Consider the following sequence of events:
-In 1945, an 82 day long battle between US Marine and Army forces and the Imperial Japanese Army was fought in the prefecture of Okinawa. This battle was considered one of the bloodiest in the pacific and resulted in the death of almost 150,000 Okinawans, roughly a third of the population. Due to widespread destruction, and foodstuffs in particular being stolen or deliberately destroyed, a huge number of civilians were left starving and struggled to return to a sufficient diet after the war. [via「琉球・沖縄史」沖縄歴史教育研究会*, pg 264]*
-In 1949, data from US national archives indicated that 85% of Okinawans' calories came from carbohydrates with sweet potatoes comprising 69% of all calories and 1% of calories coming from Fish. [R - Table 1, pg 443]
-A 2016 paper points out that the Okinawan's 1949 post war diet has a ratio of protein to carbohydrate that is similar to an experimental high carb diet used to improve lifespan in rodents.
-In January 2019, a BBC article referring to this paper comes out with the headline "*A high-carb diet may explain why Okinawans live so long.*"

Okinawan people did historically eat their fair share of sweet potatoes - the typhoon resistant tuber made for a good staple crop.[R] However, is it fair to make conclusions about Okinawans longevity based on their diet right after the war? In any case, when you dig in a bit, it becomes apparent that this BBC article lacks some very important context.

The idea of this video is to give some insight into the shortcomings of research, and to help you understand what makes for a weak or strong piece of supporting evidence for health claims.

Let's say a detective wants to determine who killed John. He will follow clues and investigate evidence while considering the strengths and shortcomings in each piece of evidence. For example, a witness saying they saw someone that sort of looked like Count Jackington's butler is much weaker evidence than a security camera capturing an image of the

butler. It's good to take a similar approach when trying to make conclusions from research.

~~Actually, the detective analogy comes from Eli Lyons, the CEO of the synthetic biology company Tupac Bio. In his current position, and as a PhD candidate at the University of Tokyo, Eli has a decade of experience regularly reading through research papers So I thought I'd have a chat with him on the topic for more perspective.~~

~~"*One thing I noticed is that well people read articles that are summaries of research articles. And then, sometimes in those summaries, that are clickbait or something, there's not even a reference or a link to the primary article. The primary research article. So that's something I've seen that's like... well, how can I start to evaluate the quality of this claim. And so… going back to our conversation we've been having which is how do we evaluate the quality of research, or if something is true or not in nutrition. Well, if I see a really bold headline and then I can't even easily find the research paper it's based on … or you gave an example and you were reading a book, and it had a reference but the reference was just a footnote..."*~~

Last year, I picked up this book with the title "The Best Diet: Simple and Evidence based guide to healthy eating" written by a doctor Tsugawa at UCLA. I saw this book around when I was making a video on Butter Coffee and the cover of this book has a big red X next to the word "Butter Coffee" so I picked it up to make sure I wouldn't have to delete my video. On page 31 that it says "Butter is a bad fat as shown by several studies."

(1) So, the first, most obvious step to evaluate a claim is to investigate the evidence the claim is based on.

There's a reference number next to this sentence about butter, so I go to reference (4) in the very back of the book and it has a footnote saying "*The*

idea that butter is bad comes from observational studies in which butter seems to raise the "bad" LDL cholesterol. However, the evidence that butter intake affects your risk for disease is not particularly strong." This footnote goes on to point out that a 2016 paper did not show an association between butter, heart attack and stroke. In fact,and that butter appeared to *reduce* the risk for diabetes. ~~I have to say I feel a little different about this chart on page 32 putting butter in the "worst foods" category after seeing this footnote...~~

~~However, this actually is a good demonstration of integrity by Dr. Tsugawa to acknowledge counter evidence like this 2016 paper and actually include it in the book.~~

This book also brings up a very often debated topic: Eggs. Eggs, especially the yolk, can be a cheap source of good nutrients like fat soluble vitamins which aren't contained in the majority of typically eaten foods. But, the book recommends limiting your egg intake to only one a day.

