Transcript: Episode 451

Danny Lennon: Hello, and welcome to another episode of Sigma Nutrition Radio. This is episode 451 of the podcast. My name is Danny Lennon and alongside me as usual is Dr. Alan Flanagan. How are you today, sir?

Alan Flanagan: That's got a good ring to it. I've gotta say.

Danny Lennon: Yes. You need to demand that you cannot be called "Alan" anymore and only "doctor", even by close friends.

Alan Flanagan: Exactly. And I can go to Florida and set up that cancer ranch I've always wanted to set up and give people greens juices, and really trade off my title.

Danny Lennon: Yeah. So when is the new weight loss book coming? I presume it's going to be imminent?

Alan Flanagan: Yeah. I was like "well, what comes after celery juice?" I was like maybe fennel juice, you know, because then you're getting people to do something really foul.

Danny Lennon: The worst tasting it is, hopefully the better, people really feel it's working then.

Alan Flanagan: Exactly. You need to suffer for sins, you know, health sins.

Danny Lennon: Yeah. But with that let's maybe just jump straight into this episode.

And today we're going to look at an area that has raised in previous episodes of the podcast. Most notably I think probably episode 375 of the podcast, where Alan and I discussed the whole topic of salt, sodium, and health. And within that, we talked about a number of things specifically on sodium of course, but then the relationship that sometimes gets brought up around potassium intake as well.

And so today we're going to focus in on potassium, but of course there's going to be mention of this interaction with sodium, and we're going to do that through the lens of a recently published study. So this was a study published just in July of 2022 in European Heart Journal. And it was a study using data from the EPIC-Norfolk study.

And we'll maybe give some context as to what this cohort actually is. It was published by a group based mainly out of the University of Amsterdam, the lab of professor Liffert Vogt, who has expertise in sodium homeostasis. And the lead author on this paper is Rosa Wouda. So this is a paper we'll link to in the show notes, if you want to go and read it in full.

But essentially this not only looks at potassium intake and impacts on blood pressure and then cardiovascular disease as an outcome. It also has some interesting questions that it tries to attempt to look at in terms of the influence of sex and the influence of sodium intake.

So we're going to walk through much of this paper specifically, but I think maybe as a good way to put some context to this, maybe I'll ask you Alan, to remind people of some of the things that we maybe had touched on in the sodium episode. Or for people who maybe didn't hear that episode, maybe catch him up to speed of when it comes to the impact of sodium intake, first of all, on things like blood pressure and cardiovascular disease; what were some of the overall conclusions we may come to? And then how does this

idea of potassium intake fit into that picture? And then any other relevant points that we may have touched on there that we should maybe open and refresh people's memory on?

Alan Flanagan: Yeah. So I think the top line to probably move from, as it relates to sodium and mainly cardiovascular disease is what we're typically interested, but there, there are associations with other disease endpoints, stomach cancer in particular cardiovascular disease is typically our focus.

There is a linear relationship between intake of sodium and increasing blood pressure. There are also age related increases in blood pressure in Western populations. Now, if you look at unacculturated populations or populations that are still living a relatively traditional subsistence farming lifestyle, and they're not adapted to the modernity of the society in which they live, and there are a number of examples around the world. You don't see age related rises in blood pressure and you typically see sodium or salt intakes of certainly less than three grams a day. They're very low. In some cases there is examples of no salt cultures.

So our mechanisms in the kidneys and the mechanisms that we have in the body are exquisitely and tightly adapted to conserving low intakes to preserve sodium status in the body.

In the context of relatively low habitual intakes in Western societies, industrialized societies, we have a range of factors that influence higher blood pressure. And one of them is obviously sodium. And we have, in addition to that relationship between sodium and blood pressure, we have a relationship between sodium and cardiovascular disease.

And that relationship is linear when we hone in on studies, that in terms of their methodology for assessing sodium intake are the most robust studies. So yes, Someone can run off and say "actually, I don't think the relationship is linear. Here's a study showing that actually too low sodium is bad for you." Well, we can almost guarantee that study has used certain measurement methods that give the appearance of low sodium intakes related to higher risk and I'll discuss what those measurement methods are.

And so we have a total body of evidence that in terms of the epidemiology. Any studies that have used the gold standard method of assessing sodium

intake, which is repeated multiple 24 hour full 24 hour urinary collections shows the linear association with cardiovascular disease.

And we have a number of really large intervention trials recently published including an updated meta analysis of intervention trials. Again, showing linearly lowering sodium will reduce cardiovascular disease risk. And then with within that, so we've evidenced both from epidemiology and large intervention trials, all supporting each other.

There are a number of important factors that relate to the potential magnitude of the effect of sodium and potassium is one of them. So we know that potassium has the. Counter effective sodium on blood pressure, lowers blood pressure. We have analyses that show that high potassium intake. Itself, it can be independently associated with lower cardiovascular disease.

