VIDEO_ Diet Doctor Podcast with Andrew Mente (Episode 15)

Dr. Bret Scher: Welcome to the DietDoctor podcast with Dr. Bret Scher. Today I'm joined by Prof. Andrew Mente. Now prof Mente has a PhD in epidemiology from the University of Toronto, he's done his postdoc work in cardiovascular epidemiology from McMaster University and he's an associate professor of health research methods at McMaster University and most recently he was one of the co-investigators on the lifestyle and the nutritional side of the PURE study.

Now PURE is this enormous study over five continents, 18 different countries, over 135,000 different individuals, that has had some pretty profound research evidence as it comes to saturated fats, cholesterol fat in general and their implication on overall mortality. It has a number of data on salt intake and mortality. And a lot of it is contrary to conventional wisdom and guidelines.

Now all that being said, this is an epidemiological study and we definitely talk about the strengths and benefits of epidemiology versus randomized controlled trial and he is a good perspective on how we really need both to further research and affect policy. So there's a lot of data here going over the PURE study and it has some pretty profound impacts on the way we should make recommendations and how we should see older recommendations and their falling.

So I hope you enjoy this interview with Prof. Andrew Mente and learn a lot about the PURE study and understand how we can use that data in our daily lives. Prof. Andrew Mente thank you so much for joining me on the DietDoctor podcast.

Prof. Andrew Mente: It's a pleasure to be here.

Bret: Now you have really become known as the PURE guy because of the PURE study and all the data that's come out of that and how that'S impacted how we see salt how we see fat and carbohydrates and how we see lipid biomarkers, three huge concepts that we've kind of been misled on. So this has been pretty revolutionary data that you've come up with.

Andrew: Yes well the unique part of PURE is that it's a large prospective epidemiological study, but it's also a global study so it covers five continents of the world. And as a result we captured broad patterns of diet globally from across a broad

range of intake, both very low levels and very high levels of individual nutrients in foods and dietary patterns.

That's important because that allows us to assess shapes of relationships between dietary variables and health outcomes. Which has never been characterized before with any high degree of statistical precision.

Bret: Yes it's such an interesting part when you talk about nutritional research and it is complicated, let's be honest, it's very hard to do, whether you talk about randomized controlled trials and observational study, a study in one type of population or a study in a large swath of a population, and each have their benefits and their drawbacks. So when you look at analyzing the data from the PURE study, tell us what you think some of the strengths and weaknesses are in that type of a study.

Andrew: Sure, obviously observational studies, we assess relationships or associations between variables, diet and health outcomes, so you don't prove causation with any one observational study, but what you do is you look for a coherent pattern of information from observational studies, both looking at foods or nutrients versus intermediate risk markers for cardiovascular disease and actual outcomes.

Of course with a large randomized controlled trials we can better assess causative effects. The problem with large randomized trials is they're very difficult to conduct with diet and it's very difficult for people to sustain a particular diet for a long term. And so there's a challenge there.

On the other hand when you have weak effects, it's harder to assess weak effects in observational studies, because you don't know if the result is true or due to residual confounding. So we tend to think of different designs as complementing one another.

So not one design being the best considering feasibility and also, you know, what is the cleanest design. But using different designs complementary to one another and capitalizing on the strengths of each is the ideal way to go forward.

Bret: Yeah, and then the harder question is how to take the data you have and incorporate it into guidelines for the entire country or the entire world to try and follow? And when is that data strong enough to support a statement that this is the way to eat? And so far it seems like we've been a little misled in that stand, haven't we?

Andrew: Absolutely, so we take the issue with the fats and carbs for instance. So the current dietary guidelines go back obviously to where that was conducted in the 50s that led to the adoption of a low-fat diet which we know it really hasn't panned out

and populations have gotten fatter and diabetes rates tripled, coinciding with the introduction of the guidelines.

So our data suggest that the conventional way of thinking of diet focusing on higher intake of carbohydrates may actually backfire, which supports what has actually happened. And so higher carb intake, and remember many parts of the world consume very high amounts of carbohydrates, low and middle income countries, and largely it's refined carbohydrates and added sugar. And we find that higher carb is related to more cardiovascular events and mortality particularly all-cause mortality, whereas for fats we see the opposite.

