DANNY LENNON: Hello and welcome to Sigma Nutrition Radio. This is Episode 387 of the podcast. I am Danny Lennon and I am here with Alan Flanagan. Alan, how are you today, sir?

ALAN FLANAGAN: I'm good. I'm slowly getting more and more freedom with every passing week.

DANNY LENNON: But more work on the PhD underway.

ALAN FLANAGAN: Yeah, so the study is still running, I've a good cohort running right now that largely came from actually the last episodes that went live. So if anyone is now listening to this, that would like to take part, do email me, and we can get you enrolled. So yeah, it's good. Sample size keeps getting bigger. Keep recruitment open till August. And yeah, on top of all of this, I can actually go to a pub. So I mean, things really couldn't be better.

DANNY LENNON: Yeah, certainly a different picture to maybe this time last year.

ALAN FLANAGAN: Yeah.

DANNY LENNON: So things are looking good. And given that your current studies are looking at things like social jetlag, chronotype and so on, is very much

related to what we're going to discuss today; and we're going to be looking at the impact of shift work on health, And there's probably kind of three segments we're kind of going to break this down into; we'll look at an overview of some of the health consequences of shift work; we'll then dig into some of those mechanisms that are responsible for causing those health outcomes; and then finally, we will try and discuss some potential strategies that might be useful for those of you who do shift work to be better able to mitigate or offset some of these issues. And so, with that, hopefully it won't be all bad news that we will get around to something where there's a bit of optimism towards the end. So to start, it's probably worth acknowledging that when we discuss shift work, there are, of course, many different types of shift work here. A lot of our focus is probably going to be looking at either nightshift work or at least in some component where there's a shift later on. But of course, there can be various different types from nights that are alternating to ones that are continuous or done in blocks, whether someone's doing eight-hour shifts, 12-hour shifts, 24-hour shifts, depending on what we're looking at. And then what we might even discuss is situations where some of these issues can be even more compounded like a flight attendant, where you're not only doing shift work, but you're traveling across time zones as well, which will be relevant as we get into that. So maybe as a broad way to open up, if we think about some of the epidemiology here and why it's even a question to discuss shift work and human health, what is, I suppose from an overview in your mind, some of the things we're pretty clear on from a population wide level of those who do shift work in terms of associations with various chronic diseases?

ALAN FLANAGAN: Yeah, I think the overall picture of research in relation to circadian misalignment generally of which shift work is and jetlag trans meridian travel are particularly extreme forms is fairly consistent in direction of effects with increased

risk for an obesity, diabetes, cardiovascular disease, and we see that particularly with nightshift work in overnight work. And there are a lot of moving parts to these potential associations that go way beyond diet. There's the effect of sleep curtailments itself or sleep deprivation in terms of a full 24-hour shift. There's the fact that circadian rhythms in the body rely on synchrony, and rely on consistent signals from the external environment in order to synchronize. And so, continually disjointing and desynchronizing those rhythms and never allowing them to appropriately resynchronize to a new routine, which is what shift work does because it's constantly changing; or jetlag, yes you can adapt, but if you're doing a three-day layover, then you're suddenly coming back in the other direction. So you've just been perhaps adjusting to a new light-dark cycle and behavioral timing, and the next minute you're on the way back from LA back to London kind of thing. And then you're back here and then wherever you go to next.

So these are all examples of where the body essentially is in a constant state of misalignment between its behavior cycles and its biological rhythms. And that, in and of itself, maybe particularly for cardiovascular disease, because of circadian rhythms and cardiovascular tissue, I mean, there's the statistic that you hear every year with daylight savings in the week afterwards. There's like a little peak and increase in incidence of cardiovascular events. So even though we're talking about one hour in the difference, the putative mechanism is reflecting how kind of tightly synchronized a lot of these biological rhythms are.