We have analyses that show that higher potassium and lower sodium is ideal and that would be the best combination to have. And, but overall there's still a lot of focus, perhaps more so on the sodium side. And we do have a number of interventions. Again the SASS study that was published last year or the year before, actually that used what they call a potassium enriched salt. So the sodium content of the salt is reduced and it's enriched with 25% potassium. There was a previous study in Taiwan, a number of years ago, but this study was a much larger study with a huge amount of actual endpoints and was conducted in China. So we know that potassium is important.

People who would downplay the associations with sodium and listeners will remember us discussing the concept of a moderating variable. So there's a difference between a factor that is causally associated with an endpoint versus a factor that moderates or mediates that association between your exposure in your outcome.

Now, sodium is independently causally associated with cardiovascular disease because the risk factor that it impacts. Is blood pressure and it's to increase that risk factor and the relationship between that risk factor and the outcome potassium, because it doesn't do that to blood pressure. It has the opposite effect is not independently associated with that increase in risk, but it moderates, how potent shall we say that effective sodium is. So there is an important relationship between the two overall. It doesn't negate the fact because people will argue well, you know, it's actually a lack of potassium.

It's well, we can actually look at this. And this study today will we'll give us some really interesting insight into the relationship. And how actually trying to argue that 'potassium itself is the factor we need to care about and we need to be less worried about sodium', which is a common argument, actually really doesn't hold up to scrutiny even with studies that use some flawed method, methodologies of measuring sodium like today's study did.

Danny Lennon: And just, as you mentioned, the SASS study for people who maybe want to dive into some of the nuance of that a bit. In episode 415 of the podcast, professor Bruce Neal who was the lead author on that particular paper came on to discuss that trial and detail. And one of those aspects that we actually chatted about was something you just raised of that these claims that the blood pressure lowering effect is solely down to potassium and not sodium. And this is a kind of a strange claim that you hear from people who try and say, look, sodium is never a problem. Right. It's just get enough potassium and you'll be okay. So, you've put some nice context of up to this point where we've had some kind of clear conclusions that we see for lowering blood pressure and then impacts on cardiovascular disease outcomes that sodium restriction or at least comparing lower sodium intakes to higher is going to be beneficial. And then we have some also an effect of potassium that increasing amounts of potassium or either supplementally or a more potassium replete diet can have a benefit. But as you've just said, there, this we consider as maybe a moderating impact.

Now what was looked at in this study, we're going to start discussing now in a moment was to not only look at this potassium intake and its association with blood pressure and cardiovascular disease, but then a couple of specific things to hone in on they looked at was this association between potassium and blood pressure and cardiovascular disease down to was there any differences between men and women?

And then secondly, how much of this association depended on sodium intake? So in other words, does that association still seem to be present at increasing levels of sodium? And so we'll maybe revisit some of that.

Now if we start looking at the kind of study design and some of the overall setup, We've already noted that they use data from the EPIC Norfolk cohort.

That was one of the centers for the EPIC trial, which we mentioned on many podcast episodes before. So the European Prospective Investigation of Cancer, this large multi-centre cohort study, and one of those locations was Norfolk, which is in England. And some of, so the data in the paper we're discussing today is taken from this.

So from that, from our initial study design and how this particular study was set up there's a few things to mention. So there's obviously the, some basics around the participants we may mention. And it also flag for people, something that Alan has just raised in relation to sodium measurement, which also will extend to potassium measurement in this study and how previously we've noted that this is a very important thing to consider in any study, we're looking at these assessments. So, so with that maybe do you want to frame this for us, Alan, in terms of some of the study design, what are the most important elements that we should make people immediately aware of before we get into maybe the details of the assessment of intake itself? What other aspects of the study design should we really flag?

Alan Flanagan: This is a perspective study. So we're looking you know, at this population over time. And you know, one of the strengths of this study is actually the average follow up time was basically 20 years. It was 19 and a half years, and there's a really large number of cardiovascular events and listeners who have.

You know, just listened to our previous study breakdown episodes. We'll probably be quite familiar now with this concept of follow up time, obviously being important, but also the power, the strength that you have from the number of events and outcomes that occur. So, you know, in this cohort and there were both men and women, so there about 11,500 men and just a little over 13,500 women. So there's a decent sample size overall. It's not enormous compared to some isolated cohorts, but this is again a subgroup of the overall EPIC study. But in these participants, you've got a nearly 55% of participants experienced a cardiovascular event.

Now that might sound to participants like, well, hold on a minute that's an enormous number of your participants to be having a heart attack or a cardiovascular hospitalization, but the average age at baseline of our participants in this particular study was bit 58 in women and 59 in men.

