Does Dietary Choline Contribute to Heart Disease?

Posted on April 13, 2011 by Christopher Masterjohn • 31 Comments

I've been writing a lot about choline lately. Most recently, my article entitled ~~"Nonalcoholic Fatty Liver Disease: A Silent Epidemic of Nutritional Imbalance"~~ contained a major section on the role of dietary choline in protecting against fatty liver disease, which itself is a powerful and independent risk factor for heart disease.

I also wrote a series dealing more specifically with choline and fatty liver over at *The Daily Lipid*, which culminated in my post on this blog, "Why Is My Cholesterol So High on This Diet?"

Likewise, Dr. Emily Deans has recently been writing about the role of choline in mental health, something I had covered in less detail in my ~~2007 article on pregnancy nutrition~~.

It may be of concern, then, that a recent paper published in *Nature* suggests that dietary choline may be contributing to heart disease:

> Wang et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011;472(7341):57-63.

Yikes! Are we to eat liver and egg yolks to support our liver health and mental health only to wind up with heart disease as a result?

Here's a diagram representing the hypothesis that these authors have offered us (image from the associated commentary by Rak and Rader):

The authors argue that dietary choline, found mostly as phosphatidylcholine, enters the intestine where our gut bacteria convert it to free choline and then to trimethylamine, a gas that smells like rotting fish. Then our livers detoxify the trimethylamine to an odorless product called trimethylamine oxide (TMAO). While this prevents us from walking around smelling like we've been swimming in a barrel full of fermenting cod livers, the authors argue that TMAO fills our arteries with plaque.

In support of this hypothesis, the authors showed that blood levels of choline, its metabolic byproduct betaine, and TMAO all correlated with the incidence and severity of cardiovascular disease in humans, although this was not prospective data showing that the occurrence of these compounds in the blood early in life predicted the development of heart disease later in life.

They also showed that feeding mice phosphatidylcholine did in fact produce TMAO, but only in the presence of gut bacteria.
Further, feeding mice five-fold or ten-fold higher concentrations of choline chloride than they would ordinarily receive, or simply feeding them TMAO itself, increased atherosclerotic lesion size, and atherosclerotic lesion size correlated with blood levels of TMAO.

There's just one major problem with this hypothesis. **Studies in humans have shown that neither phosphatidylcholine nor choline-rich foods produce detectable increases in trimethylamine.**

Here's a figure from a 1983 study by Ziesel and colleagues showing urinary excretion of trimethylamine after supplementation with different types of choline in humans:

The third bar in each panel represents the excretion of trimethylamine in the urine. Choline chloride and choline stearate led to the production of large amounts of trimethylamine, but lecithin (phosphatidylcholine), the main form of choline found in food, led to only a small increase.

It turned out, however, that their lecithin was contaminated with some trimethylamine. If they "cleaned" it to remove the contamination, shown in the fourth panel, the lecithin did not increase urinary excretion of trimethylamine at all.

A 1999 study by other authors came to similar conclusions. They looked at the urinary excretion of both trimethylamine and its detoxification product TMAO in humans. They found that 60 percent of free choline and 30 percent of carnitine, another potential precursor, was excreted in the urine as one of these two products, but that neither betaine nor phosphatidylcholine converted to either product at all.

In fact, these authors even fed 46 different foods to humans and looked at the subsequent excretion of trimethylamine and TMAO. Choline-rich foods like liver and eggs did not produce any increase in urinary trimethylamine or TMAO over control levels. In fact, even carnitine-rich meats failed to increase excretion of these compounds. The only foods that increased excretion of TMAO were seafoods, which naturally contain some trimethylamine, giving them their "fishy" smell.

Here is a representative selection of seafoods and other animal foods:

Here we see that only seafoods, naturally contaminated with trimethylamine, increase the urinary excretion of trimethylamine and TMAO in humans. Liver, eggs, and meat do not.

These authors explained their results by citing research showing that the enzyme phospholipase A cleaves phosphatidylcholine, or lecithin, into a compound called lysolecithin in the small intestine where it is efficiently absorbed. By contrast, other forms of choline travel to the colon where gut bacteria make enzymes that convert them to trimethylamine.

Should we presume, then, that it is not liver and egg yolks, but rather fish and shellfish that contribute to heart disease? Perhaps, although this seems doubtful given that populations such as the Kitavans eat plenty of fish, even in fermented form, yet appear to be free of heart disease.