If only this book came out earlier, then this poor 88 year old man could have been warned. He ate 20 to 30 eggs a day for 15 years as of 1991. Interestingly, he maintained normal plasma cholesterol despite the ludicrous amount of dietary cholesterol he consumed- we'll talk about how this affected him in a moment and We'll come back to the evidence for this Egg claim, but first, I need to explain a couple concepts.

The first is confounding variables: Here we have the grabbing headline "*High-Fat Diet Linked to Anxiety, Depression*." If we take a look at the study they're basing the article on, we see that the high-fat diet they used - D12451 from Research Diets Inc. , contains 20% protein, 45% fat and 35% carbohydrate - this is relatively high fat. However, half of the carbohydrate is refined table sugar… by weight there's almost as much pure sugar as there is fat. Do think this might confound the effect of fat?

Now, Biology is incredibly complicated - there are so many variables that may affect a given output. For example, a common challenge is isolating the effect of one food or gene on disease risk from the effects of all the other foods and genes that could also potentially increase that disease risk.

I had a chat about the various challenges in scientific research with Eli Lyons,the CEO of the synthetic biology company Tupac Bio. In his current position, and as a PhD candidate at the University of Tokyo, Eli has a decade of experience regularly reading through research papers. Afterwards I followed up on Skype to ask him about the challenge isolating variables.

"*In some of my work, I've done statistical analysis on oncogenes or high throughput mutagenesis. Oncogenes are cancer causing genes, or, genes that when mutated may drive cancer. And, what commonly occurs though is that in a tumor, for example, you may have many genes that are mutated. However, not all of the mutated genes are actually driving the cancer. So, the ones that are driving it are called driver cancer genes. And, so how do you isolate the effects or determine which genes are the driver cancer genes and which are like carrier mutations. It's also more complex because there may be some interactions between the driver cancer genes and some genes that are mutated and the interactions are very complex, but the impact may be largely due, the majority of the impact may be due to the driver genes for example. And so, it's isolating how large of an impact or, how much of the cancer is due to gene A - a mutation in gene A, and how much of the cancer is due to a mutation in gene B for example.*"

(2)This brings us to my next point, the importance of context:
A good example for why it's hard to isolate things from the context is protein. There seems to be some concern about protein for people on a low carb diet. One of the goals of doing a low carb diet is keeping your insulin low, and to achieve that people replace the carbs with fat or protein, but protein ironically *seems to raise insulin levels.* However, does the context

matter? Does protein *by itself* reliably raise insulin levels?

If we take a look at this study in canines as presented by Dr. Benjamin Bikman, we see that dogs receiving an infusion of glucose get spikes in their insulin levels when given the amino acid alanine. So, it looks like protein does raise insulin. But what about dogs without the glucose infusion? The dogs not receiving glucose didn't see their insulin change to any noticeable degree.

There's still more to be said about how different types of protein in different diets affect not only insulin, but glucagon - a hormone that works counter to insulin. But for now, imagine how this fact would confuse the data in for example a study looking at how protein affects risk for diabetes, an insulin driven disease. You might look at how many servings of meat people are having per day and then look at who develops diabetes, but the physiological effects of a hamburger patty tucked in a whole wheat bun and served with french fries are going to be much different from a steak served only with butter and rosemary.

Another good example of the importance of context comes from the work of Dave Feldman. Dave is an independent lipid researcher who has developed something called the Lipid Energy Model. He's actually been interviewed on this channel before. We all know that we are supposed to keep our LDL bad cholesterol as low as possible to prevent heart disease. However, in our interview, Dave explained the logic behind why when it comes to heart disease, LDL - the so called bad cholesterol isn't all that important in the context of high HDL and low triglycerides. That is, you don't need to worry all that much about sky high bad cholesterol if your HDL is high and your triglycerides are low.

"*The NHANES data has certainly been exciting because while it's true that if you look at LDL by itself, when you look at it grouped with high HDL and low triglycerides, it's associated with low mortality.*"

This huge NHANES data set that Dave recently got his hands on is showing that this idea that HDL and triglycerides are more important than LDL cholesterol indeed pans out surprisingly well.