So actually now to put that on context, if we just say 60, say at baseline, give or take 20 years is now extending up to the age of 80. And this is where we would expect actually to see a large proportion of individuals in the population start to have various disease endpoints, but cardiovascular disease specifically.

So that might sound enormous. But it would be slightly more shocking if this was a cohort of people who were 40 at baseline. But they're basically 60 at baseline. And I think it's also important to note where was their baseline hypertension or their blood pressure status. So, and again, bearing in mind their age, because there are some age specific considerations, but the blood pressure in men was 135 over 80 and in women was 134 over 81.

So these are just getting into stage one, hypertension. So these are participants that already have elevated blood pressure. So we've got basically an average age of 58, 59 baseline. They're not necessarily that overweight, their BMIs are 26, but they do have high blood pressure. And there's a very long follow up time of about an average of 20 years in which there are a lot of cardiovascular events that occur.

So these are all strengths of the study. And in terms of their actual method of analysis, there was a lot of strength. They considered different factors, whether there was an interaction with sodium, but also whether different estimates of sodium and potassium intake using other formulas changed the results at all.

And they also obviously stratified by sex specific men and women and how that differed. So I think they're the benefits of the study. As far as its overall kind of design for a cohort study, we want to think about size overall size number of events, duration of follow up and all of these kind of factors. So that they're all kind of general strengths to the paper.

Danny Lennon: One interesting thing that you mentioned given that not only the age of this cohort, but also the level of average blood pressure. And I think around 20% of these participants were on anti-hypertensive medication as well, which is quite a significant amount.

And that adds actually an interesting thing that we may revisit later of how the researchers went about accounting for this, because now we're trying to

get an assessment of the impact of sodium, but now they're taking antihypertensive drugs, then they. They did some like calculation, I think like adding maybe 15 (millimeters of mercury) to their blood pressure.

So something I'm sure we'll revisit a bit later on, but that is just to say that we have about 20% of these people on antihypertensive medication. So one of the other interesting things that. We've noted you, you touched on a bit earlier. That is really important to look at is obviously the intake assessment method here for sodium and potassium.

And so just as a reminder of something, you said a few moments ago, remind people again, of the different ways that this can be typically assessed. So that comparison of multiple versus single spot measure, et cetera. And then. Exactly what was used here and then the most important things to bear in mind and how they can connect the dots there.

Alan Flanagan: Yeah. So, so we typically just a and people will have heard this from our previous sodium episode that the majority essentially up to 96% of these sodium that you consume through diet. Is excreted through U and this is actually a real strength in one sense, when it comes to measuring sodium, because it means that we're not worried about other methods of excretion or elimination pathways because there's a little bit lost through sweat, but it's not a lot.

So what this essentially means is. The sodium in your urine is as accurate a reflection of your dietary intake as we could possibly get. It's a really solid biomarker, one of the best and it would be considered a recovery biomarker because we actually need to recover these samples in which the sodium is going to be found, i.e. people's urinary excretion. Flip side to this, is that in order to then get as accurate an estimate of someone's sodium intake on any given day as possible, we need to collect every drop of urine that a person excretes over the course of that day. That is burdensome on participants and it's expensive for the researchers involved.

So there are a number of methods that will and the other factor just before we discuss the different methods is. We know that people's sodium intake changes from day to day. So even though I might get a very accurate assessment of your 24 hour intake on the day that all the urine is collected for, that is not representative of someone's average intake.

So this is really important. There is a lot of within person error in sodium intake, and this is. The gold standard of assessing sodium is not just to collect one entire 24 hour urinary excretion from a single participant it's to collect multiple. Generally three is about the minimum that would start to allow you to get closer to that person's average.

And this obviously is quite expensive, so not a huge amount of researchers and studies have actually undertaken this method, but it is the most accurate. And the studies that have used this uniformly show, a linear relationship between sodium and also potassium and cardiovascular disease risk, but an opposite direction. So linear increase in risk with higher sodium intake and reduction in risk with potassium with higher potassium intake. So then the second method. They'll use a single 24 hours. So they have collected the 24 hour full urinary excretion sample from an individual and from all the individuals in their study, which is good, but they've only had that data for that one day.

And this method introduces this variation, this within person. And then obviously, then between person error, because everyone's not representative of their actual average intake and that introduces a degree of error and that error plays out in any ultimate analyses. What tends to happen is it tends to overestimate the risk associated with low sodium intake. So it gives the appearance that a low sodium intake is associated with higher cardiovascular risk and then the cheapest and easiest method. But also the most flawed is to take, what's known as a spot sample. That's basically just one urinary. Excretion in that day and that can be taken at any time of day.

So the benefits of this method from a research perspective are that it's quite flexible for researchers to do. It's not burdensome participants. You just need someone to go to the bathroom and void once, and you just need to collect that one sample, but how do you then know what someone's intake is over 24 hours?