So shift work jetlag in a classic sense, transmeridian air travel, and then less severe, but potentially equally relevant are factors like social jetlag, which is the disconnect between an individual's desired sleep-wake cycle that they might have on free days or days they don't have to work or whatever, with the enforced

waking that they may have to do for a commute or otherwise. And there are some associations now between social jetlag and an increased cardiometabolic risk, although the magnitudes of that association may not be necessarily as strong for as it would be for nightshift work in relation to multiple outcomes. And it's still there, and it still suggests that we don't necessarily have to travel from here to East Asia in order to experience this disconnect. And, in fact, this disconnect can be something that compounds over time, if our, again, behavioral cycles and our preference for the timing of our behaviors, in terms of work, sleep, waking are not aligned to our preference, and are, in fact, constantly being knocked around because of social commitments or otherwise. So there's various kind of degrees of way in which circadian misalignment can occur. I mean, obviously, for the purposes of today, we're going to focus more on nightshift work, in particular, shift work generally than some of those others.

DANNY LENNON: And I guess, when we come to looking at some of these long term chronic disorders that are at least associated with a higher prevalence in those who do shift work, there's both this direct effect that you discussed where circadian misalignment in and of itself can have this issue; but then there's also probably a series of indirect effects that occur when someone does shift work – so we know that their sleep is going to be disrupted, quantity is probably going to be reduced, we know that could probably interfere with their ability to have other types of healthy behaviors. So if we take the case of someone who does nightshift work, they obviously have less availability to get to a gym that's open or be a sports teams that do activities, etc., or even access better quality foods during a nightshift in terms of places that are open, and maybe we can discuss some of those other barriers. And then there's also the impact on their social life, family and friends, etc., that, in turn, can maybe impact their psychological health, both acutely, but then

probably longer term as well. So there's all these things tied in together that we have both this direct physiological effect of misaligning someone's circadian rhythm as well as all these other kind of secondary effects that kind of compound the issue, I guess.

ALAN FLANAGAN: Yeah, absolutely. And those secondary effects certainly may add up to essentially equate to a causal mechanism, and kind of thinking about Kenneth Rothman and Sander Greenland's causal pie model, if you have all of these secondary effects that all add up, because they're all independently factors that are not only important for health but interrelated. So if we're talking about the adverse effect of nocturnal food intake on blood glucose and insulin levels, which we know is something that is profoundly impaired during the biological night, but we can also then look at research that shows that sleep curtailment in and of itself impairs, profoundly impairs glucose tolerance. So you get into kind of chicken and egg to an extent, but the reality is, a lot of these factors all overlap.

So yes, there is, in and of itself, an adverse effect of biological night energy intake on cardiometabolic risk factors and metabolism. But then we have a negative effect of sleep curtailment and impaired sleep, and that extends into the next day. And that's something that sometimes isn't really accounted for in some of the studies on nightshift work in particular, it's like, it assumes that the exposure is like the nightshift itself and then kind of stops there. But actually, when we start to think about the knock-on effect of impaired sleep on metabolic processes as well, then we can see that the effects even of one nightshift would extend into the next day – three nightshifts in a row, and suddenly we're starting to be able to imagine that there would be quite a knock-on effect of a lot of these interrelated factors.

And I like the fact that you brought up the, I guess, more psychosocial components, because I think that's often very underappreciated, particularly in some of the nutrition literature, like, we see significant impacts on quality of life. The research that I based my MSC thesis off, and we've published one paper from that, and we're writing up another at the minute, was a sociological study into the effects of nightshift work on an entire family unit, and that was in 20 nurses working in the NHS – but reading that original research and looking at the effects that it had on their partners or husbands and on their dependent children, so I think that's a really important part of the whole equation, and it may also then – and this is the paper we're working on right now, there could be a potential impact if a primary caregiver, you know, if someone with a primary responsibility within the household, for example, cooking and food is out of the household in the evening, what's the knock-on effect potentially for dependent children in terms of their dietary intake.