“I first removed everybody that had a **low** LDL, so everyone with 159 mg per dL and lower, I took out. I went ahead and seperated out everybody with HDL cholesterol of 49 or lower. And then finally, I took out everybody above 100mg/dL of triglycerides. This was pretty exciting because now I could actually look at what the mortality data was that was left. And that mortality was pretty exciting because not only did they have an all cause mortality that was lower than the average, but, believe it or not, diseases of the heart were extraordinarily low. The youngest person in that group that was left over, once all three of these markers were accounted for, was 68. The oldest in the group? 94. And outside of those two, everybody else died in their 80’s. A total of 18 total deaths from diseases of the heart, and almost everyone died of old age.”

~~By the way, if you’d like to make a quick 1000 dollars, Dave has a challenge for anyone to find a study that finds high rates of cardiovascular disease in normal people with High LDL cholesetol and Low Triglycerides, and High HDL.~~

So, let’s go back to that earlier point about the recommendation to eat only one egg a day. The author of that book explains that, according to a 2013 meta analysis, those who ate more than one egg a day had a **42%** higher risk for developing type 2 diabetes than those who hardly ate eggs. What a meta analysis does is pile the data from multiple studies together to try and make more accurate conclusions.

(3) Here’s another point for investigating a claim - the cumbersome task of actually digging through the referenced study.
So, Let’s take a look at this meta analysis that reference 3 points to. Then,

let's go to Table 1 and see what studies are used for the data on Type 2 diabetes. Looking at references 51, 37 and 41 we get these three studies:

The data from this study[37] did suggest that high levels of egg consumption are associated with increased risk for type 2 diabetes. *However,* this study[51] found that "*No statistically significant associations [were] found between egg consumption and diabetes."* and this other study also [41] found "*no association between egg consumption or dietary cholesterol and increased risk of incident T2D.*"

But, by taking these three studies with differing conclusions and pooling the data together in a meta-analysis, the conclusion becomes "*compared with those who never consume eggs, those who eat 1 egg per day or more are 42% more likely to develop type 2 diabetes.*" At first, this seems like a good idea - more data, so a more accurate picture, right?

However, in this study [37], the women eating the most eggs are smoking the most, eating higher amounts of trans fat, eating 500 more calories per day and exercising the least. The men who ate more eggs also drank more alcohol and smoked more. The researchers do take these unhealthy habits into account and make adjustments when analyzing the data, but it is very ambitious to assume you can quantify the effects of all things on diabetes risk*, and then subtract these to accurately understand how *just eggs by themselves* affect diabetes risk.

In any case, the studies used in this meta analysis not all adjusting for potential confounding variables. This one only adjusts for Age and Sex. This one doesn't even account for how many calories the people ate along with the eggs - what if the people eating two eggs a day are getting those two eggs from a Denny's Grand Slam seven days a week*?*

By the way, remember the guy who ate 25 eggs a day for 15 years? The 88 year old had no health complaints other than poor memory and loneliness after his wife passed away. Also, he had no history of stroke, heart disease or diabetes.

So, while this kind of meta analysis study is a ***clue*** to the puzzle of eggs, I think you'd agree it's not as strong a piece of evidence as it appeared at first glance. Eggs are one of the few sources of fat soluble vitamins in the common diet, so I don't think it's a good idea to limit intake based just on this kind of meta analysis.

Of course the other reason for us being told to not eat eggs comes from the theory that fat and cholesterol cause heart disease.
The very first clue for this theory comes from research by Nikolai Anichkov.[R1,R2] Anichkov found that feeding cholesterol to rabbits had them develop very high levels of blood cholesterol and atherosclerosis.[R]

...But rabbits are herbivores, and their natural intake of cholesterol hovers right around zero milligrams. (4) So, let's move onto my next point: the shortcomings of using animals as a model for understanding humans.

"*We were talking about the problems with model organisms..."*
"Yea… The basic idea is that the mice that they use in experiments are not very diverse. Right, so they're kind of like clones and… the way they're breed is similar to having a breed of dog. If you did all of your experiments on golden retrievers. Is that really representative of what would happen if you did the experiment on ten different dog breeds?"

