DANNY LENNON: Today's topic in focus, we're going to talk about coffee and impacts on health, and there's a lot to get through here, and I think this is a big topic because either it's very common to get questions of is coffee good for me, how much coffee should I be having, what are the health benefits of coffee, are there downsides, etc., etc., which we'll hopefully address throughout this discussion.

ALAN FLANAGAN: I think it's interesting because, I mean, it's ubiquitously consumed – I had a quick Google just to see what the global coffee consumption was projected to be for the last year, and it's absolutely ludicrous. And this is 60-kilo bags are being referred to, sales expected to be around 168 million 60-kilo bags globally. So we know that coffee is one of the most widely consumed drinks worldwide cross culturally. And we also know that because of the caffeine content, it makes caffeine the most widely consumed psychoactive substance in the world. And we tend to focus and associate coffee with caffeine, but coffee itself is a really rich source of polyphenols. And in habitual coffee consumers, you could consume over a gram a day of chlorogenic acids, for example, which is a group of polyphenol compounds. And

although we tend to think of dark skinned kind of berries, fruits, dark chocolates and these foods as our sources of polyphenols, flavonoids, and a lot of interest in the benefits of those compounds for cardiovascular health, neurological health, and just overall health span across the lifecycle, coffee, in many respects, along with tea actually and wine, is one of the major contributors to dietary polyphenol intake in the population. So yes, we like it for its taste, smell, and the hit of caffeine, but, essentially, we're talking about a functional food in many respects, with a lot of the bioactive compounds within coffee; and from wider research our understanding of those bioactive compounds mechanistically and the processes that they might influence in the brain, the central nervous system, and the cardiovascular system and otherwise, and means that it's – and because of its ubiquitous consumption, I think consideration of its health effects from a nutrition standpoint, is definitely a worthy time well spent.

DANNY LENNON: Yeah. So maybe to tackle it first, if we take some of the associations coffee consumption has with different areas of health, and then maybe afterwards we can drill down into mechanistically what's going on or what is maybe contributing to impacts on risk reduction or health benefit in different manners, maybe if we start with cardiovascular disease?

ALAN FLANAGAN: Interestingly, although we tend to know that mechanistically caffeine has a hypertensive effects, coffee is obviously not just caffeine itself, as we said at the outset. And overall, the associations with cardiovascular mortality, if you compare kind of higher versus lower intakes of coffee and to define higher, depending on the study, that means often two cups a day compared to less than one or never, or two to three cups a day compared to less than one or never. And you overall see reductions in cardiovascular mortality. The significance can differ from study to study. So

in some cohorts, there is statistically significant, relative risk reduction in cardiovascular mortality, and a couple of meta-analyses have found the trend, the overall trends and direction of effect is towards reduction in risk, but they've not necessarily been statistically significant. And so within this kind of overall assessment of the long term research in terms of cohort studies going, and certainly over five years, I think the majority of them go over 10 years, and then you have one or two that go up to say 28 years, that's generally the two large, the nurses' health and health professionals follow-up studies. So overall, the trend of fat for cardiovascular mortality is toward a reduction in risk. So it seems to have positive impacts on cardiovascular mortality now we're talking about as an endpoint. Within that, there is a hypertensive effect of caffeine. Interestingly, studies that have differentiated between caffeine per se and coffee and obviously caffeine consumed through coffee suggests that the rise in blood pressure following coffee consumption is much less than the rise in blood pressure following just caffeine intake specifically. And there's also an effect of habitual coffee consumption versus non-habitual where habitual consumption will also attenuate that that hypertensive rise. Now, I think in people with hypertension, it's still not necessarily advisable to be a high coffee consumer. But overall, the potential hypertensive effects of caffeine which are well documented, don't appear to be as pronounced or as much of a risk necessarily when coffee is the exposure as opposed to caffeine itself.

DANNY LENNON: And in terms of the dose response, at least in some of the review papers that I came across, reported that with cardiovascular disease mortality, there's this U shaped curve essentially where moderate intakes maybe have the most pronounced benefit, like in that three to five cups I think it might have been – is that an association that holds across other studies that you would have seen?

ALAN FLANAGAN: Yeah. So as far as I've seen this U or J shaped curve is really consistence in the epidemiology of coffee and health outcomes. And so by J shaped or U shaped curve, what we're referring to, the technical term is it biphasic dose response. And this can apply to a lot of different exposures. Exercise is a good example. So no exercise is not beneficial for health, we know that. But over-exercise doesn't lead to beneficial outcomes. And somewhere in the middle, there is the sweet spot, and that's the J so to speak or the U. And we see this with a number of different nutrition exposures, but the consistency of the J shaped curve with coffee is pretty fascinating, and we can maybe dig into concepts like hormesis when we talk about the mechanisms. But in effect, what we tend to see, whether it's cardiovascular mortality, diabetes or neurodegenerative diseases, you tend to see that low to no coffee consumption is associated with no benefit, and excessively high coffee consumption also associated with no benefit and potential risk. And then somewhere, and it depends on the study, and it depends on the doses consumed, you can't make people consume more in an observational study, so you're taking people as they lie. But depending on the study, this dose response tends to have its maximal benefit at anywhere between one to two cups up to three to four cups a day. So broadly speaking, we could maybe say a range of one to four, depending on the study, and depending on the outcome. For cardiovascular, I think it's in that three to four range compared to none or occasional. And so we're always – the comparison here is always no intake or very occasion, less than one a day, so very occasional intake. And that dose response, interestingly, seems to hold across outcomes, and I think potentially that speaks to the, yeah, the effects of kind of xenobiotic intake, which is essentially what polyphenols are and the kind of effects of kind of low dose stress exposures.