In order to even begin supporting such a hypothesis, we would have to first see to what degree eating seafood leads to the accumulation of TMAO in the blood, and here we only have urinary data. If the kidneys efficiently dispose of TMAO into the urine after eating seafood, TMAO may be unlikely to accumulate in the blood for any length of time.

Indeed, the massive increases in urinary trimethylamine and TMAO following meals rich in seafood suggests that our kidneys excrete these compounds very efficiently.

So how, then, should we interpret the correlation between heart disease risk and plasma concentrations of choline, betaine and TMAO in humans?

Blood levels of choline are currently considered an emerging marker for destabilization of coronary plaques or ischemia in acute coronary syndrome, as reviewed here. During the process of blood clotting, inflammatory enzymes release choline from membrane phospholipids in order to also generate phosphatidic acid, which is used as an important signaling molecule. Elevated blood levels of choline, then, and perhaps its metabolite betaine, could simply reflect an inflammatory or pro-clotting environment.

Elevated TMAO could reflect dietary trimethylamine or TMAO from seafood, but it could also reflect impaired excretion into the urine, or enhanced conversion of trimethylamine to TMAO in the liver.

The enzyme *Fmo3* carries out this conversion, mainly in the liver, as reviewed here. There are a number of genetic variants affecting the activity of

this enzyme, some of which appear only in certain ethnicities, and the enzyme also processes a number of drugs used to treat psychoses, infections, arthritis, gastro-esophageal reflux disease (GERD), ulcers, and breast cancer. Iron or salt overload may also increase the activity of the enzyme. TMAO could, then, be a marker for ethnicity, drug exposure, genetically determined drug efficacy, or other conditions.

If we had strong epidemiological evidence showing that consumption of fish and shellfish early in life is associated with an increased risk of developing heart disease later in life, then the animal studies reported in the *Nature* article would present a strong justification for considering the hypothesis that trimethylamine contaminating these foods is somehow increasing the risk of heart disease.

Yet, we do not have that. Alas, we instead have evidence that islanders who eat traditional diets containing fish tend to be free of heart disease.

Perhaps future work will in fact elucidate a role for harmful gut bacteria in increasing TMAO levels and subsequent development of heart disease, in which case the clear implication would be that we should figure out how to normalize the gut bacteria. Right now, we have no evidence that eating choline-rich animal foods increases TMAO at all, so a hypothesis dependent on this apparently fictitious process is as yet an impotent one.

Pass the liver and egg yolks please. And maybe some folks fasting for Lent may say pass the fish, shrimp or octopus. Consuming these choline-rich foods will produce much better mental health than worrying in the face of contrary evidence that they are clogging your arteries.

Read more about the author, Chris Masterjohn, PhD, here.

Christopher Masterjohn

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Third Annual Raw Milk Symposium Update →

31 Responses to *Does Dietary Choline Contribute to Heart Disease?*

Cynthia Fredrick says:
April 14, 2011 at 11:35 am

Brilliant as usual, Chris. Every time one of these supposedly conclusive studies comes out and gets reported, everyone seems to have a knee-jerk reaction–in this case, to regard choline as evil. Why do they never seem to give equal time to analysis/studies which show the original study to be faulty?

Reply

Stephan says:
April 14, 2011 at 1:42 pm

Nice one. I hadn't gotten to that paper yet, beyond noting that the amount of choline they fed to the mice was massive. Needless to say, I was finding their claims hard to swallow on that basis alone…

Reply

cliff says:
April 14, 2011 at 3:42 pm

What is your opinion on choline supplements such as choline bitartrate?

Reply

E.C. Seiler says:
April 14, 2011 at 4:12 pm

So, I am confused, is supplemental choline intake, such as in the form of choline chloride or bitartrate still undesirable? 😟

Reply

E.C. Seiler says:
April 14, 2011 at 4:19 pm

Also, the data citing Carnitine's potential conversion into undesirable TMAO, could this be applicable towards supplemental Carnitine usage, but also and more particularly, to the usage of Acetyl-L-Carnitine supplementation? This has distressing potential.

Reply

Kurt Harris says:
April 14, 2011 at 7:27 pm

Nice work Chris. I don't know how anyone can keep up with you:) I am also bothered a lot by the whole data mining premise of this "metabolomics" paradigm. It is statistically bogus and likely to lead to spurious corellations when "screeining" for so many metabolites.

Reply

John M. says:
April 15, 2011 at 12:23 am

Chris,

Glad you shed some light on this. I was suspicious of this new paper when I first saw it last Friday on the Science Daily website.

Unfortunately, I am not a big fan of liver/organs and eggs. Because of this, I don't think I get enough choline in my diet. On the flip side I am probably taking in a little more fructose than I should but I am working on reducing that..