To give you a picture of how this can affect research, consider the work of Lewis Dahl. In 1963, he fed rats a high salt diet and found that some, but not all developed high blood pressure. He then went on to selectively breed rats, producing a strain of rats that were genetically sensitive to salt. Then, in 1970, he fed these salt sensitive rats commercial baby food and about half of these salt sensitive rats died. He concluded that the high salt content of the baby food formula was to blame. After his study was published, the US senate issued a mandate for lowering salt in baby foods.[R] Does anything sound odd to you about this sequence of events?

Anyhow, let's get back to our discussion on mice models:

"*It's well known that mice models are not always very good and the pharmaceutical industry knows that really well - there's a lot of literature on it, but it's really easy to think about - which is well, how do drugs get approved for humans? Well, one is they do early stage pre-clinical work which is usually on cell lines and then on mice and then they move maybe to canines and apes or something and then they start human trials. But, you may be familiar that with the phenomena that in clinical trials 1, the drug passed but it failed in clinical 3 trial. But if you imagine like, it failed at one of these human based trials but, well, it passed the mouse trial. I think that right there gives you some idea of that well, the mouse model did not*

model what we expected to happen in humans. Why does that happen? Well… mouse is different from a human, and also the model they make where the mouse has a certain type of tumor, that tumor may not perfectly model the tumor in humans. Diabetes in mouse might not be the same... like the model they make."
"This situation where like you'll pass the mouse phase, but then you fail at the human phase. That's not a rare occurence?"
"Not rare o at all, it's probably the opposite."

With all this said, studies based on mouse models are still pieces of evidence - not to be completely dismissed whenever we don't like their findings. But, we should try and investigate the specifics of *why* a particular mouse model wouldn't be appropriate for emulating humans. For example specific differences in physiology.

"*One of the easiest different to point out is just that their lifetimes are shorter. So… they mature faster. Right, so, I'm just looking for easy differences to spot between mouse and human ... in my old lab I was doing some retinal development research, like studying how the eye develops, but like, somehow it's kind of a weird model to use because mice are born blind… And then like humans are not… so that's kind of odd. These are just some things you'd want to start to think about when you're thinking is this a good model to use of humans*."

Let's say it's a typical Saturday morning, you've just made your coffee and are sitting down to read a paper like this one and you see the words "high fat diet induced obesity." "High Fat diets" are commonly used to induce obesity in animals for studies trying to see if they can make some metabolic ameliorations to the animals via some intervention. But *you* are considering doing a keto diet to lose some weight, and you think "*If a high fat diet is a reliable way to produce obesity in rodents… Why would I want to do a high fat keto diet?"* However, we should first investigate if there are some

specific metabolic differences between rodents and humans.

The high-fat diet for the mice used in this paper, D12492, is 20% protein, 60% fat and 20% carbohydrate. An actual ketogenic diet for humans would need to be restricted to around 10% or even 5% carbohydrate, but at 20% of calories coming from carbohydrate, this rodent chow is actually a relatively low carb diet for a human.

It's thought that most of the weight loss magic from a keto or low carb diet comes from lowering insulin and entering ketosis. However, rodents don't enter ketosis as easily as humans. According to Dr. Benjamin Bikman, in rodent experiments, without calorie restriction, to get them into ketosis, you need to reduce their diet down to just 1% carbohydrate, 9% protein and 90% fat. Even a diet that is 95% fat barely rodents gets rodents into ketosis.[R,R2] By the way, a 95% fat diet would be like an entire cup of butter and about 80g or 8 thin slices of bacon - but any more bacon than that would be too much protein.

Simply put, the amount of carb restriction that qualifies as low carb or keto for a human does not qualify for a rodent. These kinda specific differences should be acknowledged when using rodents as models for humans.