So with shift work we see impacted quality of life in terms of mood, we see impacted quality of life in terms of then increased reliance on stimulants, and a lot of this has to do with the fact that the rest of the individual working nightshifts, the rest of their social structure, their friends or their family are operating as the rest of society does on a day social routine. So if they want to go to kids' play and school or match after, you know, they have to be functioning during the day, and the ability to suddenly just adapt to nightshift work doesn't happen because of our biological rhythm. So yeah, I think the quality of life impact on psychosocial health and on the wider friends and family and social structures that any individual that works nightshifts has is a really important part of the equation that sometimes gets overlooked.

DANNY LENNON: Yeah, and it's something I try to remind myself of when we're thinking about, well, what

potential recommendations could we give someone, and so, we'll probably discuss this in a bit more detail later on. But for example, even if we're to try to hypothesize what ideally would someone's diet look like, trying to do that in the context of a situation where we now know someone not only has to have restricted sleep and this circadian misalignment that then can have direct impacts on say, their mood acutely, but then that's also in the context of maybe straining relationships, or not being able to have their usual support circle, all these other psychosocial factors you just mentioned, and then trying to layer in ideal nutrition or exercise guidelines, it's hard to make those changes if you're in a certain state of mind, I guess, or, at least it makes it more difficult. So I think before we dig into some more of the details, because you've brought up circadian misalignment and the idea of social jetlag, and the fact that this is something you're working on right now, I think it might be really useful just to lay that out in even a bit more detail, not only when we're talking about circadian rhythm disruption, what is actually going on, so in terms of, well, what happens with these kind of circadian clocks, but then how does that actually translate to having an impact on these various body systems that are negatively impacted by it?

ALAN FLANAGAN: It's always helpful to remind ourselves of what we're, because the word itself, you're kind of like, okay, circadian. So it comes from the Latin circa-around, and dies meaning day. So around the day, basically reflects the fact that these biological rhythms run over a period of around 24 hours, and these rhythms exists in all animals, all organisms, for the most part, and the length of the rhythm may differ in humans – our rhythms are slightly longer than the 24-hour day. And so, because they're slightly longer, if we were to take a group of people and put them in a cave with literally no light input, no other environmental cues to let them know what the time was, no clock or anything, then their rhythms would become desynchronized

from the outside world, and would run at a period that's a little over 24 hours. But they would still follow a rhythm in that environment. They would still be low at a certain point and peak at a certain point. They just wouldn't be synchronized to any external cues.

So in order to synchronize them to the 24-hour day, because the day is 24 hours, we rely on different cues from the environment. The primary cue is light, and that is something that our eyes sense. We have special cells in the eyes that relay the information that they're detecting from light to a special place in the brain, that then gives this master clock, as they call it, this global signal that it is daytime, it's nighttime, and it can start to use that light information to make sense of the external world. But now we really appreciate that there are all of these other clocks in every tissue and organ throughout the body, and they call them peripheral clocks, previous thinking would have been that these peripheral clocks would have been subservient to the master clock. Now we know that they can actually function independent enough. So for example, if my main clock in the brain is synchronized to the normal light-dark cycle as it is here in London, but if I suddenly changed my mealtime, then the clocks in my liver could shift and become synchronized to a new meal time without changing the timing of the clocks in my brain. So there's an independence of these clocks. But in order for optimal physiological function to happen for an organism, you want synchrony between these clocks throughout the body. And so, these rhythms that would run and they're all synchronized to a particular period, run best when the cues that they're getting that may just be obviously beyond light, it's the timing of nutrient intake, it's the timing of activity and behaviors, it's the timing – it's even things like temperature.

So there's all these different inputs from the environment that coalesce to create a state of

synchronization between all of these rhythms to the 24-hour day, so that they can time their rhythms and when they rise and when they fall appropriately. So what we're talking about with circadian misalignment is when those rhythms become desynchronized, and they're getting different time cues, or the main clock in the brain is getting weird light signals because people aren't outdoors enough, or then in the evening, they have highly illuminated homes from plasma screens and this kind of thing, and then there may be erratic timing of other behaviors in terms of meal timing or exercise or any of these other variables, social interaction. So it can make for an internal set of different rhythms that are all pretty confused about what the actual time is externally that they're being asked to synchronize to.