In the meantime however, I was wondering if you thought supplementing with choline would be beneficial? I was considering choline citrate versus phosphatidylcholine to reduce my pill burden. I can get one 650mg tablet of Choline Citrate which supposedly has 221mg of actual Choline. I would be interested in your thoughts.

Thanking you in advance.

Respectfully,

John M.

Reply

John says:
April 22, 2011 at 3:23 am

God Bless you sir! I need to take PPC (polyenylphosphatidylcholine) for liver disease and the Nature article was quite distressing.

I had read before that choline chloride was the wrong way to supplement choline, and phosphatidylcholine was the way to go. Your data seems to support this theory.

Reply

MarkL says:
May 5, 2011 at 8:29 pm

Easy there lil pony. As consistently brilliant as the reviews and studies you (thankfully) put forth are….they're all gonna come gunnin fur ya…layin waste to their horse-hauckus studies–as your rather knowledgably lucid and objective insights so often trend–these vain and competitive greedy black-hearts will want some pay-back, couldn't you imagine?

Of course, there is always that, but please, keep your course as I'm somehow certain you will….and keep feedin on truly good healthy food cause you're gonna need all the energy you can, what with clearin the PhD and fightin off all the overwhelming preponderance of frauds out there; not to mention discovering stuff that can be of genuine benefit for those well-enough-tuned to keep an ear to the heavens and earth.

You're one very usefully contributing life, from my humble perspective, anyway, which is
how we should all learn to live our lives: to
contribute to the fulfillment of an eventual harmony here on this planet…amongst all living things. One way or another, life ultimately is tethered to the language that the nature of the universe speaks, and not the notional nonsense of so many

weakened minds divin for dollars to get through the day. Yes, everybody's gotta eat…but exactly what? Find the best answer to that question for one's self and family, and sustainable health often prevails…and always with the caveat that everyone is different, so don't get too enamored and cocky with one of our greatest impediments to significant and meaningful learning: Beliefs…as they come and go as do the sea's changing tides.

So again, my gratitude for your fine research efforts and the sharing of, and,

All the best, especially inHealth,

Mark

Reply

Sue says:
October 21, 2014 at 12:24 pm

Huh?

Reply

Christopher Masterjohn says:
May 12, 2011 at 10:56 pm

Responses to Cynthia, Stephan, Cliff, EC Seiler, Dr. Harris, John M, John, and Mark L.

First, I apologize for the late reply everyone!

Cynthia, thanks! I think part of the problem is lack of people doing the critical analysis and submitting it. If I have time, I'll write a letter if it's not past their deadline when I can.

Stephan, thanks! A little hard to swallow indeed.

Cliff, I would only use phosphatidylcholine.

EC, yes I would stick to phosphatidylcholine. Acetyl-L-carnitine may act differently than the carnitine they used, as does food carnitine. I will try to look into it.

Dr. Harris, thanks! On the data mining, I think they offered it some legitimacy here because they went out with a specific hypothesis to look for the association in a different cohort. Of course, that still doesn't indicate causation.

John M, you can make up for choline by getting more B6, B12, folate, and betaine. If you supplement with choline, I would, in light of this data and the *potential* for harm, stay on the safe side and stick with phosphatidylcholine.

John, you're welcome and thanks!

Mark L, thank you so much for your kind words.

Reply

E.C. Seiler says:
May 24, 2011 at 10:48 pm

Hello Chris…..Any likelihood that supplemental brands of PC, such as NOW Foods or Jarrow, could be contaminated with TMA? Also, does a supplement such as DMAE or CENTROPHENOXINE pose a problem, it would not seem to me as it does as it is rejected for breakdown by gut flora and does not require this conversion process. Also, does DMAE and CPX serve as an essential dietary Choline source, or would PC supplementation/intake still be advisable to achieve AI? All the best!

Reply

Christopher Masterjohn says:
June 26, 2011 at 2:58 pm

Hi EC,

I would ask the company about contamination. Seafood has such contamination, however, and I eat it. I would get choline from food, unless you have some condition that choline might treat in higher doses, in which case I'd use PC because it most closely mimics what is found in food, unless there are clinical trials showing superiority of something else for some therapeutic use.

Chris

Reply

E.C. Seiler says:
May 24, 2011 at 10:49 pm

p.s. Were you able to determine whether ALCAR should pose any problem, seems like it should be OK to me….?