We see higher fat intake related to lower risk of mortality and saturated fat related to lower risk of stroke. So this kind of challenges conventional wisdom on diet, but it is consistent with the trials, because you look at the randomized trials that replaced saturated fat with polyunsaturated fat, that haven't really panned out. Largely neutral effects. And other observational studies too have shown neutrality looking at relationship with saturated fat and clinical outcomes. So our findings, if anything, are supportive of previous studies.

Bret: Let's jump into the study a little bit. So you mentioned 18 countries, 5 different continents, over 135,000 individuals and what was the timeframe that you followed them?

Andrew: So for our papers that came out last year in the Lancet it was eight years of follow-up. This year we had a paper that came out on dairy that was nine years of follow-up, because the follow-up is ongoing and PURE is still during the follow-up and we hope to follow people for at least another 5 to 10 years.

Bret: So you mentioned the data on the saturated fats and carbohydrates. So with a higher carbohydrate diet starting at 68% of the calories there was an increased risk of all-cause mortality. Now we need to talk about hazard ratio, because you know we're quick to point out that smoking with a hazard ratio of 3 1/2 is a dramatic change.

The red meat leading to colon cancer at 1.17 is a small hazard ratio. So the hazard ratio here was small at 1.17 and 1.28. So how do you help us interpret that in terms of it was a fact because of how many patients there were, but yet the hazard ratio was small and it's sort of against what the guidelines say. So how do you incorporate all that into how we should interpret that data?

Andrew: Dietary effects are weak. If you look at the collective literature whether it's nutrients or foods, largely effects are weak up to the degree of like 10% change in risk, relative risk change. So that's a very weak effect, unlike smoking, where you see a 20 fold increase in risk of smoking versus lung cancer.

So that's a challenge with diet, studying diet in observational studies, but if anything, you look at the data of other cohort studies and if you focus on the studies that looked at carbohydrates versus mortality as a percent of energy, you also there see that higher carb intake shows an increase in the risk of mortality.

Now some studies have looked at calculated diet scores or carbohydrates scores and so what goes into that is different coating of our carbohydrate foods. So you can select almost any food you want to go into a carbohydrate score and you'll get different results, but the studies that looked at percent of energy from carbs, you see a positive association with mortality.

Now there aren't that many free living populations with very low carbohydrate intake. So don't misread me, I'm not saying that going as low as possible would be beneficial because that has yet to be demonstrated but certainly appears that there is an optimal range between 50% to 55% of energy from carbs that appears to be associated with lowest risk. At the low-end it's a little more murky, we really don't know.

Bret: And then the problem comes in of the quality of the food that you're eating. So there's really no control for the quality of carbs, because it's free living people like you said, in some of the poor countries, underdeveloped countries, it's going to be a lot of refined carbohydrates and refined grains.

So not a surprise that a higher level of carbohydrate increased mortality risk. Now what maybe was a surprise that the higher level of fat intake decreased mortality risk, I think that's where the real headline is, that is so counter to what we're being told. And now you broke that up into monounsaturated fats, polyunsaturated fats and saturated fats in terms of their mortality risk; so tell us how those varied.

Andrew: Yes, so first of all each individual type of fat, saturated, mono and polyunsaturated were associated with lower risk of mortality, so they all directionally went toward protection. Now with looking at saturated fat we found-- because remember we're covering low and middle income countries here where saturated fat in many parts of the world is very low, and so saturated fat going up to about 13% of energy was associated with lower risk of mortality.

Now what this suggests is that when you go to low levels below 10% and further do you actually see the increase in mortality? Which is actually what the guidelines recommend; to go to those lower-levels. Now we are not saying that our data supports consuming 20% or 25% of energy from saturated fat, only because that's not captured by the natural distribution of saturated fat in free living populations.

And certainly some societies you see consumed 3 to 4 decades ago much higher amount of saturated fat. So our data is not capturing that high level of saturated fat,

but up to about 13% or 14% of energy we see a lower risk of mortality compared to people consuming lower amounts of saturated fat.

Bret: Now interestingly the mortality also for fat in general and saturated fat was neutral for cardiovascular mortality and beneficial for all-cause and non-cardiovascular mortality. I mean is that one other surprise or is it what you would expect to see?

Andrew: Well we look at the randomized trials, at Cochrane review by Hooper in 2015 of randomized trials, where they replaced saturated fat with polyunsaturated fat, again a direct test of the diet heart hypothesis, the summary estimates were neutral. So our results were consistent with that.