And I think the best analogy could be that of an orchestra, right? So you have the master clock as the conductor, and you have all of the pieces of the orchestra as different clocks in different peripheral tissues, and the orchestra is capable of ignoring the conductor and playing on its own, but it would sound terrible. And the whole system works best when the orchestra play in a way that's in sync with each other, and in a way that's following what the conductor is doing. And when every different piece in the orchestra, when the violin goes off and starts getting weird signals and doing its own thing and playing its own tune, and the oboe is playing its own tune, and whatever else, the clarinet's playing its own tune, well, then we have a mess, and it sounds terrible, and that essentially is kind of what happens in terms of internal desynchrony and misalignment. And when those things are misaligned, well, then really important processes that relate to our cardiovascular function are our blood glucose regulation, insulin, a number of metabolic processes, even things like cognition, all of these factors start to get perturbed. And over time, the hypothesis is that this chronic level of desynchrony then adds up to disease.

DANNY LENNON: At this point, I mean, one way to think about it is, in an ideal world, we want, if we were to think of that daytime period, is where we're going to get the exposure to light, particularly early in that daytime period, it's going to be when we are consuming food, because that's again, one of these other environmental triggers, and it's where we're going to be active. And then at nighttime, that's typically where we'd want darkness, we'd want to be fasting, not consuming nutrients, and then we're going to be at rest, i.e., asleep. So a change in one of those is where we have this misalignment that's going to occur, and that is going to be essentially desynchronization between either these behavioral rhythms and these internal rhythms, or even between different clocks within the body. So as you outlined, there could be a difference between what the central clock is and the message getting versus the one at the liver, for example, and that's going to make some of these various processes go awry, whether that's glucose tolerance, etc. So because of that, that's why we think about, well, how can we time light and dark exposure appropriately, how do we time eating etc. And I think given all of that you've laid out from a shift work perspective, this is why, again, the type of shifts may have a role here, where we know that, I would say, probably the majority of people that do some degree of nightshift work, don't usually do it continuously all the time, it tends to be in these rotating shifts. So based on what Alan just said, when we get these phase shifts and this desynchronization, that makes it even more problematic if you have to change these shifts very regularly, particularly, if it's happening every day, every second day, or changing shifts across the week. Whereas at least for someone who, let's say, continuously only does nights, whilst not ideal, that has at least some chance of maybe an adjustment, so to speak, from – and maybe we can get into potential to adjust to it, but there's at least these alternating shifts are kind of giving the least chance of being able to adapt because of that constant changing time.

ALAN FLANAGAN: Yeah, and I think it's really important to clarify that the system is inherently adaptable and flexible. And we know that, and I'd say most listeners in the modern world know that because most of us, I imagine, have experienced some degree of jetlag. And in an extreme example, if I flew from here, from London to Sydney tomorrow, I would be going into time zones, and I would get somewhere where there's a nine-hour difference between where I've come from and where I'm now at, I would be discombobulated; my internal clocks would be anticipating this, it's an anticipatory system. So I would be anticipating it to get light at a certain time and dark at a certain time, and it would be the exact opposite, essentially, and I would be anticipating to eat at a certain time, but I would eat at a time, which in my body, in terms of its time would be like 2:00 a.m., and my gut wouldn't feel great and this kind of thing. But over time, over a course of maybe a couple of days, I would eventually adapt to that new time zone, and then I would adapt there, and I would certainly be on that timing.