Reply

Christopher Masterjohn says:
June 26, 2011 at 2:55 pm

Hi EC,

I haven't been able to look into it yet, but will write about it when I get a chance. I'd favor consuming liver, heart, and so on for some of these more obscure nutrients, but I've supplemented with acetyl-l-carnitine and R-alpha-lipoic acid in the past and felt good from it.

Chris

Reply

John says:
April 19, 2013 at 12:30 pm

Normally I get rash from Acetyl-Carnitine (a known side).

After read carnitine/TMAO warning, I started using transdermal (the molecular weight is low enough to cross, especially using a carrier).

Oddly: I think transdermal prevents the rash.

To check if actually was absorbing, I will repeat after discontinuing for sev days ..always get dopamine rush when I do.

Anecdotal and totally useless for you I suppose – but does indicate there may be something happening in gut – leading to inflamation (skin).

Reply

Chris Masterjohn says:
April 19, 2013 at 12:47 pm

Hi John,

There is definitely something happening in the gut, because supplemental carnitine has been shown (including by Zhang et al, 1999) to increase TMA/TMAO, which presumably is occurring through TMA production in the gut from intestinal bacteria.

Chris

Reply

Edward J. Edmonds says:
June 28, 2011 at 4:32 pm

Interesting. What about strokes? Looking at these maps it seems that coastal and island populations that would typically eat a lot of fish also have a lot of strokes. Is TMAO a risk factor for strokes?

http://www.who.int/cardiovascular_diseases/en/cvd_atlas_16_death_from_stroke.pdf

http://www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf

Reply

George Henderson says:
May 23, 2012 at 5:35 pm

The maps don't seem to confirm that.

Coastal areas have more industry and pollution in most countries.

Reply

Jay says:
July 17, 2011 at 10:33 pm

Great read. I was quite concerned when I read those studies as I've been taking a lecithin supplement and wasn't sure now how safe it was. Each serving contains 2g of Phosphatidylcholine along with 1g of Phosphatidylinositol. Is that safe?

Thanks

Reply

Mike says:
October 12, 2011 at 12:15 am

Chris, you seem to say that much excretion (such as with the choline chloride) does indicate the potential for ill health. However, you later suggest it might simply indicate efficiency of the body to get rid of TMAO? Obviously we can't have it both ways? Meanwhile, the authors of the observational study did correlate choline, betaine, and TMAO with cardiovascular problem. Are you saying that the authors with their "excretion measurement" didn't measure something meaningful to their conclusions. And therefore you say that choline is probably healthy?

Reply

Chris Masterjohn says:
November 25, 2011 at 4:22 pm

Hi Mike,

Yes, I can have it both ways, at least in the senses in which I was using the data. If TMAO is efficiently excreted into the urine, then it is unlikely to cause harm except in people where its excretion is impaired, thus causing its accumulation in plasma or other tissues. However, in a crossover trial with the same subjects, who clearly would have similar efficiency of excretion from one food to the next, the absence of any excretion suggests that no TMAO is generated. In any case I took these in the context of other data, and not alone. The fact phosphatidylcholine doesn't seem to generate TMAO is consistent with our understanding of how it is absorbed. The fact that seafood seems to generate it is consistent with the fact that seafood is contaminated with it. And so on. If TMAO is a problem, then it is likely to be the seafood that should be problematic. So this has to be interpreted within the context of other data suggesting whether seafood contribute to heart disease, and so far the precise opposite argument has prevailed, and for good reason.

I don't know what "excretion measurement" you're talking about. I provided examples of confounders that could account for some of these associations.

Chris

Reply

Kevin Lee says:
December 13, 2012 at 11:09 am

I know that I am about a year behind on this one, but here goes:
(And by the way, I am a reviewer that you don't want to get in the peer-review process.) And before I tear this to shreds, I would like to make it known that I believe this to be a well-conducted experiment (in general) which has important implications for mouse (as well as human) health, especially in relation to the gut microbiome.

Figure 1b: Why aren't the other metabolites determined? The authors say that they just looked at the three that were most correlated (and therefore likely in the same metabolic pathway), but usually, we are interested in the ones that are either most significant or have the highest effect size, and clearly, there were other compounds that had higher effect sizes.

Figure 2 (showing that anti-biotic treatment suppresses TMAO production in mice). The question is: what kind of gut flora leads to an increase in the production of TMA? In mice, the gut flora that develops when on a standard lab chow is necessary and sufficient to lead to the generation of TMA (when supplemented with choline). But what about my gut flora? As you so adeptly pointed out, our flora does not seem to produce TMA.