The Women's Health Initiative trial which compared the low-fat diet to a higher fat diet again found no significant change in risk for cardiovascular events and mortality. So that was another large study, cost half $1 billion. So if anything our results are consistent with that.

Now if you look at cardiovascular disease mortality and non-cardiovascular mortality, directionally we did see that different types of fats were beneficial, although it wasn't statistically significant but directionally. And in carbs directionally was harmful versus cardiovascular death and non-cardiovascular death. It was the nonfatal events were as large and neutral.

Bret: Now are we able to breakdown the non-cardiovascular deaths anymore, whether it's cancer, infection or the various different causes?

Andrew: Well the main non-CVD causes right now in PURE are cancer and respiratory mortality. So those two, those were the main drivers of it. Now of course PURE is a large cohort that is still ongoing, so we are following people up.

We don't have enough event rates right now to characterize cancer or respiratory events alone or individual types of cancer. But as the cohort gets older the event rates will pick up and we'll have more events. So that's why it's very important in PURE to do the follow-up over the next 10 years than we can assess individual types of cancer and diet.

Bret: Right, now you with a study like this that goes against our guidelines and goes against what you can say that the most common dogma is now, would you say this is strong enough evidence to say things have to change now? Or do you think this is sort of one blip on the screen and we need more to come in order to affect policy and make a change?

Andrew: Well, I think collectively looking at our data and other studies as well we could relax a bit on the threshold for saturated fat and given the population on average in the US for instance, the average intake of saturated fat is about 12% of energy. So it's only slightly above the WHO recommendation of 10%. So it's not like we have a saturated fat emergency, so I would say that's fine.

What we're consuming else, fine, we could even consume a little bit more. We're not saying consume unlimited amounts, we need data for that still, but what we consume now appears to be right and we don't have to put in stringent cutoffs to get people to lower their saturated fat.

Bret: Now also there's concern about-- like we talked about earlier, data quality, so is this mostly from food frequency questionnaires that people filled out and how often were they filling that out and is there any concern of reliability for that?

Andrew: Yes, so the food frequency questionnaires were extensively validated and developed specifically for each region and there were long-frequency questionnaires, so captured detailed aspects of diet. So for instance we have 150 items measuring diet in a particular population. So that's a very in-depth analysis into diet.

Now the downside with these questionnaires of course is random measurement error. And so that adds noise but that more dilutes associations toward the null, and that is a factor in every epidemiological study. So it is the best tool we have at the moment for large epidemiological studies and that's what we use.

Again that's why I say complementing randomized trials, focusing on risk markers would be optimal. So the major strength however is the fact that we cover again a broad range of intake across different parts of the world, again characterizing those extreme ranges as much as they are represented by human consumption and that's really where the advantage of PURE is.

Bret: Now you mentioned comparing the trials to randomized trials using risk markers. And that's one of the parts of PURE that I really enjoyed most, was looking at the risk markers. So you looked at... as they increase carbs their LDL decreased and so did their HDL and their triglyceride to HDL ratio increased and their ApoB went down a little bit. So their ApoB to ApoA ratio also went down.

So then you looked at outcome data in terms of what these markers all met. And what did you find in terms of the difference between LDL cholesterol, the ApoB to ApoA...? Share that data with us.

Andrew: Yeah, so as you said looking at the risk markers, saturated fat had an increase in LDL with higher saturated fat, but the effects on the other lipid markers

were largely beneficial. So when you look at the ratio of total cholesterol to HDL, which is a stronger risk marker of future cardiovascular disease, that's just a potential beneficial effect, because the ratio went down and we know that that risk marker is a better predictor of future events.

And when you look at ApoB to ApoA, which remember in INTERHEART and INTERSTROKE, two large international studies, was the strongest lipid predictor of heart attacks and stroke, we found that the ratio goes down with higher saturated fat, which again suggests a beneficial effect since that is the strongest risk marker and that goes down with higher saturated fat.

And then what we did is we modeled... we said okay assuming we don't have any data on clinical events, let's model and use the lipid markers to project what the effects of diet on cardiovascular risk would be. And then we did that, we modeled using LDL and we found a positive association as you would expect.

After all saturated fat is positively associated with LDL. But then when we map that versus actual events, we found that LDL was a poor predictive marker of future events when you look at the observed associations. On the other hand ApoB to ApoA ratio was much better at projecting the effects of diet on health outcomes.