Now a question that I've had before, particularly from people who work shifts or are extreme either morning people or night owls, tend to get this more from night owls, is they say, well, how can I change my time of day preference, how can I kind of make myself a morning person, can I make myself a nightshift worker. You can't really change your chronotype, which is what they call it, because it's largely genetic, although it is influenced by behavioral factors. So even if, although it's an adaptable system, once I got to Sydney, once I adopted to Sydney time, I'd still have my time of day preferences, because they're my time of day preferences. For shift work, and it's a really important concept is what you just described is the effect of just never allowing the system to adapt in the way that you would if you flew to a new time zone, and you were spending a couple of weeks there. You're working late evening shifts, then a day shift, then a nightshift, and

maybe as they tend to use rotational nightshifts, where you might work two to four nightshifts in a row, some people might work five, then rotate out and work, have days off, have a series of day shifts. And that's potentially more deleterious because you're never adapting to anything and you're essentially living in a constant state of desynchrony.

In an ideal world, if someone did work nights, they would essentially do what you would do with jetlag, and live and use different light cues and meal timing and essentially adapt to being a week during what would be the nighttime in wherever they live. That would be the same as adapting to a new time zone. But that's not a particularly nice way to live your life when everyone else is pottering around during the day. So for that reason, because of the social incompatibilities of that approach, rotational shift patterns tend to be the norm within professions that work shifts, whether that's healthcare or otherwise. But the knock on effect then is you're kind of constantly living in a state of circadian misalignment and you're never actually adapting to the nightshift, and then you're never really adapting to the day shift, because then you're back on nightshifts and all this kind of stuff.

DANNY LENNON: Yeah, there's a couple of really interesting components to that. So I think on the chronotype issue, where some people are morning types, and some are later types, that would kind of give rise to the idea that there's at least some interindividual difference in how people may tolerate certain types of shifts. So for nightshift work, for example, it may be easier for someone to adapt to, if they're typically late chronotype, whereas someone doing a very early shift, getting up at 3:00 or 4:00 a.m. might find that easier to adapt to if they're an early type than someone who has a late type, for example. But given that most people are probably some type of intermediate that that may be difficult, and the fact that

most people are going to have to take through them, it may be not worth trying to think about changing your chronotype. One of the interesting things are on the adjustment, and I think there's more of a practical issue, because you mentioned that for someone who is doing, say, only nightshifts, and if they were permanently nightshift workers, they then theoretically have the opportunity to adapt to that and stay basically just living at that level. However, the practical thing is most people who even are permanent nightshift workers, won't choose to do that because of things in society that tend to be open during the day, social interaction, so on. And I think there was actually one paper that I read where they looked at permanent nightshift workers and kind of asked that question, did they show circadian adjustment, and I think there was like less than 3% of them had complete adjustment based on their endogenous melatonin rhythm to the night work, and one in four showed a sufficient level of adjustment. But again, that's probably owing to the fact that behaviorally, the way they were living their life, they weren't going to completely switch to just living as a nocturnal being forever.

ALAN FLANAGAN: Yeah, as a nocturnal being, yeah. And so, that's where the social factors influencing really the whole picture become quite important, because in many respects, they're deterministic of the kind of shift schedules that places tend to work, and, like you say, even where there's an opportunity to be exclusively a nightshift worker, the idea that someone then just adapts to their timing based on that, and essentially inverts local day and nighttime where they are, it just doesn't happen in the real world. So you, and I think this is also helpful for conceptualizing even social jetlag, because if someone has an individual time of day preference for being what they call a night owl, the research shows that night owls don't tend to compensate, even if they have an early wake time, they don't compensate by going to bed earlier, because they're just not tired. It's 9:00

p.m., and they're just like, I'm just hitting my stride. So they go to bed when they're tired, as most people do, but then they curtail sleep on the front end, so to speak. And that means that they're kind of constantly going through their working week with this state of sleep curtailment accumulating this kind of sleep debt, and then on the weekends, they may choose to go to bed at their usual time, maybe it's a one o'clock or midnight, but rather than have to get up at 5:30 for a commute, they're now able to sleep till 9:00 or 10:00.