3d: Greater lesion area in mice that had choline supplements. This figure looks impressive, but I would like to see replication

in another mouse model (if this effect is in fact replicable); furthermore, this is the data for only the female mice. And if we look at Supp fig 9a, we see that it is not significantly replicable in the males which brings up an entirely different and important discussion of gender differences in atherosclerosis, especially because human MALES are more prone to CVD and MI.

Figure 3e is perhaps statistically misleading (while normally distributed values are not required for linear regression, the variance of the both the independent and dependent variables appears to be a function of the mean, heteroscedastic error variance). This data is not normally distributed and so the authors could have more usefully used a non-parametric statistical test (or transformed the data to make it normal). Most of the data is TMAO50 shows basically a random scatter. In fact, if you eliminate all of the data to the left of 175 TMAO, then it looks like there is a protective effect of TMAO on lesion size above this level. Further, this is a plot of two dependent variables, neither did they manipulate. Here, they are simply showing correlation, and reporting that correlation represents a very low p-value.

Figure 3f, same story. It is a plot of two dependent variables. Neither did they manipulate (directly).

Figure 4a and b (Fmo3 against lesion size and HDL-C): why did they not show the graph of lesion vs HDL level. Since Fmo3 expression and HDL are so highly correlated, I would expect the HDL to be well-correlated with lesion size, as well; and perhaps more so, especially because decreasing HDL is a known risk-factor for CVD. This correlation may be the causal mechanism for this effect, but we can't know from the data presented here.

Figure 4d is not too convincing, either. Remove one or two outliers and the statistical significance would disappear. Which is funny considering we know the mechanism for FMO3 converting TMA -> TMAO. Even the effect that I would expect to see is unclear in this work.

Figure 4f,g (macrophage scavenger receptors actived by the diets). This is an important question. And if this effect is real and replicated, there is no reason to only do the tests on just the atherogenic-prone mice; it should be observable in the other strain, as well. Why did the researchers not show the same effect in the non-atherogenic-prone mice (to which they had access). Or did they test this and it wasn't significant? Perhaps there is something about these inbred atherogenic-prone mice (C57BL/6J) that leads to this kind of increase in response to TMAO.

Figure 5 is beautiful.

Figure 6: I wish that they would have used a mouse instead of a human for this schematic because that is where they demonstrated it.

Reply

Chris Masterjohn says:
December 16, 2012 at 10:00 pm

Hi Kevin,

Thanks for your contribution! Regarding your third-to-last point, C57BL/6J have a genetic defect in NADPH metabolism, which in turn leads to deficiency in mitochondrial glutathione, which could play a role.

Chris

Reply

DanielMatosi says:
April 7, 2013 at 5:28 pm

So, should we continue taking CDP Choline and ALCAR??? So many of us do and this is so worrying especially in light of the news today that Carnitine in meat is the culprit of heart disease.

Reply

kali says:
April 8, 2013 at 12:17 pm

Yea, count me in on the worried column. I also consume ALCAR and phosphatidlyserine and they work well for brain function but am I basically ensuring that I have a heart attack by 50?

Reply

Fred Hahn says:
April 8, 2013 at 8:32 pm

Chris –

What do you make of the recent NYT article?

http://www.nytimes.com/2013/04/08/health/study-points-to-new-culprit-in-heart-disease.html?pagewanted=all

Reply

Dawn says:
April 25, 2013 at 10:00 pm

Here is another 'study'

http://www.cbsnews.com/8301-204_162-57578422/carnitine-chemical-not-fat-may-explain-link-between-red-meat-and-heart-disease/

Have you heard of/read the book by Broda Barnes called Solved; the Riddle of Heart Attacks?

Out of print but can be re ordered at the broda barnes foundation. His take on it was completely different though it does stem from damage to the mitochondria.

Reply

Chris Masterjohn says:
April 26, 2013 at 10:28 am

Hi Dawn,

I critiqued that study here:

http://www.westonaprice.org/blogs/cmasterjohn/2013/04/10/does-carnitine-from-red-meat-contribute-to-heart-disease-through-intestinal-bacterial-metabolism-to-tmao/

Yes I've read the book by Barnes. Thanks for your comment!

Chris

Reply

Alkan says:
June 7, 2013 at 6:02 pm

I also take citicoline 750 mg daily with good results for my old brain. It helps my stroke aftermath.

Should I quit as I would not want a heart attack?

Reply

Bukowski says:
June 19, 2014 at 6:21 am

New study that has been released that clearly shows that eggs can increase TMAO:

http://ajcn.nutrition.org/content/early/2014/06/18/ajcn.114.087692.abstract

Reply

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