DANNY LENNON: I'm sure we'll probably cover this later, but for much of the general recommendations based on that kind of moderate consumption imparting health benefit, how much of that gets discussed as a function of caffeine as opposed to coffee?

ALAN FLANAGAN: I think the caffeine, from what I can see, and I may be getting this interpretation wrong, but the caffeine limits are kind of set at around 400 milligrams a day, this is kind of the safe upper limit, and general population intake seems to fluctuate between 80 to 400, give or take. And that seems to me to be more a kind of general tolerable upper limit for the population that maybe within that range. There are particular health benefits to caffeine per se, for example, attention and certain other cognitive domains. But generally, I think that seems to me to be something that's being set from a safety perspective, and the reason that I think it's difficult to extrapolate that to coffee consumption is simply the caffeine content of coffee can differ significantly relative to processing methods. So the contact time with water, for example, or the pressure, so the caffeine that you get out of a French press can differ to what you would get out of an Aeropress, can differ to what you would get. And even there was a cool study two years ago, a year or two ago anyway, that looked at the caffeine content of Nespresso pods relative to what's stated on the website, again, found quite high variability in the caffeine content of commercially available Nespresso pods. So I think it's difficult to equate caffeine recommendations and safety thresholds for caffeine at a public health level to coffee consumption per se, because the idea that three cups of coffee a day, for example, in the Japanese cohort, equates to the same caffeine content as three cups of coffee consumed in an Italian cohort. I just don't think we can make that, so we have no way of knowing that that's equivocal. So I think it's often for this conversation, particularly because of all these other bioactive compounds, more useful to

focus on coffee as the exposure of interest, and ensure we can discuss the mechanistic implications of caffeine and chlorogenic acids and other polyphenols. But actually, it's coffee, that's the exposure, it seems, independent. But what I find interesting though is has studies that do differentially assess caffeine per se versus coffee, tend to find differences in the effects of – so, for example, with some of, if I remember this correctly, for some of the associations with type 2 diabetes, for example, you see the associations for coffee, but not necessarily a strong for decaf coffee. So again, suggesting some sort of kind of overall effect of this, I was going to say whole food matrix or whole beverage matrix, so to speak.

DANNY LENNON: Yeah, and we'll definitely circle back to caffeine specifically, maybe later in this discussion. One thing I did want to ask about in relation to cardiovascular disease, purely based on kind of one paper I happen to stumble upon where they looked at, I think they were comparing filtered, unfiltered and different types of coffees as well as caffeinated and decaffeinated, and the impact of coffee on serum cholesterol levels. As far as I remember, for the unfiltered coffee, which is common in some cultures, that you saw a relatively significant increase in serum cholesterol and maybe even triglycerides, although I think the intervention may have used coffee oil as opposed to just drinking coffee per se, the idea being that with filtered coffee and you use a paper filter or something, that catches the oil which contains some of the potential compounds that are reported to be the ones that are causing the increase in cholesterol, I think cafestol and things like that. Is there consistency in that in terms of certain types of coffee beverages can lead to increases in cholesterol? Is that any way significant or worth being aware of?

ALAN FLANAGAN: Yeah, so there's these compounds called the terpenes, and they're some of the bioactive components of coffee, which mechanistically have been shown to increase LDL cholesterol,

total cholesterol, and have adverse, in the sense of increasing blood lipids. And I think it's also important to remember that coffee has lipid content, and they're hydrophobic, so they don't like water. And so my understanding is that when you're using a method that will filter, so across paper or even with a kind of French press or some sort of infusion or Italian coffee, when it kind of brews up, they're using pressure, an Aeropress would use pressure as well and filter across paper. But there is a reduction in those compounds, and so the filtration of coffee in that circumstance removes some of these hydrophobic lipid compounds, structures that do have a kind of cholesterol raising effect. And so, it's trying to tie together these mechanisms so that there is that effect. And yes, you're right, there is this differential evidence in studies that have looked at coffee and filtered versus unfiltered. When we think about maybe the effect of filtration, which is, I would imagine how most people commonly consume coffee, but we also then think about the fact that overall, it's associated – coffee consumption is associated with a reduction in cardiovascular mortality. I think if we saw the opposite, it might be more cause for concern, but in the absence of that association and in the relatively consistent direction of effect for cardiovascular disease risk of this kind of moderate level of intake of say, three cups a day, then I think, yeah, I'm not sure yet how biologically relevant that effect is.

DANNY LENNON: Particularly because it's such a transient effect as well.

ALAN FLANAGAN: Right.

DANNY LENNON: So one of the big areas of disease risk that I know you want to touch on is related to brain health, and there's probably a few different sub components of this. So if we maybe lead off with Alzheimer's and dementia, where do you see the current conclusions in relation to associations?

ALAN FLANAGAN: Yeah, I think one of the challenges with this area is coffee, for how ubiquitously consumed it is, is not necessarily a common exposure of interest in a lot of studies. And although you do get many studies that look at coffee specifically, you get less that look at kind of hard endpoint neurodegenerative disease, whether that's mild cognitive impairment, dementia, Alzheimer's or Parkinson's, certainly relative to other conditions like cardiovascular disease. So there's a smaller overall pool of studies that have looked specifically at coffee intake with one of these kind of neurodegenerative disease outcomes, but the direction of effect, particularly in some of the kind of larger cohort studies, which gives us a bit more confidence – so in studies of over 3000 people in any of the cohorts of over 3000 people, there's quite a consistent reduction in risk for dementia and Alzheimer's. And we've seen that in a couple of populations, we've seen it in Japanese populations, we've seen it in Italian population, we've seen it as kind of subgroup follow-up of some of the Seven Countries study known as the FINE study, so it was Finland, Italy, the Netherlands, the cohorts that were in that original Seven Countries study that Ancel Keys conducted followed up in the early 90s, that didn't look at any of the neurodegenerative disease outcomes. So it's often left out of meta-analyses. What it did look at was actual cognitive scores the MMSC cognitive score, and looked at how much coffee consumers were protected against cognitive decline, relative to non-consumers and the difference was quite significant over a decade, and the dose in that again was this kind of three cup a day evident with this J shaped curve.