A number of formulas have been developed to try to take the sodium present in that single spot sample. To use it to estimate that individual's 24 hour sodium intake, the most common are the Kawasaki formula, the Tanaka formula and the inter salt formula. The present study used the Kawasaki formula as its primary assessment. But it also calculated sodium and potassium, excretion estimates using the Tanaka formula. And again, a

strength of this study is that, although it used the Kawasaki formula as its primary measurement method, it also analyzed the data according to the Tanaka formula to see if there was any difference.

Now, in, in both cases, this is a moot point because they're the reason they're flawed is because these formulas rely on including other data. For example, they'll include age, weight, height, create an eye in excretion and potassium. The issue with that is that several of those factors are themselves independently associated with outcomes, particularly cardiovascular disease.

So weight and potassium are both factors that are associated with the outcome. So there are limits to these formulas, essentially because the, in addition to sodium. The variables included in the formula to calculate the association with risk to calculate the estimate of 24 hour sodium excretion or potassium excretion.

And therefore that relationship with risk also have factors included that are strongly related to cardiovascular events and mortality. So there's confounders included in the calculation and we know from other research that has compared each of these methods to. The gold standard, multiple 24 hour collections.

That the problem with these formulas is that again, they will underestimate risk. They will underestimate risk or sorry, sodium intake, and they will overestimate risk. So you will get this appearance that lower sodium intakes are associated with higher. Now that's more specific to sodium, but it's important to clarify at the start that these estimates are not even as robust as a single 24 hour full 24 hour urinary collection. They're based off one single void. In this case, the participants provided that sample when they were having a physical examination at baseline. And then this, these formulas are used, which also include other variables.

Themselves associated with cardiovascular risk, like weight and potassium intake in the estimation, ultimately. So they're, they have used the weakest. Measurement method for assessing sodium and potassium intake and then their relationships respectively with ultimately cardiovascular risk.

Danny Lennon: Yeah. And I'm sure we will revisit that point again when we try and formulate some conclusions towards the end of this podcast. But with that context set up now of we've understood the basics of the study design, some of the intake assessment and how that was gone about maybe we can start looking at, okay, what did they actually see in terms of the potassium and sodium intakes within this particular cohort? And of course, if you look through the results of this paper, you can see that they not only look at estimated potassium intake as an average for both men and women, but then you can break that down into tertiles in this particular study. So into groups of three of the in terms of levels of potassium and sodium and again, as we've known in this case, when we're looking at excretion of sodium and potassium, this really good, accurate way to assess intake of sodium and potassium. So we can essentially use these interchangeably for our purposes for the moment. And so within these levels, what we're seeing at an overview level for potassium intake was something around for men 2.8 grams per day, as an average for women, it was 2.6 grams per day.

And then for sodium for men, you're. 4.9 grams per day. And for women 4.2 grams per day. But of course, then there is some variance when we compare the top and bottomtertiles of intake, which we might start getting into. When we actually look at some of the outcomes of interest, like we've mentioned at the start, there are two main.

Different outcomes we're looking at. One is just directly first on blood pressure and what's happening there. And then afterwards we can maybe consider cardiovascular disease itself as an outcome. So let's start by looking at some of the results here for blood pressure. And I think maybe the first thing that is immediately noticeable and there's a nice graph within the study that shows this quite markedly. As soon as you look at it, is that at higher levels of potassium intake, you see lower systolic blood pressure in women, and you see a kind of pretty linear drop as potassium intake increases lower systolic blood pressure, but you actually don't end up seeing this relationship in men.

And instead that graph looks like just a straight line across almost. What are the first kind of things that came to mind on seeing this? And I, I think because we haven't mentioned yet, why were, would we even maybe look at sex differences here based on previous work when it comes to both sodium

and potassium but in this case, what were the first few things that hit you about those findings in relation to increasing potassium intake?

Alan Flanagan: Yeah. So when it was just looking at potassium intake in grams a day alone like you said, this really went up to. About a maximum of six grams of potassium intake a day. And across the range from zero to six, you basically saw no change in systolic blood pressure in men, but the effect in women of increasing potassium intake was a straight line in a reduction, i.e. It was linear as potassium intake increased in women. The effect was larger in terms of lowering systolic blood pressure. I think there are a couple of things that potentially play into this that are important for people to be aware of. The first is that this is not necessarily an entirely a novel finding entirely.

There's quite a big body of work into sex differences in what's known as salt sensitivity, i.e. You know, the to be salt sensitive is essentially to be responsive, to changes in dietary sodium intake or to factors that will help lower blood pressure. And so, we know that there are a much, or there is a much higher prevalence of salt sensitivity in women than in men.

