pooled Data from Four Intervention Trials in Tromsø," yet? If you don't have any future subject material lined up already, I'd be very interested in reading your thoughts/analysis of this study's findings.

Reply

tomas says:
April 15, 2013 at 10:32 am

Hi Chris,

don't you know when exactly was the time interval between the last shot of antibiotics and the post-ATB challenge?

Because we know that ATBs suppress bile salts, we could speculate that this might have influenced conversion of TMA to TMAO – FMO3 seems to be dependent on the status of bile salts.

Reply

Brendan Coburn says:
April 15, 2013 at 4:15 pm

Chris,

I am not an expert on the biochemistry of all of this, so your input would be much appreciated. Regarding the study you cite showing that fish increases urinary TMAO… what about serum TMAO? Isn't that more relevant as far as the carnitine study? I'm not sure of the relationship between serum and urine TMAO, but knowing that beef doesn't increase excretion of TMAO doesn't seem to prove anything. What about TMAO in the serum?

Reply

Chris Masterjohn says:
April 16, 2013 at 3:47 pm

Hi Brendan,

So far no one has shown that beef or any other food increases total TMAO in the blood. For whole foods, we only have urinary excretion. The TMAO has to enter the blood to exit into the urine, so we know any food that raised urinary TMAO increased the flux of TMAO through the blood, but we don't know that entered the blood quickly enough and exited it slowly enough that had venous blood draws been taken, the increase in total TMAO would have been of sufficient magnitude to be of statistical significance or potential clinical relevance. Based on the data of Zhang et al., it would appear that fish and shellfish but not the other foods are the foods we could expect to be candidates for raising plasma TMAO. With respect to the hypothesis of the Hazen group, they do not postulate that beef raises TMAO by inhibiting its excretion into the urine. Their hypothesis is all about generation. So with respect to their hypothesis, in evaluating the objectivity of their approach, and in the absence of contrary evidence, it is quite reasonable to assume that the half life and fractional excretion of plasma TMAO derived from beef is the same as that from fish. For it to be otherwise would mean that these foods contain substances that have quite powerful effects on those parameters, which no one arguing from any angle has postulated. For example for beef to raise plasma TMAO but not urine TMAO, while halibut led to a 107-fold increase in urine TMAO, would mean either that beef is not a substantial

source of plasma TMAO or that beef is a similar source of plasma TMAO as halibut but contains something that decreases its fractional excretion 107-fold. It's a much more parsimonious interpretation to tentatively conclude what is rather straightforward when one considers that fish contain TMAO itself, which is that fish but not beef are major sources of TMAO. And again, no one has shown that beef *or* fish raises blood TMAO. Make sense?

Chris

Reply

Brendan Coburn says:
April 17, 2013 at 11:56 am

Absolutely, makes perfect sense. Thank you for the thorough response, that really helped!

Reply

NH says:
April 15, 2013 at 4:40 pm

"Some Pacific Island groups that subsist largely on seafood, such as the Kitavans, appear to be free of heart disease"

Way to skew things in your favour.

Kitavans eat mainly root vegetables like sweet potatoes and starches. Considering that fish are around 50% fat, 50% protein, and Kitavans ate less than 20% fat a day, coconut making up the majority of fat. The Kitavans ate very little fish.

Which means your "subsist largely on seafood" claim is bullshit. Which you probably already knew.

Reply

Chris Masterjohn says:
April 16, 2013 at 3:38 pm

I suppose "largely" wasn't the best word, but in the context I think it is fairly reasonable in the sense that it is their main animal food, which is the sense in which I was thinking of it. Lindeberg (AJCN 1997) estimated they consume about 5% fish by calories.

It would have been better if I'd written, "who consume seafood regularly."

Chris

Reply

david says:
May 5, 2013 at 8:54 pm

There is no context, even one which requires anyone reading your words to be a mind-reader in order to divine that sense in which you meant it, in which "subsist largely on seafood" has the sense of consuming an amount of fish that would make up 5 percent of calories.

Reply

Chris Masterjohn says:
May 7, 2013 at 6:06 pm

I agreed it wasn't worded well and changed it, so it's immaterial now. Thanks for your input.

Chris

Reply

Chris Masterjohn says:
April 16, 2013 at 5:21 pm

Hi NH,

I changed it to "regularly." Thanks for pointing that out.