So it seems overall, that there is a, again, consistent direction of effects. Interestingly, if I recall, this effect also isn't observed for decaffeinated coffee. So we're still talking about the kind of caffeinated version, and obviously there may be some specific kind of mechanisms and also interactions as to why, and that will be

the case. And so, yeah, the larger cohorts going over kind of 10-year periods in different populations have tended to find that this region, the Japanese cohorts were generally one to two cups a day, and the European cohort slightly more, but they've found that in this U-shaped curve of one to two to two to three cups a day pretty significant reductions in dementia and Alzheimer's risk, statistically significant reductions; the order of magnitude I think is between, say, kind of 20 to 30%, give or take within that range of risk reductions.

DANNY LENNON: Yeah. So again, it's that long term habitual intake that we're seeing correlated with...

ALAN FLANAGAN: Yeah, actually that's a really – the Italian longitudinal study on aging, if I'm getting the title of the study correct, but yeah, you're right, so what was really interesting in that was the protective effect was only in habitual coffee consumers. So kind of occasional or whatever, so again, this seems to be something that comes back to kind of habitual long term consistent consumption of these thresholds. The other thing that I'll say as well, just for the inevitable, well, epidemiology is useless. Coffee, generally speaking, coffee can be part of food frequency questionnaire methods of assessing intake. But one of the benefits of trying to assess coffee intake is it's relatively similar to assessing cigarette smoking in people, which has much more general accuracy from an epidemiological standpoint, because people tend to know that they smoke 10 a day or 15 a day or whatever, the exposure is quite defined. People also tend to be similarly more firm on their habitual coffee intake, and so a lot of studies, you don't necessarily need to use a food frequency questionnaire, they can use kind of self-administered questionnaires, or even just simple straight up, how many cups of coffee do you consume a day. You can get fairly reliable answers out of people that have quite a high correlation with them measured true intake. So I think that the doses that we're

getting back have a degree of reliability to them.

DANNY LENNON: So with relation to some other diseases, I know with Parkinson's disease I'd mentioned because it seems to be relatively similar to what you just reported with the Alzheimer's and dementia, in that there is this dose response relationship that we observe, but it seems to be that caffeine maybe here has been more attributed as what's going on.

ALAN FLANAGAN: Yeah, I found Parkinson's interesting, because of the neurodegenerative diseases, it's the strongest association. So dimension, Alzheimer's definitely, but if I recall, the Parkinson's association is even higher as like in the 30 to 40% relative risk reduction, and that's in a number of cohort studies, and a minimum benefit of maybe 20% reduction. So of all of these conditions, mild cognitive impairment, dementia, Alzheimer's, Parkinson's appears to be the strongest and most consistent association with coffee intake and health. And so, I think one of the kind of mechanistic plausibility hypotheses is to do with the actual psycho stimulation effect of caffeine itself, and increasing kind of sympathetic activity, increased dopaminergic activity; and I'm possibly missing out on one or two other potential mechanisms, but that's the one that sticks to mind is that kind of effect on the motivation reward system that is degraded over time with the kind of loss of dopaminergic function that characterizes Parkinson's.

DANNY LENNON: And again, much of that is on the long term habitual intake, and it seems to have this reduction or at least delaying the development of Parkinson's. A bit earlier, you'd mentioned the nurses' health study I think. I know there has been some papers based on that that have looked at depression and coffee consumption, as have a few other meta-analyses as well which we can get into. That seem to all trend in the same direction, from what I can tell. And

actually, I was quite surprised by some of the effects that they were reporting.

ALAN FLANAGAN: Yeah, it's... And that again, is something that's a relatively consistent direction of effect, often with quite a large effect size and lower risk of depression, evident in individual cohort studies and also in some meta-analyses. And again, this seems to be something that's dose related as well, because we do know that that high caffeine consumption can have kind of adverse effects on jitters as a physiological response, but anxiety and some other kind of related outcomes. But the influence on depression was interesting, because, as it relates to these neurodegenerative conditions, a lot of them have depression as almost proceeding risk factor. And we're not talking about like, just, you know, we're talking about clinical depression, not just kind of low moods that everyone experiences as part of normal life. So it's often essentially a comorbidity or a proceeding, a lot of these conditions, so it's an important risk factor in and of itself, but some of the mechanistic research particularly with Parkinson's disease, interestingly, if I remember, one of the reasons why caffeine impacts on sleep is because it inhibits this, I don't know, A2 receptor, it's A2 receptor. And that allows for, or prevents adenosine buildup, and it's one of the reasons why it has the kind of impairment of sleep, close to sleep. But interestingly, it also seems that the inhibition of adenosine and adenosine receptors or concentration dopamine areas of the brain, and so it maybe comes back mechanistically to this kind of interaction with the dopaminergic motivation reward system. So there are some – and then the other interesting thing, and this comes back to polyphenol content is one of the more, I guess, established mechanistically effects of certain polyphenol classes of compounds is kind of neuroprotective effects against inflammation, and there's quite a strong kind of inflammation hypothesis of depression. And a lot of the nutrients that are focused on for brain health, like EPA, for

example, appear to mediate depression, have the beneficial impact via modulating inflammation. And so potentially, there's a role for caffeine and coffee in protecting the brain from – and actually having kind of anti-inflammatory effects in the brain. So it's potentially one mechanism by which you get that anti-depressive effect.