And so, that's how epidemiologically, social jetlag is computed – you look at the midpoint of an individual's sleep when they're free to choose their sleep-wake cycle, and you compare it to the midpoint of sleep during their working week, and you correct for a bit of sleep debt, and then you get this score in hours that reflects their social jetlag. And again, what we've seen in some of the studies that have looked at this as the exposure is that increasing social jetlag is associated with adverse cardiometabolic outcomes. So it's important that, I guess, shiftwork in general, and nightshift work would have more profound effects over time, but we can have more consistent but less extreme disruption or misalignment can also add up over time.

DANNY LENNON: If we think about then some of those indirect effects and, maybe for our purposes, one of the more central ones is impact on dietary choices, this is something I know that obviously you've looked at in terms of some of those healthcare workers in the NHS that you've done work on; but there's also other various surveys and case studies around the place looking at nightshift workers and the impact, number one, on food choices during their shift compared to say off days, but then potentially even in the day afterwards, where we're going to see sleep curtailment. So in terms of those changes in food choices, and I know we see things like increased snacking or maybe the types of meals that end up getting consumed, and we can talk

maybe in a moment about some of the reasons why that's the case, but what are some of the most common findings that tend to get reported in terms of food choices or changes in maybe food habits that occur when someone is doing nightshift work, specifically?

ALAN FLANAGAN: Yeah. So I think one of the most interesting findings in the literature, particularly where it's compared nightshift work to a fixed day worker, is that there's no evidence really that nightshift workers consume any more total daily energy in a given 24-hour period. And this is important because previously the associations with increased diabetes and cardiovascular disease risk, the kind of hypothesis was, well, if you're just awake longer, you eat your normal daily food intake, and then you eat more on top of that. So it's the energy surplus, increasing adiposity, that kind of thing. But we actually don't have any real evidence from different cohorts and different populations that nightshift workers consume any more total daily energy compared to a fixed dayshift worker. So again, this kind of suggests that the pattern of energy intake and the timing of, you know, relative to nightshifts is important.

So what we tend to see is a redistribution of energy into leisure time bin, so to speak, from nine o'clock to say 7:00 a.m., you tend to see a redistribution, so that proportionally more energy is consumed during that nightshift phase, and that's been shown in a number of studies. You tend to see an irregular meal frequency, and so eating patterns, even on nightshifts can be quite erratic, and that can extend into the next day as well. So you end up with this kind of erratic pattern of eating that is kind of very irregular and changing. It correlates with increased frequency of snacking, as you mentioned, kind of preference for hyper palatable foods that tend to be rich in sugar, starch and fat. That may relate to sleep curtailment as well. It may also simply relate to psychosocial factors like comfort on a

nightshift. Or it can also relate to just the need for something that's energetic and easy to consume.

There's some evidence that, for example, there'd be higher sugar sweetened beverage consumption on nightshifts, lower dietary fiber intake, higher animal fat intake, all factors kind of from a dietary perspective associated with nightshift. So I think the best way of characterizing it is a disruption to the pattern of energy intake and to meal timing, more energy intake obviously coming during, what we would call the biological night, at a point in the circadian cycle when the body is not anticipating food intake, and our metabolic processes are not aligned for anticipating food intake, so we have adverse responses to food intake at 2:00 a.m. or 4:00 a.m., and patterns of dietary characteristics that reflect the kind of energy dense, low nutrient type of foods.