Chris

Reply

Brian Self says:
April 16, 2013 at 11:11 am

Hi Chris:

It is clear you did the real scientific and unbiased research on this. Thanks for taking the time to be so thorough and deliver this info to our community.

Reply

Blaine Kennedy says:
April 24, 2013 at 6:45 pm

Prevotella bacteria seem to be the inciting agent of TMAOs, yet the study done does not focus on pre-existing infection with the organism, and the sources thereof. Im not a microbiologist, but it seems that people have the bug in their oral cavities, just ask a dentist. The study did not examine patient exposure or risk factors for Prevotella exposure, such as dental disease and stomal infection. Perhaps there is a difference between vegans and omnivores in the oral bacterial population, and the gut flora develops in omnivores from chronic seeding from the oral cavity.

Reply

Markus says:
April 26, 2013 at 12:21 pm

And the craze goes on. Now the group is demonizing eggs over the same mechanism, just published yesterday @ NEJM.

http://www.nejm.org/doi/full/10.1056/NEJMoa1109400

Reply

Windy says:
April 26, 2013 at 5:04 pm

Would Citicoline [stabilized CDP Choline (cytidine 5'diphosphocholine)] be considered a salt of free choline that would generate TMAO? And if so, would that increase heart disease risk? I take a choline supplement of citicoline and do not want to take it if it might increase the risk of heart disease.

Reply

Chris Masterjohn says:
April 26, 2013 at 6:48 pm

Hi Windy,

No I don't think so, but I'm not sure how it's metabolized. It depends where it's absorbed. If it's efficiently absorbed in the small intestine, it should

be safe, but if a substantial portion reaches the large intestine, it could generate TMAO. That said, I'm not convinced that this increases the risk of heart disease.

Chris

Reply

Noah says:
November 19, 2014 at 2:55 pm

Sin entrar en la pole9mica sobre la uditilad real de los probif3ticos actuales o del Lactobacillus patentado por Danone, mi impresif3n es que esto variare1 de unas personas a otros, dependiendo precisamente de la composicif3n de la flora intestinal de cada uno. Pero claro, no hay estudios al respecto Lo que sed se desprende de todo esto es que deberedamos evitar el exceso de lecitina, que -por cierto- es el nombre comfan que se da a la fosfatidil-colina , un ledpido que este1 en la membrana de las ce9lulas, y que se utiliza tambie9n como emulsionante en algunos alimentos. Es muy frecuente que te intenten vender la lecitina (de soja, sobre todo) como ff3rmula me1gica para bajar el colesterol malo y subir el bueno , pero las evidencias cientedficas al respecto son me1s bien escasas

Reply

steve naples says:
April 28, 2013 at 5:16 pm

Chris, I've never written into a blog. but I found you analysis thoughtful and interesting. I lost my grandfather, Dad and Brother to sudden death from heart all at 57. So at 52 I am very interested maybe too much, in this topic. I've looked at Macro biotic, vegan, vegetarian Palao, etc. I presently eat a 80 percent plat based diet. anyway, I was wondering. has anyone ever looked at the fact that alcohol drinkers (alcohol at most meals like the French) may work as an antibiotic on the Lecithin, and L carnitine. to basically render it harmless in the creation of TMAO? Thoughts? Thank you

Reply

Chris Masterjohn says:
April 28, 2013 at 11:40 pm

Hi Steve,

I'm not convinced that TMAO is harmful, but that's an interesting idea and I'm not sure the answer. Thanks for writing! If you find anything interesting on it, please let me know.

Chris

Reply

Mike says:
April 29, 2013 at 1:16 pm

Hi,Chris. I am probably one of many folks who check this site regularly to see if you are going to critique last week's egg/tmao study. I hope you do. As someone who eats a lot of fish, eggs, peanut butter, red meat and cabbage, I seem to have a vested interest! After reading Hazen's meat study, where he categorized into 4 groups based on whether their carnitine was high or low and whether their TMAO was high or low, and then described how only 4 of the 53 subjects had the prevotella predominance, I wondered if maybe only a very small percentage of people actually have "dangerously" high TMAO assuming Hazen's theory is correct. But last week's egg study actually broke the TMAO levels into equally divided quartiles, which suggests either that an extremely high percentage of people with the highest levels within the top quartile had heart problems, or roughly 25% of the population has "dangerously" high TMAO. Also, I was confused by the fact that the omnivores in the meat study had roughly a 45% higher baseline TMAO. Does this 45% higher level fall within the top quartile in the egg study? Or is it just that 25% of all us, ominvore or not, are "unlucky" enough to have "dangerously high TMAO and the rest of the ominvores have harmelessly higher levels of TMAO than the vegitarians? It was hard for this nonscientist to try to compare the numbers between the two studies. It does make me want to become a scientist though:) On behalf of the many readers who trust your take on these types of reports more than anyone else's, I hope you give us your take. Thanks. Mike