DANNY LENNON: Yeah, there's one of the meta-analyses, I think it was Grosso is the lead author on it that I had made a note of, because I think it ties in with some of the other aspects that you've mentioned, related to other diseases in that we see that J shaped curve again, with the dose response, and the peak protective effect in that particular meta-analysis was 400 milliliters of coffee per day, which depending on the average sized one is probably again three to four cup range. But yeah, so it fit in very similarly with what we're seeing in other areas, which was quite interesting to see. And you had a pooled risk reduction of 0.76, yeah, it was just interesting, and I think you see kind of similarly good reductions in that nurses' health study as well.

ALAN FLANAGAN: Right. And again, the appearance of this J shaped curve, which crosses, I mean, if we were putting umbrella, sorry, depression under the umbrella of kind of cognitive conditions and the J shaped curve was only observed there, fine. But it's the reality that it's observed with each of these cognitive conditions, and additionally then with cardiovascular disease and with diabetes. So it's kind of cross outcome as well.

DANNY LENNON: And there's also, on the other side of that, obviously anxiety is separate, but oftentimes can be related. There is that relationship between high caffeine intake and anxiety, most notably in people who maybe don't usually have high caffeine intakes or maybe as we'll talk a bit later maybe, genetically more susceptible, but with relation to some of the impacts on anxiety, beyond avoiding high

intakes of caffeine, does the ability to habituate to higher intakes seem to translate then to a better ability to tolerate that or reduced anxiety – does that play out?

ALAN FLANAGAN: It seems to. It's the habituation and tolerance factor. I mean, it seems to have received most attention in the kind of sports performance round due to this, obviously, idea that, well, if you habituate to caffeine, you lose the performance benefits. I haven't kept abreast of that area, but I do recall, Asker Jeukendrup doing a post a while ago about how maybe that's not the case anymore, but maybe you've been paying attention to that. But the habituation does appear to attenuate some of the kind of, shall we say, kind of transients adverse effects that people might experience, whether that's kind of like jitters or anxiety or even the hypertensive effects which attenuate with habituation as well. So there does appear to be an effective habituation to consumption, and perhaps that explains why the benefits in long term cohort studies do appear to relate to habitual coffee consumers. Well, yes, that's another kind of point of speculation. Do you know, is that, in the sports realm, has that whole tolerance thing gone out of the window?

DANNY LENNON: No, I wouldn't say, it's gone out the window, but I actually probably, maybe over two years ago now, there's an article on the Sigma website that people can read, that I kind of wrote on this topic. It's just called Should You Restrict Caffeine Before Competition To Resensitize To It, and it's kind of just discussing the idea that it's typically been thought of, you want to say cycle off caffeine before an event for that same reason to resensitize to it. And there is some literature suggesting that you don't need to do that to still get the performance benefit of that. Now, again, you could probably have different discussions and people come down on different sides of it. But I think the kind of conclusion that I came away with was certainly on an individual level, it's worth maybe trialing, and

then also, as part of that risk reward evaluation, if you have people who are used to consuming a lot of caffeine, and then in the week leading up to an important event or a competition, you withdraw them from caffeine and that increases their stress, maybe gives them symptoms like more irritability or headache or so on, you have to factor that into your decision making, versus just letting them continue to have their normal cup of coffee in the morning, particularly in weight class based sports where we know people are dieting already and the one thing that they can look forward to during that kind of final preparation is some coffee. And so, yeah, it was just kind of some pause for thought, but yeah, if people can reference that.

ALAN FLANAGAN: Yeah, that's jogged my memory a bit from his, I think it was a study maybe he had done or been involved in, but what it suggested was habitual consumption doesn't tend to come near to the doses required for performance benefits. And that if you simply took a high enough dose, you can still get a performance benefit, even if you're a habitual coffee consumer.

DANNY LENNON: I think the paper I referenced in the article was one out of Brazil on cyclists, that sounds very similar where they had – they looked at low, moderate and high consumers, and then they had a placebo versus caffeine, I think it was 6 milligrams per kilo, so a relatively high dose, and then also a no-supplement condition too. And you saw that time trial performance was improved with caffeine ingestion, compared to the other two conditions, regardless of habitual intake as well. And so that would suggest that, yeah, even people who started from low or high intake, still gain the same benefit from the caffeine.

ALAN FLANAGAN: The 6 milligram dose per kilo, when you actually figure it out, it's high.

DANNY LENNON: It's good yeah.

ALAN FLANAGAN: It's going to have a kick!

DANNY LENNON: I had someone at a seminar I did a few years ago, it was one of the ones I did in London, and one of the guys at the time said he had been taking a gram of caffeine before his training sessions. I was like, that's legitimately – that's a high dose.

ALAN FLANAGAN: That's intense, yeah.

DANNY LENNON: But the other thing I've also wondered is people who cycle off caffeine, and then go back and take some and obviously there is a sensitization of how they respond to it, and that kind of alertness and things like that, that maybe then there's a kind of placebo effect that could possibly – the athlete could gain a benefit of, like, oh I feel so much more ready than I have over previous days.