Let's move on to my next point: Food vs. Compounds in food - We'll start with chocolate. In his book "Doctoring Medicine," Dr. Malcolm Kendrick talks about a headline he saw saying "*Chemicals found within chocolate protect against heart disease.*" He explains that, according to the research, "*catechins and procyanidins, found in dark chocolate, inhibit the enzyme Angiotensin Converting Enzyme (ACE).[R] When ACE is blocked, blood pressure drops."* This is actually how blood pressure lowering drugs work, so it makes for compelling reasoning behind a compelling headline.

The only catch is that there wasn't any actual clinical effect… while dark chocolate did result in an 18% drop in ACE activity… there was no actual

drop in blood pressure in those taking cocoa extract.

Another example is the idea that a compound in such and such food has been found to cause disease, so that food itself must cause disease. For example, there is the idea that heterocyclic amines in cooked meat cause cancer. However, the studies finding that these heterocyclic amines are cancerous were giving rodents amounts of HCAs equivalent to 1000 to 100,000 times the normal amount consumed by humans. As this paper says, "*Comparison of the carcinogenic dose in rodents and the actual human daily intake suggests that the latter is definitely too low for cancer production to be explicable in terms of HCAs alone."*[R]

One last example is red wine - you've probably heard that it protects against heart disease. This review article from the Journal of Cardiovascular Disease Research discusses the quote "*accumulating evidence that suggests that red wine possesses a diverse range of biological actions and may be beneficial in the prevention of CVD.*" However, if we look at the references, most of them are looking at *compounds within red wine* - namely polyphenols and resveratrol. One study found that the rat equivalent of one glass of red wine worth of polyphenols had beneficial effects against heart disease. Then again, does that mean a glass of red wine itself with its 200mg of polyphenols and 10000mg of alcohol prevents heart disease in *humans*?

By the way, the compound in red wine resveratrol has gained a lot of attention for its promising anti aging effects. However, one of the researchers investigating this compound has said that, in order to get the anti aging benefits, "*the sad news is you'd have to drink about 1000 bottles a day, which I don't recommend.*"

In any case, the point is: claims like "such and such food prevents or cause disease" are very different from claims like "*compounds* in such and such food prevent or cause disease."

My next point (6) on what to consider when evaluating pieces of evidence, is why and from where certain ideas arose. For example,
why did people think to start looking at red wine to see if it benefitted heart disease? Well, sometime around 1991, people were trying to make sense of the fact that the French ate very large amounts of saturated fat yet had low rates of heart disease. One idea was that this so called "French Paradox" could be explained by France's high red wine consumption.

This is called an *ad-hoc* hypothesis - a hypothesis added to a theory in order to save it from being falsified. In this case, because saturated fat and cholesterol must cause heart disease, it was assumed that there *must* be some protective factor in the French diet. Put another way the logic is "let's construct a *new* hypothesis (red wine prevents heart disease) to explain data that does not support our initial hypothesis (fat causes heart disease)." Now, just because a hypothesis is ad-hoc, doesn't mean it's wrong, but it deserves scrutiny.

And what really deserves scrutiny are things that go quickly from the idea stage to clinical practice. An example provided in Dr. Malcolm Kendrick's book "Doctoring Data," is how a good idea arguably killed millions of people. From the early 1900's for about 50 years or so, it was thought that strict bed rest for about six weeks was the appropriate prescription for someone who had just had a heart attack. It sort of makes sense, after such a traumatic event it sounds like it would be best to let the heart rest and keep exertion minimal so as not to stress the heart. And I really mean minimal - to quote Thomas Lewis, a prominent physician from the 1930's: "*The patient is to be guarded by day and night nursing and helped in every way to avoid voluntary movement, or effort.*"

So what exactly is wrong with bed rest?
As Dr. Kendrick explains, First, lying in bed stationary for six weeks means that there is a very good chance of developing a deep vein thrombosis

(DVT) in the legs. A high percentage of these break off, travel to the lungs, and block the arteries in the lungs causing a pulmonary embolus (PE) – an event with a very high mortality rate. In fact, even a several hour plane flight carries this risk. In 1977, the term "Traveler's Thrombosis" was coined for people developing deep vein thrombosis on flights. Low oxygen, low humidity , and low cabin pressure at high elevations plus sitting in a chair for several hours is a good recipe for thrombosis.