And we've seen this in another, a number of wider studies. We did see it in the Intersalt study, which I mentioned in terms of they came up with a formula, but interal is one of the largest cross. Country studies into the relationship between salt and blood pressure. And there was...

although potassium specifically wasn't looked at, there was a stronger association between blood pressure and sodium excretion in women. And that was in quite a large and diverse cohort conducted over 32 countries. We've seen it in other interventions as well. Some of the evidence from the dash diet has shown when you stratify the blood pressure responses to this well-established intervention you see a greater blood pressure decrease in women compared to men.

So there are some mechanisms we probably don't necessarily need to get into. All of them. The differences appear to be that male regulation of sodium appears to be exclusively at the renal level, the level of kidneys. Whereas there are some suggestions that women have other. Potential mechanisms that might mediate a greater responsiveness to sodium in the diet.

And then particularly the effects of sodium reduction. Now what this study has particularly added on what this analysis makes interesting is this is suggesting that actually it. This salt sensitivity might actually relate to an effect of potassium specifically. So that's what this kind of offers us to start thinking about in terms of this, finding that we know that there is this clinically significant difference in salt sensitivity between sexes and this study is offering us to think that maybe higher potassium intake in women produces greater responses in blood pressure.

Danny Lennon: That actually sets things up pretty nicely for one of the other findings that they also try to drill into in, in a bit more detail. And it's actually on that. If we look. At women specifically, then we can go and look at these plots that they had for both men and women.

But the women's one here is of most interest where you can look at the effect based on tertiles of sodium intake. So comparing highest to lowest tertile of sodium intake. We can then look at what is the effect of potassium intake on systolic, blood pressure. And indeed, when you stratify. This out by sodium intake, you for the highest sodium intake in women.

So for the women, with the highest sodium intake that, that tertile of highest intake, you do see that kind of same relationship that as potassium increases, you see this kind of drop in systolic blood pressure, but that isn't really apparent at the lowest tertile. So it seems that the. Women with the, in the highest Teria of sodium intake they are really seeing the benefit or the impact of daily potassium intake being higher.

And I think in the study, they actually. Summarize it as for every one gram increase in daily potassium intake, you have this associated with a 2.4 milligram of mercury reduction in systolic blood pressure. So this kind of adds the next layer of, okay, we're seeing these differences in women, but it also seems then to relate to sodium intake is being able to describe, at least some of this association we're seeing with.

Potassium intake.

Alan Flanagan: Yeah. And so this is where things start to get interesting. I think for this study overall, even we're still talking. Blood pressure, but we can actually move on to talk about cardiovascular endpoints as well in a

minute, but we talked before about urinary excretion, generally being a good marker because you excreted all.

Now, obviously we want 24 hour measurements, but there's an important point within that, which is the fact that the same sample is used to assess sodium and potassium. They're really highly correlated. A given individual is U or urinary output. And this means that you really have to factor in a lot of thoughtful consideration for the potential interactions between the two and.

Although this particular study's method of measuring sodium and potassium is essentially the weakest available. The one credit the authors really deserve is really working at multiple levels to consider this interaction both in terms of including these factors, mutually adjusting for them in their models.

But also, and I think this is more inform. looking at the effects of increasing potassium at these different levels of sodium. So they've really worked hard to tease out this interaction effect between sodium and potassium because they are so tightly correlated. And I think this is particularly interesting for this P for this specific finding that we're discussing in terms of systolic blood pressure, because in men, what you see is essentially no effect.

Whatsoever of higher potassium levels at higher levels of. And this is important because this is a cohort that actually had quite a high salt intake. Now, bearing in mind that the baseline assessments in this study were conducted in the late 1990s. This was before salt reformulations started in the UK in 2003.

But if we look at sodium intake in grams per day in men, for example, and we convert that into salt. The highesttertile are consuming basically over 16 grams of salt a day. And the lowest are still consuming, you know, around eight grams, nearly nine grams a day. So the population average would actually be closer now to the lowesttertile.

I think that's an important point, but what we're seeing. Is that at these higher levels of sodium intake in men, anywhere between eight to, to nearly 16, to nearly 17 grams, we're seeing no effect of higher potassium on blood pressure. And then in women who salt intake is not as high, but is still going from about six grams.

About a little over just five grams a day up to 14. We're seeing that actually in the women that we're consuming around 14 grams of salt a day, this high level of potassium is associated with a 2.4 mercury millimolar lower systolic blood pressure, but we're not seeing that effect in the middle and the lowest.

Third of potassium intake in the middle third, we're starting to see that trend toward a reduction in systolic blood pressure, but it's not significant. It's only a 0.8 difference. And then by this higher level, you're seeing this big difference. So, this is interesting because again, it is suggesting.