Reply

Chris Masterjohn says:
May 1, 2013 at 2:58 pm

Hi Mike,

I've been swamped, but I do plan on reviewing the study. In all likelihood, though, I won't post anything on it until next week.

Chris

Reply

Simon Reves says:
April 30, 2013 at 2:57 pm

Hey Chris, we've never spoken before, but I'd like to say that your articles are extremely detailed(!) and that I really enjoy the reads. Felt a bit like Robert commented; as though you're making the pieces of a "mystery novel" fit together for all of us out there that don't have the time to sit-down and thoroughly analyse a study like this.
I find it striking, though, how much analyses of the same data can differ so much – take a look at Dr. Michael Greger's (not surprising) point of view, for example – Who thought the media didn't go far enough with pushing "cartinine –> atherosclerosis".
http://nutritionfacts.org/video/carnitine-choline-cancer-and-cholesterol-the-tmao-connection/

Thought it was brilliant of Mark (Sisson) to link to the caritine supplimentation study by James J. DiNicolantonio et al. weekend following all the fuss.
http://www.medpagetoday.com/upload/2013/4/12/jmcp_ft88_

I like, though, that he (Greger) takes the time to present the data of actual studies to support his opinion(s), but I feel that there is a lot of epidemiology, and occasionally really irrelevant emphasis on the findings of certain trials, in the mix. Take for example the studies that found that saturated fatty acids help along LPS-tranlocation – would it not be relevant to mention that the storage proteins of some grains would be able to do the same ? Or that, despite increased LPS, inflammation (as a measure of TNA-alpha) was no higher in the group fed the cream than dextrose?
http://care.diabetesjournals.org/content/33/5/991.short
And that endotoximia occurs as a result of intense exercise as-well?

On that note, is there any chance you can cover/have covered whether the relationship between dietary choline and prostate cancer risk + advanced prostate cancer risk is casual or causative in nature. Of all people, you seem to be the choline "expert", so I figured you'd be the one to ask.
Could there perhaps be sense in telling men with advanced prostate cancer to lay of the eggs and get their choline from vegetable sources of betaine / suppliment betaine, or even reduce all forms of choline + predecessors?

It's articles like yours that gets me extremely skeptical towards conventional ways of thinking. I like that you always take a broader perspective than the reductionist point of view of most nutrition (e.g. fish is good for it's long-chain n-3's). But I suppose, on the occasion, conventional knowledge gets to be right sometimes. So if you ever get the time: Choline and cancer – what's the connection?

Simon.

Reply

Theresa says:
May 21, 2013 at 10:36 am

Chris,
I am looking for information/research in choline levels in people with paeudocholinesterase deficiency. Are you able to help me out?
I find your articles about choline very informative and easily understood. Thank you.

Reply

Chris Masterjohn says:
May 27, 2013 at 2:21 pm

Hi Theresa,

Unfortunately, I don't know anything about that condition at the present time, but perhaps if you have very specific questions about interpreting whatever you find, I could try to answer them if I can find the time.

Good luck and take care,
Chris

Reply

Paul M says:
June 8, 2013 at 2:50 pm

I once wished that every medical school would make it a requirement for their students to read westonaprice.org. Now I wonder if it would it do any good anyway.

I just got done watching a contributing physician today on Foxnews using the Koeth RA, et.al. Nat. Med. carnitine study as definitive proof that vegetarians live longer than people who regularly eat red meat.

I also recently had a physician friend turn completely vegan based on this study. He had been contemplating going vegan for a while, despite my objections and continued references to this site. It wasn't until he saw the carnitine study that it nailed his decision down for him.

sigh

Keep up the great work you're doing Dr. Chris Masterjohn.