So this suggests that if we focus on LDL we may be largely misinforming diet for populations. ApoB to ApoA ratio, which is a measure of small dense LDL particles that are more atherogenic than LDL appears to be the much better predictive marker to project the effects of diet on health outcomes.

Bret: Are you able to quantify that to give us some sense... like how much better, how much more associated it was? Or is that data sort of hard to quantify that way?

Andrew: What we did is we calculated the I-squared value, which generally assesses the degree to which the actual estimates agree with one another. And so when you calculate that statistic you see that the estimates from the ApoB to ApoA ratio, projected estimates versus the actual observed estimates agreed and it was a good agreement.

Whereas with LDL they diverged in opposite directions. So the projected estimates showed an increase in risk, whereas the actual effects of saturated fat on the events go down slightly. So they diverged in different directions. It would suggest that LDL is not very good for projecting dietary effects. It may be very good for projecting statin effects on health outcomes, but not for diet.

Bret: That's so worth repeating; that the projected effect would be that the risk would go up and the observed effect was that it actually went down.

Andrew: That's right.

Bret: It was completely discordant. And that calls into question every single dietary study that's looked at LDL because the presumption is if the LDL level goes down, this diet is therefore beneficial and protective. And you really don't have to look any further than the sort of the older studies that looked at giving polyunsaturated fatty acid oils, seed oils, which showed LDL went down and that's what was publicized, but then a re-examination of the data showed that mortality actually went up, but that's not been talked about very much.

So my hope is that this study would cause just a huge snowball effect of people realizing that LDL-C is not the marker we should be following. Yet I don't feel like I've heard enough about that in the media and in the scientific circles. Is that just because old dogma dies hard and people aren't ready to hear it? Why do you think that's the case?

Andrew: Well, you know, LDLs is considered by the-- You're conventionally thinking of it as an infallible marker.

Bret: Right.

Andrew: And so people think of it in a very reductionist way, many scientists. So they figured that, if anything, that adversely affects LDL, it must be harmful. And you could ignore all the other biomarkers. But diet is much more complicated than that. So you take foods, natural sources of saturated fat, that contain saturated fat but they also contain monounsaturated fat. They also contain protein, they contain vitamin Bs, including B12.

They contain zinc and magnesium. So this is all thrown out and we treat food almost like it's a single nutrient saturated fat that's infused into our veins. And that's used to project the effects and really is an absurd way of thinking if you really think about it deeply. So for diet we have to think much more multidimensionally than that.

Bret: Absolutely, I think that's a great statement, because we do like reductionist thinking, we do like to try and make things overly simplistic and this is the mess we get into when we do that. I know your study did not specifically look at a low-carb or ketogenic diet, but in those circles the main concern is, "What about the LDL?" The LDL goes up and that's why doctors are hesitant to prescribe it, that's why a number of guidelines will not include it because of that concern and yet looking at this data if the ApoB to ApoA ratio stays the same or gets better it shouldn't matter what the LDL does.

So I think that's why this evidence is so powerful and we need to be seeing this from the rooftops more to say we need to reevaluate dietary changes and their effects on cholesterol. And quick, to point that out... It may not be the same for drugs, it may not be the same for genetics, but for dietary changes that's what we need to look at.

Andrew: Absolutely yes and we need to study a much wider range. So you look at the PURE study because the level of carbohydrates and fats only cover a particular range. That's where the randomized trials are needed... like Virta for the work that Dr. Hallberg is doing to capture the lower end of the carb distribution.

So it's very important to look at that to see what the effect on the risk markers here are for very low-carb intake. Which PURE does not capture, because it's largely representing parts of the world that consume from moderate to high carb. So that's why Sarah's work is very important.

Bret: Right and since you brought Sarah's work at Virta Health, you know, at their one year data mark the LDL-C went up by about 10% with no change in their ApoB and their HDL went up, so their ApoB to ApoA ratio improved. And so based on this that is a net benefit for mortality and that's what we care about.

Andrew: That's right.

Bret: Yeah, it's so fascinating. The tide is changing maybe a little too slowly, but it is certainly changing.

Andrew: Yes.

Bret: Now this study also had other aspects to it. So the next one was increasing fruit, vegetable and legume consumption decreased mortality starting at three servings per day, with really no difference between the three and eight servings per day. Now I am curious about that, because fruits, vegetables, legumes, they frequently do get bunch together.