Even at a, an intake and this might relate back to this sex difference in salt sensitivity, but we're seeing a protective effect of high potassium intake in people, women specifically that are consuming you know, or an average of about 14 grams of salt. A but we're not seeing that really at any levels at any other levels of sodium.

And we're not seeing it at all in men.

Danny Lennon: As we've already discussed this impact on systolic blood pressure. Let's move to the outcome of actual cardiovascular disease. Now the outset of this conversation you discussed, how one of the really nice things about this particular cohort is the follow up time of about 19 and a half years and the high degree of cardiovascular disease events that we saw around 55% of participants having an event, which huge numbers which is obviously.

Not great for participants, but from a research perspective gives a lot of evidence, right? So we see these large amounts of events. So yeah, 13,000 events something like this in this particular trial. And one of the first findings roads of cardiovascular disease that we can look at is a. When you have this fully adjusted model, you can compare people in the highest Teria for potassium intake, and then compare that to the lowest and see, what do we see in terms of risk of cardiovascular events?

Specifically with this, we see a hazard ratio of 0.87. In other words, this kind of 13% risk re. In highest compared to lowest tertile of potassium intake. So that's the first overview level. And then there's a number of layers beneath that, which we can also get into, of looking at differences then between men and women specifically.

And again, this is of interest. So based on what we've just said of looking at Teria of potassium intake, as opposed to just looking at the whole cohort. Now we can look at what is the impact in men and what is the impact in women. And whilst you do see some association here, you have the hazard ratio for women being 0.89 for men, that being 0.93.

But so you see this greater risk reduction for women than in men, which might be unsurprising given what we've seen in relation to blood pressure. But there are some other layers of nuance, which I'm sure we'll get into a bit afterwards when we look at grams of intake and so on. But from this initial.

Level of potassium intake and cardiovascular events, w with this particular outcome, what are the notable things that we should highlight

Alan Flanagan: in terms of the full analysis? Again well thought through adjustment model. They're adjusted for factors like age BMI. They're also adjusted for sodium intake.

So remember I just mentioned, we want to see mutual adjustment so that there isn't that kind of cross confounding. And they're also adjusted for smoking stylist, alcohol actual disease history. Remember, we've got a cohort here that are elderly and are a lot of them are going to go on and have, you know, health issues.

And so they've adjusted for diabetes, history of cardiovascular disease and otherwise, and then they've also included. An interaction by sex. So I think as far as this high versus low potassium comparison goes, what we're seeing is a, in terms of the overall effect a fairly modest or moderate risk reduction.

the effect in the total cohort is quite a, it's a precise enough estimate of effect. I think, you know, the actual finding is not a shaky finding necessarily But when we stratify it by sex, we actually see that there's a greater magnitude. It's not an enormous difference. We're talking about a difference of, you know, 4% in the magnitude of risk reduction, 4% greater in women compared to men.

And you know, if we are thinking about this study with the limitations of the assessment methods for potass. But we're then stepping back and thinking about the wider research. It's also a finding that's largely congruent with the

wider evidence base that yes, a higher potassium intake is a good thing as it relates to actual cardiovascular disease endpoints.

But of course this analysis is our kind of our main analysis. And while it's adjusted for sodium intake, it's not telling us what the relationship between these two variables at different levels of intake might be. Yes.

Danny Lennon: And we also note then when intake is expressed in grams per day, we can see a similar picture here of and similar to what we noted earlier.

there is a degree of risk reduction in terms of cardiovascular disease events for men that actually didn't reach significance. Whereas you do have a significant risk reduction in women has ratio. There are 0.92. So that was for grams of intake per day. But like we, we noted that there. No interaction.

It seems between the sodium intake for the association between potassium intake and cardiovascular disease events. When we look at men and women. So there's a number of D. Elements that we can look at within these results. But I think as always it's worth placing this into some wider context, which kind of gets us to, I think that the main part of interest of the discussion of given these initial findings that we're presented with, and that we've just outlined in terms of those numbers, what do we go and do with that?

On a few different ways. One on, in terms of this individual study, Might we assess it and what we need to be aware of. And then two, how does this fit into previous literature and the overall evidence base and some of the other aspects that we've discussed before? So if we start working through that, the first part will be very much a bit of a summary of a number of things we've already mentioned when it comes to this specific trial, what do we need to be mindful of when we.

Either the results or certainly just the kind of takeaway headline we might take from this paper. What are the things to bear in mind about this study? That will place some of the findings we just discussed in a bit more context. Yeah. I think

Alan Flanagan: the top line is their assessment method of both sodium and potassium is unreliable.

And that's the reality of it. We have not been we can know from the use of either formula, they've used one as their main one, the Kawasaki formula. And they've used the Tanaka formula as a secondary, just to see whether they're similar results, they are similar results, but that doesn't mean that the formulas themselves are are robust.