Reply

TH says:
June 8, 2013 at 5:58 pm

> As I pointed out in my last post on this topic, lots of foods seem to increase TMAO in humans and red meat does not stand out among them.

Hazen's work is intended to demonstrate that TMAO levels are correlated with past eating habits. Unless you can clearly disprove that (and you seem to avoid saying you have done so), prior studies that do not control for the eating habits of the participants– vegan, omnivore, etc.– shouldn't be taken as evidence against his thesis.

> red meat should be no more dangerous than potatoes and carrots and the real killer should be seafood.

Without knowing the eating habits of those 6 volunteers in the 1999 study, we shouldn't conclude anything about potatoes and carrots relative to red meat.

But as for seafood, suppose the Hazen hypothesis is correct. That means excessive dietary carnitine/lecithin nourishes TMAO-generating bacteria in the gut, causing future meals containing carnitine/lecithin to impose an extra TMAO load on the cardiovascular system. That could be like eating fish 3

times a day every day. I doubt any studies show that eating fish that frequently is healthy.

Reply

dahlia says:
June 9, 2013 at 6:06 pm

Wow- I wish I could analyze studies the way you do. Thank you so much.

Could you address carnitine supplementation- we recommend it to cardiac patients quite a bit- in hefty doses along with CoQ 10 and d-ribose. What is your opinion now about doing that?

Thanks,
Dahlia

Reply

Chris Masterjohn says:
June 10, 2013 at 9:04 am

Hi Dahlia,

You're welcome and thanks! It appears to be beneficial from what I have seen. If I have a chance in the future to review the literature on it more thoroughly I'll write something on it.

Chris

Reply

David I says:
June 19, 2013 at 3:06 pm

Excellent article.

On behalf of the Cartilagenous Fish Anti-Defamation League, however, I feel it necessary to point out that skate are not invertebrates.

They should not be grouped of mollusks, crustaceans, octapods, and decapods. They belong with sharks and rays.

Sincerely
Sk8rBoy

Reply

Chris Masterjohn says:
June 19, 2013 at 6:56 pm

Thanks! Good point. I changed it to bony and boneless.

Chris

Reply

Zenaida Zody says:
June 24, 2013 at 3:18 am

Carnitine plays a critical role in energy production. It transports long-chain fatty acids into the mitochondria so they can be oxidized ("burned") to produce energy. It also transports the toxic compounds generated out of this cellular organelle to prevent their accumulation. Given these key functions, carnitine is concentrated in tissues like skeletal and cardiac muscle that utilize fatty acids as a dietary fuel "-..:

All the best

Reply

Phil Nicols says:
March 2, 2014 at 8:17 am

if vegan or vegetarian was bad for us, then all the vegans / vegetarians would be dead by now.. or at least sick.

instead, we have gold medal olympic athletes, top MMA fighters, boxers, football players, extreme sports competitors, bodybuilders…. in fact the strongest man on earth today is vegan. If its "good enough" for them, then its good enough for the average keyboard warrior.

2) its not all about me.. it takes 25 times as much land to feed cattle as it does to feed people, then after the cattle is brutally slaughtered, only 35% makes it back to the tables of humans.

3) besides land, it takes immense amounts of water and energy to do this.
2500 gallons of water = 1LB of meat
750 gallons of water = 1 quart of milk
55sf of rainforest = one 1/4 lb burger pattie
we lose 65 acres of rainforests every minute of every day due to factory farming alone
10 years ago it was estimated that we only have 50 years of

rainforests left.
rainforests act as the liver of the earth filtering out toxins that we pump into it daily…. pollution is going up and our natural defense against this is going down. without a liver, earth gets “liver failure”

4) then theres the horrific cruelty. there is no such thing as humane slaughter. if there is, would you trade places with a cow pig, sheep, cat, dog, or anything else thats on the menu these days?

we lose nothing by making some different choices in life but we help the big picture.

Reply

sharonrays says:
June 1, 2015 at 3:23 am

Very informative post.Thanks.

Reply

James says:
July 16, 2015 at 6:18 am

The food we take constitute mostly to our health condition.Our health is determined by the food we ingest. Heart disease is not an exception. Thanks for creating awareness.

Reply

Leave a reply

Comment

Name *

Email *

Post Comment