And I think it's a sign of somebody maybe being a little more health conscious, because that's what we're told as a healthy way of eating, but was there any parsing out individually of how vegetables are different than fruits and different than legumes individually?

Andrew: Yes, absolutely. So the beneficial effect was largely driven by fresh fruit, raw vegetables and legumes. It's the cooked vegetables, when you put that end into the equation, that's when you start to drown out the beneficial effect.

Bret: Interesting.

Andrew: Yes. So if you look at versus CVD and also looking versus mortality, fruit, raw vegetables and legumes were beneficial, but when you look at cooked vegetables that's when you see no effect on CVD and maybe even directionally maybe even a harmful effect. So maybe cooking methods and what we add to food while cooking may be an important factor.

Bret: Yes, I wonder if this is because they're cooking in Omega six seed oils or they're cooking in like heavy sugary sauces or something. It certainly makes you wonder because that's not what I would expect. So of course everybody's got their bias. When you see something you don't expect you want to find out what makes it wrong and that's part of the trouble we get into and I need to catch myself for doing that.

Because interesting, with increased fruit intake, if somebody was diabetic or had metabolic disease, you would think that would have a deleterious effect, but over the whole sample, fruit intake was beneficial.

Andrew: Yes, well we have to also remember that PURE represents general population, people living in communities, so it may very well be different for diabetics. The diabetics may need to restrict the very high sugary or high G.I. type of fruit in their diet. But for general populations fruit was largely beneficial. So I guess it depends on the population that you are studying and diabetics may be different.

Bret: Yeah and I think is important to point out for the general population, fruit, vegetables, legumes can certainly be part of a very healthy diet but in certain populations we need to measure their effects specifically on that individual.

Andrew: Yes indeed.

Bret: And then the other part of the study was salt. So salt and saturated fats have to be the two most misunderstood and misrepresented components of our food intake. What you saw from a salt intake was that a higher risk below 3 g of sodium and a higher risk at above 6 g of sodium. So first before we get into the details tell me the difference between grams of sodium and grams of salt, just so we're all speaking the same language here.

Andrew: Yes so 1 g of sodium is 2.5 g of table salt. So the WHO recommendation is 2 g of sodium which is 5 g of table salt or 1 teaspoon.

Bret: One teaspoon! Tiny amount.

Andrew: Yes, very difficult for most people to consume in the short term let alone the long-term and that's the recommendation.

Bret: Yeah, so the recommendation I think is less than 2.4 g, or is it less than 2 g?

Andrew: Now depends on the guidelines. WHO is 2 g, the US dietary guidelines 2.4, for high risk population the American Heart Association recommends less than 1.5 g per day, which is only 0.7 teaspoons of salt per day, very low amount.

Bret: And there was a study showing only less than 3% of the population adhered to the less than 2 g per day.

Andrew: Correct, and when you adjust for random error, it's well below 1%. And when you look at people who meet the sodium and potassium recommendation it's only 0.001% of the population who meets the recommendation. Now what we currently recommend is what nobody eats.

Bret: Right, and this completely seems undoable. So where does recommendation come from?

Andrew: Well, the entire field hinges on an assumed benefit considering the effect of sodium and blood pressure. So given that sodium is associated with higher blood pressure, it's assumed that this will translate into a cardiovascular benefit if we lower sodium. Now of course this assumes that sodium affects only blood pressure and has no other effects on any other biological systems in the body.

But because sodium is an essential nutrient it doesn't quite work out that way. So we agree that at high levels you get toxicity and increase in blood pressure, but at low levels you get deficiency. And so what that does is it activates certain mechanisms that are built into our bodies since salt is an essential nutrient. So you get renin angiotensin system activation at low levels.

And this has been shown repeatedly in intervention trials. And so you have dual competing mechanisms, which is consistent with an essential nutrient. Toxicity at high levels, deficiency at low levels, sweet spot in the middle. And our findings reaffirm that and other studies as well reaffirm that.

There is not one single study ever that has shown that low-sodium at currently recommended levels is better than average sodium, that sweet spot of 3 to 5 g per day, versus cardiovascular events and mortality. High levels above 5 g per day, certainly, we should get those populations down to moderate levels, but there's absolutely no evidence to support low levels versus moderate levels and yet that's what we currently recommend again based on an assumed benefit, looking at blood pressure.