ALAN FLANAGAN: I mean, anecdotally, I've tried both. I cycled off caffeine for a month before a meet. You throw a load down, and you are, it's this kind of, oh I'm back. But I just, yeah, I just enjoy coffee too much to then... I was just like, did I really get enough of a benefit that that's worth doing relative to just like not drinking coffee in the morning. And so, then I did other meals, where I never cut out, my habitual coffee intake remained the same, and then I would just get that like 6 milligram per kilo, which for me was, I think, at the time, like, maybe the guts of 700 milligrams. And that was just like a noticeable difference still. So at that point, I was just like, I think I'll just go with the high dose on the day.

DANNY LENNON: Yeah, if you're doing a powerlifting meet, you're going to be consuming a lot more caffeine than your normal day anyway, and probably the final week before your meet, your caffeine intake's probably going to drop because you're probably not going to be smashing 700 milligrams in the sessions that you're tapering off. So yeah, it's probably going to decrease, so yeah, probably kind of the effect

settles where it needs to. Some of the other things I think may be interesting to get to that we want to touch on are more maybe acute effects as opposed to some of the long term stuff. There's lots that we can jump around here, so I'm happy if there's a particular place you want to start, maybe one just to be square off on the impact around sleep.

ALAN FLANAGAN: Yeah, it's probably the most common question, I think that people have on their minds for their kind of habitual coffee consumption. Caffeine is the kind of compound of focus when we're talking about coffee and sleep. And, as we alluded to earlier, there's two processes that align to make you want to go to sleep in the evening. One is just simply the natural kind of rhythm, biological rhythm in your melatonin, and that will relate to two kind of sleep processes, your sleep death, like, how long you've been awake, and then this pressure to sleep. And part of the kind of pressure that you would feel to sleep and heavy eyes and all these kind of signs that you're ready for bed relies on the buildup of a byproduct in the brain called adenosine. And caffeine directly acts by inhibiting adenosine receptors and preventing that buildup. So that's why you get the wakefulness effect of coffee, and that's why people use coffee to try and stay awake, and they're racing against a deadline or crushing for an exam. But it's a mechanism that is worth paying attention to for people that struggle with sleep. And a really important variable in this respect is the fact that caffeine's half-life is give or take around six hours. And so that means that even after six hours, caffeine has only come down by 50% in the blood and remains. And that half-life again is going to be influenced by genetic variants and caffeine metabolism, some people process caffeine quite quickly, so there's a shorter kind of time course of that elimination, and some people metabolize caffeine quite slowly, so there's a prolonged circulatory life of caffeine. And this really is impossible to give kind of any individual recommendations to, so what I

typically say is if you are struggling with sleep, particularly getting to sleep or feeling like you're not sleeping deeply, like you're not really remembering dreams or anything or you're waking up unrefreshed the next day. You know, do an audit of your coffee intake and caffeine consumption and be honest in that regard, because I think, and I know this from experience, it's easy to have a lot of cognitive dissonance to your coffee intake relative to your sleep.

So I think it's obviously because all of these individual factors, people will tend to know themselves if they're kind of slow or fast metabolizer without a genetic test simply because of how they respond to caffeine; and whether they do get quite jittery and kind of hypervigilant and maybe transient anxiety, that not might suggest that they don't metabolize it quite quickly. And in any event, I think that when we factor in the half-life, and that's just the half-life, I do think that coffee is best kept to the early part of the day. It's impossible to give hard cutoffs again, because of the individual recommendations, I tend to try not to consume that much coffee past kind of like one. But again, that's just giving my kind of personal anecdote as an example. Yeah, it is something to bear in mind. There's very well-known mechanisms as to why caffeine interferes with sleep, and coffee should be considered and coffee consumption and the timing of that consumption should definitely be considered in that respect, because there's no point in trading off on sleep quality, if we can avoid doing it.

DANNY LENNON: And yeah, anecdotally, I have a very similar kind of aim of 1:00 p.m. usually being the latest I will consume any caffeine, maybe pushing that to 2:00. And interesting, actually, a few days ago, I went through a squat session, and it was like 4:30 in the afternoon, I decided to take 200 milligrams of caffeine, well, in an energy drink, which I know for me is quite light, and legitimately did not sleep that night. And so, I

know I'm much more sensitive where, man, I see, Arthur goes into the gym, trains at nighttime and will actively drink coffee or cans of Monster at like nine o'clock, and I was like...

ALAN FLANAGAN: And still sleep.

DANNY LENNON: Okay, that's just...

ALAN FLANAGAN: Yeah.

DANNY LENNON: Yeah, he seems to report no issue. Now that to me sounds like something strange is going on.

ALAN FLANAGAN: Or superfast metabolism maybe, I played rugby with a guy that would have, you know, make a French press in the evening, 8 pm, sit down drinkers, and he'd go to bed and sleep. And I was just like, how quickly is this, you are processing this.

DANNY LENNON: Yeah, I looked at some of those differences in clearance rates, and obviously, there's a genetic difference, like, I think there, most notably it seems to be a polymorphism with that adenosine A2A receptor. But interestingly, I found a paper that showed other things that had differences reported that reach statistical significance, that were actually pretty meaningful, if I remember correctly, but one was, smoking seems to increase clearance rates, particularly for people who smoked 20 or more cigarettes per day. And then the oral contraceptive pill seems to slow it down from at least what this paper was showing as well.

ALAN FLANAGAN: Right. The effect of OCP is interesting, because I think one of the reasons why caffeine has deleterious effects in pregnancy is because I think it's been reported that the half-life of caffeine doubles during pregnancy. Now, what hormonal milieu that kind of relates to I'm not sure, I didn't dig into it to that level. But that's just interesting that there is, like, I wasn't aware of that the OCP will have that effect of prolonging half-life as pregnancy will as well.