The second issue with bed rest is that without any exercise, and especially after a heart attack, the heart degenerates very rapidly. It becomes weaker, and deadly heart rhythms develop, so you are far more likely to die of ventricular fibrillation. Dr. Kendrick estimates that hundreds of thousands of people were dying from bed rest each year, and this approach wasn't being questioned until the mid-1950's. So where did the idea come from?

Well, in 1912 Dr James Herrick of Chicago published an article titled 'Clinical features of sudden obstruction of the coronary arteries,' Where he essentially described the first documented heart attack. In that article, he stated, '*The importance of absolute rest in bed for several days is clear' postinfarction…*" To quote Dr. Kendrick "*...Herrick managed to describe the world's first heart attack in 1912 and then, without missing a beat, he immediately knew that strict bed rest was an essential form of treatment – for a condition never before described."*

Another example of seemingly good ideas harming people is that of Hormone Replacement Therapy. It had been recognised that women under 60 had far lower rates of heart disease than men of that age. For various reasons it became accepted that female sex hormones were what was protective against heart disease. According to Dr. Kendrick, one key piece of evidence amidst the limited evidence for this concept was a 1987 observational study - observational studies are widely accepted to be very weak pieces of evidence in general.

Yet, the idea was still accepted so well, in fact, that replacing the declining female sex hormones in menopausal women became incorporated into the 1992 American College of Physicians' guidelines. In the US, failure to prescribe hormone replacement therapy for menopausal women was akin to medical malpractice.

Later, a randomized primary prevention trial using hormone replacement therapy involving nearly 17,000 women published its results in JAMA in 2002. This trial found that *"...there was a 29% increase in coronary heart disease risk, including an 18% risk of coronary heart disease mortality and a 32% increase in risk of nonfatal myocardial infarction."*
I wonder how many women would have accepted hormone replacement therapy if they knew the practice originated from a sorta good idea paired with a weak observational study.

My very last point of what to consider when analyzing evidence for this or that claim... is the circular situation where existing ideas can influence research in a way that biases the research towards acting as evidence for that idea. So… what do I mean by that? Dave Feldman who we spoke with earlier has a good example of what I'm talking about:

"One of my problems with cholesterol research is it often lumps soft endpoints with hard endpoints and this can be a bit of a challenge because our existing opinion on cholesterol can make a difference in how the data is recorded. So, to give you an example on the patient side, let's say that you and I have a steak dinner tonight and then afterwards we both go our separate ways. But, each of that night experiences a thirty minute prolonged chest pain. And for me, this is the warning I had been hearing about from my doctor this whole time. After all, he's been telling me about my high cholesterol and I need to do something about it or I'm going to have a heart attack. Sure enough when I go to the hospital, it does in fact prove true that I did have a non-fatal myocardial infarction. So all of that data then becomes record. You on the other hand, did also have a

myocardial infarction, but the difference is because your cholesterol has been low, you went ahead and took a TUMS because you felt like it was heartburn, went to sleep, and that data never ended up anywhere inside of the hospital record. That's a big deal is both of us are already part of a study. But this also plays into the hands of medical professionals, because after all, if they would likewise have the same opinion that high LDL is a risk factor just the same as something like C-Reactive Protein, then that may be relevant for a judgement call on the margins. Certainly a lot of heart attacks that you survive are not on the margins. And most medical professionals would agree. But, some are on the margins and that's a soft endpoint. I like hard endpoints like mortality because they're pretty easy to diagnose. Everyone knows whether you lived or died, and as such, that data is a lot stronger to look at in the long run."

...And, there are several studies that use the subjective, soft endpoint Dave is talking about here.

So for now, this concludes my points on what to keep in mind when trying determine if a piece of evidence behind this or that health claim is strong or not. I realize some of this can be confusing or disheartening and that nobody has time to dig through 50 research papers just to decide what to eat for breakfast... but for those of you who enjoy digging into things to deeper understand what makes us healthy and why, hopefully these points serve as tools to help you analyze articles and research more effectively.