Bret: Right, an assumed benefit and a lot of people will quote the DASH study, thinking that this was the end-all be-all conclusive study on salt intake, that the DASH study really was the moving force to inform the guidelines. But tell us a little bit

about the DASH study and maybe why that wasn't such a good idea to use that to base our guidelines.

Andrew: Well, the DASH study was a proof of concept study, it was an excellent study in that it was a randomized trial and people were provided the food during a 30 day period. So it was a feeding study. So it was an excellent study in its own right in that way. However the problem is how we interpret the data from PURE-- sorry from DASH, how we interpret the data from DASH to make dietary recommendations for cardiovascular disease prevention.

Because there are a number of limitations we have to point out. One is that we have to remember that this was largely a salt sensitive group of people, a lot of hypertensives and pre-hypertensives, and we also need to remember that potassium intake was low at baseline.

So when you put someone on a very low potassium diet, lowering or changing their blood pressure will result in changes-- changing their sodium will result in changes in blood pressure. But when you give people higher amounts of potassium, put them on an all-around healthy diet, like the DASH diet, that contains many of high potassium foods, then the effects of sodium will be largely mitigated.

So that's what DASH found. That when we consume a low potassium diet you see large changes in blood pressure, which doesn't surprise really anyone given that, but when you give them a high potassium diet then sodium becomes less important and so the important point is DASH is only 30 days. So we look at the long-term effects, we need studies with longer follow-up to look at the effects in the long-term.

So some studies like TOPP have looked at longer term follow-up. TOPP originally was designed to look at blood pressure, so people were followed up for a period of 36 months, but what TOPP found was that people initially... they never reached the 1.8 g per day target, they lowered their sodium a little bit to down to 2.5 g per day, but then by around a year they migrated back to their original sodium intake.

And so even though they followed people up over time, we don't even know what people were eating during the course of the extended follow-up. But there's every reason to believe they were not even following the low-sodium recommendation.

So we really don't have any data from randomized trials, so we have to look at the data on long-term clinical events and that's where the cohort studies come into play and there's consistency across a dozen cohort studies showing low-sodium is either associated to harm versus moderate sodium or there's no change in risk. But no study is suggesting or showing a lower risk with low-sodium compared to average intake.

Bret: Yeah, and that's what so frustrating about this whole concept is that it's one thing to make a recommendation that has a neutral effect. It's another thing to make an official recommendation that actually might put you in harm's way and that's what this seems to suggest and that's what happened with the carbohydrate recommendation that sparked our diabetes and obesity crisis, and that's happened with the salt as well.

The official recommendation based on your studies says you should be following a sodium intake that is going to worsen your health. Why is there not a public outcry about this? I mean that's unbelievable.

Andrew: Yes, so science works that way in that when we have a position for a long time, change takes time. It's always been like that and so this is no different. And so eventually in the long-term the truth does win out. And so the only thing we can do is just keep publishing our science and the truth eventually works itself out.

Bret: The other important point I want to go back to about the DASH trial that we don't hear much about is the difference between the high and low sodium diet-- sorry, high and low potassium diets and how that affected blood pressure response to sodium, that's definitely worth repeating. So on the low potassium diet there was a larger blood pressure effect with increase in sodium. On the higher potassium diet was essentially no blood pressure impact on increase in sodium or a very small amount.

Andrew: That's correct.

Bret: Now when we say, what examples of low and high potassium diets, when I think of a high potassium diet I think of fresh vegetables, when I think of a low potassium diet I think of potato chips and pretzels and packaged foods. And so I think where the salt is coming from and what type of diet you're having clearly makes a huge impact.

So as a supplies, the low-carb community, if someone is eating their broccoli and their cauliflower and their spinach and they're putting their Himalayan salt on it and having it with their know, chicken, meat, fish, eggs and cheese, that's a perfectly reasonable diet where you can be having the higher end of sodium and based on the DASH study you would say would have no effect. Is that a fair statement?

Andrew: Yeah absolutely, so you need to consider the overall pattern of the diet, which is what you're saying, so that needs to be taken to account as well. So it's not only necessarily a potassium effect, but also potassium is a marker of the quality of the diet. So if you have a higher potassium diet you're consuming an all-around balanced healthy diet with plenty of foods containing high potassium; fruits, vegetables, dairy and nuts and seeds for instance, all are potassium foods.