DANNY LENNON: Yeah, well, that's what seemed to be reported, and I think there does tend to be these trends towards slight differences between men and women with women slightly longer, at least from some studies, but I don't think it's actually that large a difference. But that would again would tie in, obviously, with adding to the impact of the oral contraceptive pill. But I find it interesting more than anything, that these things can impact that ability of clearing caffeine, and then potentially how that would tie into sleep disruption for different people.

ALAN FLANAGAN: Yeah, and I think the depth of sleep is also an important consideration because, yeah, like you, I've had that – I try not to train in the evening for multiple reasons. I find it hard to switch off afterwards, particularly, if there's been caffeine. But I find that if I do the odd time just out of necessity, and I've had caffeine, say, later in the day than I usually would at like 4:00 pm, I still get to sleep just because I'm fatigued after the day and then after training, but I don't sleep deeply at all. I'm kind of just like in this almost semiconscious state until I wake up and then I'm pretty knackered the next day, and it's a cycle that isn't good to get into, because, of course, getting up the next day then is just like, oh this would just be one of those days where I'm knocking back double espressos for fun. And it's easy to get into that cycle with, you know, modern life is busy and we're on the go, and people have demanding jobs or they've young kids at home and they didn't sleep well the night before, and definitely caffeine can be, and coffee can be a good tool. But I think it's not allowing that tool to become a crutch is the important bit to be honest with.

DANNY LENNON: Yeah, the impact on my sleep is very similar, in that I will fall asleep, but as it happened the other day, woke up at 3:00 am, and had inability to go back to sleep. And between then, I'd say 7:30-8:00 was like maybe falling into periods of 20 minutes of sleep at a time, and it was just awful. And I am not one of those people that functions well with low sleep or can

even function. Some people are just really good at it, like, they get on with it. To me, it just ruins everything about my day, like, I'm just terrible for being able to cope with it. My eyes physically hurt me, and it's like my body is saying, what are you doing.

ALAN FLANAGAN: Yeah, I understand.

DANNY LENNON: That's just me being soft, maybe.

ALAN FLANAGAN: No, I've never...

DANNY LENNON: “I’ve gotta push through!”

ALAN FLANAGAN: I just can't – I can't function on low sleep. I can't function cognitively. I could get up and do, you know, run errands and stuff fine. But if it comes down to actually engaging the brain, lack of sleep is definitely, I would take good sleep over if I had to choose, gun to my head right now, and someone said, you can never drink coffee again, but you will sleep a perfect eight and a half hours a night for the rest of your life, you know, knowing the health implications, I would take the sleep and I'd suffer the lack of coffee. So I think, yeah, I think it's important to know that that is something that can have an impact.

DANNY LENNON: One area that I think is not super clear cut because there's many elements to it is related to coffee intake and how that has different impacts within the gut, and there's different areas here maybe we could look at. I know there's some emerging stuff looking at the gut microbiome, but I think more from the acute effect, where it's often seen referenced is the elimination of coffee is common in a lot of elimination style diets or as acute interventions may be for someone with IBS like symptoms or having some degree of gut distress that for a period of time people are recommended to remove coffee along with other things, whether that's spicy foods, etc., or as well as other foods are known to have some degree of high prevalence of intolerance. What is your kind of

reading on the situation in relation to coffee intake as it pertains to something like, say, IBS, or similar things?

ALAN FLANAGAN: I think it's one of those interests, so coffee has well established impacts on gastrointestinal motility and increases motility and transit time and often stimulates bowel movement. And this, interestingly, is one – so there's quite strong associations, again, with protective effects of coffee on some kind of internal organs, on internal cancers, and potentially with regard to colorectal cancer this may be one of the reasons. And so by increasing motility of the large intestine and with some of the antioxidant compounds and otherwise bioactive compounds in coffee, it may confer kind of a protective effect. Nonetheless, it's still stimulating motility in the bowel, and is something that can obviously kind of have an aggravating effect then on any kind of potential symptoms that relate to hypersensitivity and distension, which are two big parts of IBS and their terms of the sensitivity to motility and distension. So yeah, I think I find IBS a really kind of difficult area to, because even with regard to interventions like the low FODMAP diet and conjunction with that you do get this general recommendation to avoid, it's like spicy foods, chili peppers, coffee, dark chocolates and these foods, but you still may not even get symptom resolution with this intervention which I think speaks to a very psychosocial element, and I think there's a really big overlap with IBS prevalence in relation to either current prevalent or historic prevalence of mood disorders or otherwise. So I think that's an important variable because potentially there is the, you know, effects on gastrointestinal motility per se, but also potentially effects on some of the things we were talking about earlier, like, anxiety and kind of otherwise. So with IBS, yeah, just the more I look at, I'm always trying to factor in the kind of the fact that it's as much as there is nutrition related stuff going on, there's also clearly a lot of psychological related stuff going on, and it may

be important to try and always kind of juggle the two and consider the two. So that's my understanding, if we're just talking about the kind of physiological effects of coffee, my understanding is it's that effect on gastrointestinal motility. That's the kind of focus.

DANNY LENNON: Yeah, that point on IBS is something actually I talked with Anna quite a bit about, in that, oftentimes, when people are looking for a resolution to IBS, and they're going to a dietitian or so on, the focus seems to solely be on the diet, whereas she was like, there's like really clear and strong implications for things like stress, anxiety, other psychological issues that you mentioned, that can be driving this, and it may not be, and, like, she was kind of making the point that people are trying to jump to a low FODMAP diet, where that's like a level 2 intervention, and there's all this other stuff that needs to be put in place first to see if that gives this resolution of symptoms.

ALAN FLANAGAN: Yeah, general healthy eating pattern.