They're not robust. So we are dealing with a misestimate of. Sodium and potassium. And we can say that with a degree of confidence that these are not accurate assessments of levels of intake. And we do need to bear that in mind, as it relates to particularly these analysis across, you know, different levels of intake, either as tertile or as grams we need to be mindful that the assessment method potentially is.

It might catch the risk at higher levels, but it is likely going to be insensitive or indeed misestimate relationships. As we get down to lower levels of each of these levels of intake. So I I think that's really the first thing. I think the second thing is if we just put that to one side and think about the findings on the merits of this particular study, there, there is a lot here that isn't necessarily I think surprising in some ways and in some senses it's congruent.

I think a very telling figure for this is actually in the supplementary data figure eight is that's looking at potassium intake in tertile in terms of cardiovascular events but across the thirds of sodium intake and what you actually see in men in the lowest level. Of sodium intake is that the highest level of potassium intake is associated with a 13% lower risk of cardiovascular offense.

Now it's a much kind of why the confidence interval is literally just Chi it's 0.99. So it's not a particularly precise estimate, but in the intermediate potassium intake, there's a that's an 11%. It's not quite as much, but a reduction in risk. And then once you get above that into the second, third and highest third of sodium intake, you no longer see this association.

And the reason I found this interesting over thinking about wider research is this is what other well conducted studies specifically interal would suggest interal analyzed. The relationship between sodium and potassium and systolic blood pressure, not necessarily cardiovascular events at different levels at each. And this was divided into fourths, quartiles of sodium and potassium intake. And basically what it showed was that the relationship was

more pronounced at lower sodium intake and higher potassium intake. And this is important. People argue that again, "it's not sodium. We should be worrying about it's potassium". You know, "don't worry about sodium, just eat more potassium". And that's really not necessarily what the data tells us overall. So actually, when I looked at that outcome in men, I thought, well, this is interesting, because this is telling us a degree of what we would think from the wider literature that at low sodium intakes and high potassium intakes is where you see a benefit now what this paper has added and what deserves to be thought through more, because what I've just described was in men is actually the finding in women.

Again, if we look at the stratification of. Three tiers of sodium intake relative to low intermediate or high potassium intake in the high potassium group. Even in women in the low sodium intake, there is a reduction in risk. It's not statistically significant. And then you get to the middle tier of sodium intake or the highest tier of sodium intake.

And again, both the intermediate and high levels of potassium intake are associated with the lower risk. Now at the highest intake of sodium. In women, it's only the highest intake of potassium that's associated with a lower risk. That's a 15% lower risk. So really what this study is inviting us to think slightly more about is this sex difference in responsiveness and how this concept of women who we know are prone to greater salt sensitivity.

How this might actually relate to risk and what this is really suggesting is that yes, in women, even with a high salt, Remember the highest in this group is 14 grams. A high potassium intake appears to attenuate. And the proposed mechanism is that the high potassium intake will increase the rate in women of sodium excretion.

So yes, what they've got a high sodium intake, but they, the potassium is acting to actually get that sodium outta their body, basically. So I think this is really what the interesting finding is. I think in men, it's giving us a degree of congruence. With what we know, I, that ideally you want low sodium with high potassium, but what it's suggesting is that in women with high sodium, that hypo potassium might actually be protective, whereas in men, and this is important, because people could potentially misinterpret some aspects of this data in men, high potassium intake did not protect at high levels or even

middle levels, moderate levels of sodium intake. This was only observed in women.

Danny Lennon: Yeah. And as I'm sure we'll speak to in a moment I don't think this certainly suggests that we can now start saying, oh yeah, sodium intake is now irrelevant. You can go as high as you want as long as potassium is sufficiently high, just eat more. And just to emphasize some of those things you said in relation to this trial, not only. Important limitations that we've outlined multiple times in relation to the intake assessment when we're thinking about, and this is more of a general point, but when we're thinking about something like cardiovascular disease outcomes, of course, we can try and adjust for as many factors as possible.

And the there's a relatively good job done in this of adjusting for confounding variables. But of course it's hard job to. It for everything. And particularly when we're looking at intakes that people have from their diet and impact on something like cardiovascular disease, we need to bear in mind.

Well, well, what type of diet would confer a high potassium intake? And you try looking at sources of potassium in the diet. So if someone tends to have a. Naturally high potassium intake. That is probably a, almost like a marker for a overall healthy dietary pattern because of the types of foods that they're getting to provide potassium, like plenty of fruits, vegetables, that type of thing.

So with that it's a possible it. There's definitely a lot of good adjustment done here, but there's still the possibility of some residual confounding in cases of very high potassium diets, as an example. So with all that, to note about this particular study, if we then translate that to, okay, some practical, pragmatic conclusions for people of number one, how do I place this places and context for other data that we've discussed of sodium potassium that we just hinted to?