So we have to consider within the context of the dietary pattern. And DASH is important in that respect because it shows that salt sensitivity is not an immutable trait. You can mitigate it by eating an all-around healthy diet. And when you do that we find that salt becomes less important. So the messages just concentrate on consuming an all-around healthy diet and you don't need to be worried about individual nutrients like salt and saturated fat.

Bret: Yeah, and the other component about salt I want to bring up was you also broke it down between those with hypertension and those without hypertension. And there was a difference between the low-end and the high-end. So for both groups, whether you had hypertension or not, the risk increased at the low-end of sodium intake below 3 g.

But at the higher end if you didn't have hypertension then that risk was mitigated, the risk did not go up as much. So would that suggest there may not be much of an upper limit if you don't already have hypertension?

Andrew: That's right, that's what that data suggests. So if you don't have hypertension there's no increase in risk even at the high-end. So if we take a cautious approach, would say well, still that's aimed to get people in the middle, which is where most people are anyway. But the people who are hypertensives, we did see an increased risk.

So this would suggest that rather than a population wide strategy, best we target people with hypertension who also consume high amounts of sodium exceeding 5 g per day and get them down to moderate levels. At the low-end, what's interesting, we see an increased risk, as you said, irrespective of blood pressure.

So whether you have high blood pressure or normal blood pressure, you still see the increased risk at the low-end versus clinical events, cardiovascular disease and mortality. And what that suggests is another mechanisms that play here. And again consistent with other data, showing activation of the renin angiotensin system, which we know is vascular damaging.

And you get exponential rise in these hormones with low levels of sodium and therefore you see the consistent results across different subpopulations. It's been shown repeatedly in people with hypertension and without hypertension, people with diabetes and without diabetes and people with vascular disease and without vascular disease. It's a consistent finding.

Bret: How about congestive heart failure? Where are the data on that?

Andrew: So congestive heart failure... there was one study looking at data from the EPIC-Norfolk that found in healthy people there was a lower risk of heart failure with moderate sodium compared to low-sodium. So even versus heart failure as a primary outcome, in healthy people we see a beneficial effect with moderate sodium rather than with low-sodium.

And looking at heart failure patients there are some trials that are ongoing right now looking at low-sodium versus average sodium in heart failure patients so we will have to see what the results are for that.

Bret: I think it's fairly well accepted that heart failure exacerbations and hospitalizations increase with increased sodium intake in severe poorly controlled heart failure patients. I have to re-examine whether it's a mortality effect or not or more of a symptom and hospitalization effect.

And then at what levels you break that down, at what level of renin angiotensin activation because most of these people are on ACE inhibitors or ARBs, which are really angiotensin blockers, there's definitely a lot of other factors to incorporate for the heart failure patients.

Andrew: That's right, that's one of the bigger challenges with heart failure patients is that they are on all these different medications. So we need more data on what the effects are for heart failure. Certainly there is compelling data that again high amounts of sodium, exceeding 5 g per day is certainly harmful. So the question is whether very low amounts is better than moderate levels. Really that's the research question and we need more data on that.

Bret: Well, this has been a great discussion of the PURE study and I mean for one study to upend our common wisdom in dietary guidelines for saturated fat, for salt and for lipid biomarkers is pretty remarkable. So I think you did a great job with the study and in representing the results and I hope there's more to come. I mean you said it is ongoing and there's more data coming. When can we expect the next installment? Do you know?

Andrew: Yes, so right now we're working on our other dietary papers. So obviously we collected using a long food frequency questionnaire, we're now looking at all the different types of foods versus cardiovascular events and mortality. So we want to spend the next two years to publish all these papers and then also one looking at the dietary pattern as a whole. That would be a key paper as well.

So this is what we are going to publish in the next year or two and also we'll do more dietary assessments during follow-up and that also helps improve the precision and accuracy of the estimates of diet and then continue the follow-up as much as we can

to look at effects on less studied outcomes like cancers and respiratory events and infectious disease as well.

Bret: Great... If people want to learn more about you and more about the PURE study where can you direct them to go?

Andrew: There is a website online. If you go to PHRI.ca there is a link that takes you to the PURE study. If you want to read up more on it, it's there.

Bret: Great, Prof. Andrew Mente thank you so much for joining me today.

Andrew: My pleasure.