DANNY LENNON: Yeah, and including some of that psychological stuff, so yeah, that's a well-made point. Just actually while we're on the gut, and I mentioned the gut microbiome, which again is another area which is very hard to make strong conclusions about to say the least, I did find it interesting, I looked at one of the papers that Glenn Gibson and his group at the University of Reading published, just because he was on the podcast recently, and they did an in vitro study. So obviously, this is not in humans, but it's a kind of model that they used of the colon in the lab, but they showed that coffee with the highest levels of those chlorogenic acids led to the significant increase in the growth of Bifidobacterium. So that would indicate that, potentially, there's an impact on the gut microbiome of coffee ingestion, and it could come down to some of those polyphenols, those carbonic acids that you've already mentioned, as opposed to some other element of it. So

again, an in vitro study, but it's kind of interesting to note that there's potentially an impact on the microbiome...

ALAN FLANAGAN: And that would be consistent with some of the wider kind of polyphenol flavonoid and anthocyanin research in particular that has looked at the gut microbiome, microbiota as a modulating factor and quite an important one, because it's the metabolism of these compounds by bacteria that creates these kind of secondary metabolites that are then absorbed and have biological activities. So yeah, that seems to me, in terms of if we're talking about chlorogenic acids, which are polyphenols, that that would be kind of consistent with some of the other kind of research looking at the modifying effects of the microbiome on this.

DANNY LENNON: Speaking of those chlorogenic acids, they tend to be one of the things people point to when the topic of coffee as an appetite suppressant comes up. So I mean, for the longest time, people have talked about using black coffee when they're either using intermittent fasting in the morning and then their black coffee helps them keep hunger at bay, or people who are just dieting over a long period of time may self-report that it reduces hunger at certain times. With that area of research, do we have anything solid that's actually showing that coffee actually does suppress appetite in any meaningful manner?

ALAN FLANAGAN: I think there is some mechanistic support for – and I think there's some human intervention support for the kind of short term appetite suppressing effect of caffeine that is secondary to its sympathetic nervous system activity in terms of increasing that. And I can't recall, like, magnitudes of effect, and obviously a lot of these things are gauged subjectively, so it's kind of difficult to say what that would mean for an individual. But yeah, I do recall that that is an effect secondary to the increase in it – again, we can draw on other lines of evidence

that tend to support the downregulation of appetite in situations of heightened sympathetic nervous system activity. To what extent someone could use it during fasting, dieting, at the end of the day, hunger will typically, I think, eventually outweigh appetite in conditions of prolonged caloric restriction. So yeah, for short term, intermittent fasting or time restricted feeding where the window is kept consistent from day to day, and if someone was skipping breakfast and fasting until midday, then yeah, like, that kind of transience effect of caffeine might be enough. But for long term dieting, it's difficult to see how that would consistently weigh out over the effects of caloric restriction, which would eventually win, we know that would win.

DANNY LENNON: And as with much of this stuff, it's difficult to piece back to what mechanistically is the reason if there is observed lower hunger levels, let's say, if we're looking at coffee as a beverage as a whole. One study that I did see that showed lower hunger, I think, as a self-report, but also higher levels of PYY, which would indicate there's some degree of physiological effect happening which could impact hunger, actually showed a slightly better impact for decaffeinated coffee than the caffeinated version. But then when I looked into, I think they had to make the beverages in whatever way they were trying to standardize it, there was 40 grams of the caffeinated coffee used versus for the decaffeinated it was like 57 or 58 grams. So if it was something like chlorogenic acids, let's say, that was responsible maybe just because more often because it was more ground coffee used, as opposed to something specific about the caffeine...

ALAN FLANAGAN: The caffeine, yeah, because that's, I do remember a study that looked at different levels of caffeine followed by an ad libitum meal, but they were looking at a dose, not coffee, as in it was coffee, but they were specifically adding the dose of caffeine which was quite high. And I think with the highest

intake you had this reduction in the amount of food consumed, so then they have the coffee different milligram doses within the coffee and then an ad libitum meal is presented. And if I remember, then the people with the highest caffeine consumed less at that ad libitum meal. So it suggested some kind of acute effect that seemed to be mediated by the caffeine, not coffee. But yeah, there does seem to be, whatever the mechanism is, there does seem to be certainly an acute effect of kind of appetite suppression.

DANNY LENNON: One other thing that I do want to ask you about, in particular, given the area of your research would be around circadian rhythms and caffeine, and either, in one sense, how someone could negatively impact some of the aspects of circadian biology, but then on the other side, using caffeine in a targeted way to overcome some of those things, whether that's jet lag, social jet lag, etc. What are some of the main things you would typically tell people to be aware of that relationship between caffeine ingestion and circadian rhythm?

ALAN FLANAGAN: So there's still a little bit more research to go because it's not as well-known yet, and obviously, as far as what are know as chrono-therapeutics, as in, therapeutic either kind of interventions or supplements or medicines that impact, a lot of the focus is on melatonin, supplemental melatonin even for jet lag and otherwise. But it is known that caffeine has a kind of a chronotherapeutic effect, and if I recall, it's generally to kind of like delay melatonin rhythms and that can be helpful in the context of overcoming jet lag. So parking for now the sleep factors and considerations that we discussed previously, which still stand, but they assume you're just in your habitual time zone, if you were, for example, to fly from Dublin to New York and you've got this kind of five-hour time difference where your two o'clock in New York is 8:00 am there but you have this differential where you're now facing extended wakefulness, in that circumstance,