And then second, what does this mean for actual. recommendations we could give either at a public health level or then at a individual clinical level in relation to things like sodium and potassium. So where is, where does your thoughts go when you think about the pragmatic conclusions that were left with either not from just this trial, but putting that in context, what are the things that people should be left with?

Alan Flanagan: For me, I think it is really important to bear in mind that the levels of intake in this cohort are likely no longer what we would see in the population, except it may be more extreme ranges, salt, reformulation. In the food supply has lowered average population, salt intake, it's maybe somewhere around between eight and 11 grams a day now in the UK population. So actually it's now where the kind of mid tier to the low tier of sodium in this cohort where relative to the high tier. So. I think that's important, there are already changes in the food supply that are occurring and people, whether they know it or not largely have a lower salt intake.

But it's still a nutrient of concern in the population. I think what this study has really confirmed is that. Overall in the population. Yes, it is good to consume more potassium. No, that potassium will not necessarily just offset a high salt intake, but in women it actually might in terms of provide more benefit I, while I'm summing up what this study is ultimately telling us, the assessment method makes me too uncomfortable with those conclusions overall, even though there is a degree of congruence with the wider field, as it relates specifically to the sex differences, I would not currently based on this study, be too quick for women to be like, great. I can, I don't need to bother thinking about my salt and intake, because I can just consume more potassium and I'm going to be fine.

The assessment method in this study, doesn't give us enough reliability to be confident in that conclusion. So I would keep the powder dry on that as a specific conclusion for now. But I do think that this study overall almost in spite of its assessment method for sodium and potassium has on the whole provided a degree of congruence that you know, that there is a relationship that's independent for potassium. It's a good thing. But it's not necessarily going to save you from high sodium intake and whether it does in women or not because of the assessment method in this study. I don't think we can say that with confidence and I think we need studies. Have a more robust assessment of potassium and sodium excretion sex stratified before we can actually come to that conclusion.

Danny Lennon: Yeah. So I think then for pragmatically, for people, there are certain things that we can still be quite confident in terms of giving recommendations.

And then there's these other additional areas. They're interesting to know, or there could be an effect, but we certainly wouldn't have the same degree of confidence. So if people are thinking, okay, well, what is that baseline there that we can probably be pretty sure on? Will it be something like having a potassium rich diet may have a beneficial health impact relative to a potassium poor diet. Right. So if you really low potassium intake, probably having just an overall dietary pattern that has more potassium, rich foods may have a benefit there specifically based on what we've discussed today. This could have an important impact on blood pressure and therefore the risk of cardiovascular events and containing or consuming, therefore, a healthy dietary pattern with the variety of potassium containing foods.

Could be a recommendation that we could have some degree of confidence in. However, we've also noted that sodium intake can independently impact blood pressure and cardiovascular disease risk a again, if people haven't heard much of this discussion I suggest you go back and listen to our sodium specific episode for much of the details there.

But overall, we see this weight of evidence strongly suggesting sodium intake in the diet should probably be limited. Below limits typically set by public health agencies. And certainly we shouldn't be listening to advice of saying, go and go on these high sodium diets because it's not a problem. With relation to potassium I think one of the conclusions that, that you gave in that sodium episode, Alan, and I think you would probably still stand by now, is that on the totality of the evidence whilst potassium is beneficial in the context of blood pressure and CBD, it's more likely that we can think of it as moderating the effect of sodium as opposed to completely abolish abolishing whatsoever despite what we saw in this kind of one stratification for women, this specific study. So yeah, we can probably still err, on the side of saying a high sodium intake is still going to be detrimental overall, even in the context of high potassium. So it could be moderated. It might not be as bad as if you're potassium is really low, but we certainly can't say it's now no problem.

Or it's safe just because your high potassium intake is there. So what we could say maybe from this study is that there is blood pressure lowering impact from increasing our potassium intake, that may be sex specific. There may be a difference between men and women here, but we certainly won't go as far as to say, this is now enough grounds to say women don't need to worry about sodium just get enough potassium. So I think that is, is as a way

to think through many of those conclusions together. Okay. Well, I think we can leave it there. I hope everyone has enjoyed this episode and continues to enjoy the podcast. If you are a Sigma Nutrition Premium subscriber, then remember you can get detailed study notes to this episode where I'll put a number of those graphs that we have discussed throughout this episode, some other background context and a whole series of things that will help you. Revise or dive in deeper into some of the aspects that were brought up. They'll be over the show notes page that will be at Sigma attrition.com/episode 4 5 1. If you are listening on our public feed and are interested in subscribing, then just click the link in the description box, where you're currently listening to. Alan and myself will be back with another episode very soon. But thank you for listening in. I hope you found it informative and we will talk to you soon.