caffeine can be quite useful not only for the wakeful effect, but over the course of the next couple of days of adjusting to the new time zone, caffeine in the morning timed with adequate outdoor natural light exposure can, it seems, have a contribution to resetting of your kind of rhythms in melatonin aligned to that new light-dark cycle time zone that you're in. There's way less on that then there is for melatonin as a supplement. So obviously, supplemental melatonin, is still, but that's not always available. So it's not so, yes, caffeine can be useful in that context, it can be useful. Flying east is generally the hardest. Just as an anecdote, I remember going to Sydney through, so Dublin-Dubai-Dubai, and then that Dubai-Sydney flight was like 14 hours, and going down for a wedding, so I was only going to be there for a short amount of time, and I didn't want to be that jet lagged. So I started kind of doing some shifting in the three to four days before I flew. But I was landing into Sydney at 10 o'clock that night, and so I slept a Sydney night's sleep. What would be Sydney time? The night before I left. And then on the flight from Dublin to Dubai, which coincided with that, and then I used coffee, I just basically drank the Galley on the Emirates flight out of coffee to stay awake, to use that as the means of achieving extended wakefulness. By the time that I got to Sydney, I was so knackered that I went to bed at 11 o'clock Sydney time and slept a normal night's sleep. So you can use now, but that was me being an antisocial weirdo, like, flying on my own, I was able to do all this stuff where I was timing exactly when I was going to sleep and wake relative to the time zone that I was going to. Not everyone's up for that.

DANNY LENNON: You've got to cut people out of your life and take this seriously!

ALAN FLANAGAN: Yeah. So I wouldn't have been great company but yeah. So yes, caffeine can be useful for traveling both east and west in different circumstances, generally as a means of

achieving extended wakefulness to help adapt to either where you're going or where you've got to. Both there does appear to be a kind of chronotherapeutic effect of caffeine itself in terms of maybe delaying melatonin rhythm. So it could be useful if you're, for example, in a new time zone where internally melatonin is like, oh it's biological nighttime now, but it's not, you're in LA and it's now 8:00 am. Having caffeine at that time point, in addition to natural light exposure, may help kick that melatonin rhythm back and back and back. There's only a limit to how far it can go back, which is why even if you do all these hacks, you can still only shift the timekeeper in your brain by about an hour a day. So there will always be a residual effect of jet lag, but you can do your best to mitigate how brutal it is, particularly, if you're flying to Australia or kind of going east, it's always worse going to Asia from Europe. I think it is maybe worth mentioning that, like, when it comes to a lot of the research on, say, the kind of acute effects of polyphenols and otherwise on cognition, a lot of those interventions are using different polyphenol rich foods. With coffee, there is the additional effect of caffeine, and caffeine is interesting because it no doubt increases alertness and attentiveness in tasks for which those domains are important, but it’s not a panacea as far as like short term – there's a trade off in terms of some of the tasks that require fine motor skills, for example, or are kind of reliant on, like, accurate as opposed to just speed, reaction times, you'll see a decrease in that. Now, we're talking about kind of very small effects in acute circumstances, but I think I've always found that interesting because we tend to obviously use caffeine for alertness and wakefulness. But it does appear that there are some tasks where you would get better performance from green tea than you would from caffeine or coffee. So I think that's a kind of cool area of research. And yeah, you can tailor your tea and coffee consumption to whether you're doing something that requires kind of like more focus

and attention to just like pure alertness and that kind of reaction.

DANNY LENNON: Hopefully, your surgeon isn't taking a gram of caffeine or so on maybe.

ALAN FLANAGAN: Yeah.

DANNY LENNON: There might be some tradeoffs. Yeah, I think that covers nearly most of those. The only thing I think I've actually made a note of and some of the acute effects that are sometimes asked about is fluid balance because of this diuretic effect of caffeine. But I think, largely if that's consumed as coffee, what diuretic effect you have is more than compensated for by the water content of that beverage. And so, it's my understanding that there's a probably net positive impact on food balance as opposed to a net negative impact on food balance or hydration status.

ALAN FLANAGAN: Yeah, I think if I remember one study that was pretty cool, they did it up altitude, because being at altitude is known to impact on fluid retention and water balance. So it's a potentially dehydration environment anyway, and looked at like coffee and tea consumption and found no change in hydration parameters, because yeah, you're still getting the fluids. So yeah, I think that idea that coffee or even tea is dehydrating is now kind of put to bed.

DANNY LENNON: So as a general conclusion, we could leave people with broadly that for most health impacts of coffee consumption tends to be a positive impact at what seems to be moderate intake to that three to four cups per day range, and we have this typical J or U shaped curve for most of those things, and that the downsides would be either specifically when someone is consuming that or if there's some sort of individual susceptibility to metabolism let's say.

ALAN FLANAGAN: And those kind of individual considerations, yeah, aside, the general recommendation – or

it's not a recommendation, but the general, yeah, sweet spot would be seemingly anywhere between one to four cups a day is safe and broadly associated with a kind of a range of health outcomes. And then, there's obviously the caveat of kind of pregnancy, but there are specific guidelines in relation to that now, and it's quite clear that caffeine is recommended to be minimized in that life stage. But other than those specific considerations, yeah, I think there's a fairly consistent body of evidence for benefits.

DANNY LENNON: One thing that we probably might not need to mention with our typical audience, but I think is worth mentioning is that all of this, and when we talk about these health benefits, and these dose responses couched in the presumption of it being like a black coffee, Americano or something similar with some, maybe a splash of milk, but not a large Frappuccino filled with cream and tons of sugar...

ALAN FLANAGAN: Tea frappe with whatever else.

DANNY LENNON: In that context, if we're talking about coffee across the day, you have to factor in, if there's sugar, syrup, cream, etc., all added in and what that does. So, yeah, we're talking actually about the coffee itself.