DANNY LENNON: Yeah, and I think it's interesting to think about some of those barriers to making healthy food choices, because looking at some of those research papers that include surveys or qualitative studies looking at nightshift workers, it's interesting reading through some of what they're reporting. So one, for example, would be many of them report like a lack of an actual break during a nightshift to be able to access appropriate food. So I know there was one in paramedics where they would say, in order to save time on their shifts, because they don't have a set time where they can get a meal, if their partner that they're working with, their colleague that day is getting a takeaway, then they were much more likely to go and purchase takeaway food, they're not going to try and say, we'll have two separate breaks for me to prepare my own. You look at the workload for typical shifts, and particularly in healthcare, where if you talk to nurses, yes, maybe the hospital is less busy during the night, but it's also vastly understaffed in most cases, I would guess, access to food whilst working. So it's interesting to consider things like long haul

truck drivers who are doing like 24-hour shifts continuously, who are often driving throughout the night, what food they have access to is typically be where they can stop and get convenience foods, or, even in healthcare settings, oftentimes, you'll find cafeterias within a hospital typically closed during the night. So again, it's relying on can you bring in your food which requires time to prepare ahead of time, etc., etc. So there's all these barriers beyond just knowing which foods would be better or not to consume.

ALAN FLANAGAN: Yeah, I remember also speaking into someone, I can't remember what NHS trust they were in, but they closed the canteen, so whatever about the little cafeteria not even being open at night, but they then shut the canteen – devastating effect on morale generally, because now there's just nowhere to even just put the feet up and take a break. And yeah, I think all of those barriers, I remember studying firemen in Australia. It was qualitative as well, which is really interesting, because you were getting a sense from the qualitative interviews that they were conscious of the effects of shift work, they were trying to eat healthier, but there's all of these barriers that then, like you described, access the pace of whatever the work shift actually is, particularly if it's paramedics or policemen or people in kind of public services, they're not getting a lot of breaks.

And then it's not particularly great being awake at 3:00 a.m., whatever you're doing, if you're trying to function. And so, there is some of that research that suggests that cognitive fatigue leads to a self-selection for very energy dense foods. So maybe that's playing into it as well as the kind of just access and culture components. So yeah, it's really difficult to unpick. I mean, as an anecdote, I remember just the study, the lab study we were running, where participants were – it wasn't even fully, but because they were simulated jetlag, they were awake till 4:00 a.m. or 5:00 a.m., and I remember at one phase, it was probably about 2:00 a.m. and

there was this Jamaican ginger cake in the nurses' canteen, and like best laid plans of mice and men, I think I ate about half the thing. There were no breaks in the brain saying stop, so that was an experience that definitely, because I've never worked nightshift, so that the closest I've ever come to was being kind of awake for that study. And there is nothing in your head that can convince you it's not a good idea to eat all the ginger cake at 3:00 a.m.

DANNY LENNON: And it's interesting, because again, most people that are working in those settings, it's not like they're even in charge of that food environment anyway, because food is either provided there or someone else orders in food; typically, it gets ordered as a group, or there's just food and...

ALAN FLANAGAN: People bring it in.

DANNY LENNON: And some candy left around, yeah. So yeah, it becomes much more difficult. I think one of the really interesting things, as maybe we start transitioning towards actual strategies that people can think about using, that is a difficult balance for people to strike and to think through is that we typically give people recommendations about good sleep hygiene, how to get good quality sleep, and there are kind of like a set number of standard things that we do. However, then we take someone who does nightshift work, and who needs to perform whatever task they're doing, both physically and cognitively, for example, you mentioned that people are looking for a source of energy as they're going to be busy throughout that nightshift. There are other kind of best practices for fatigue management. So common examples would be like, say, the use of caffeine or regular frequent napping throughout the day, etc. that can offset some of this fatigue, that in a fatigue management world would be best practice, but sometimes are at odds with typical things we talk about for best quality sleep. So I'm wondering how do you tend to kind of weigh up those two things?

ALAN FLANAGAN: Yeah, I mean, I think the first thing is, if it's rotational shift patterns that we're talking, well, then the kind of two to three shifts in a row, nights in a row, we know that that's not sufficient for adaptation. So the idea that one kind of becomes adapted to that phase in that short time period, it's not likely to happen. So it's potentially about mitigating the effects of the nightshift, while trying to broadly maintain more alignment to the actual daytime or the day-night cycle, shall we see, for the reason that when the nightshift period is over, you're hopefully more kind of aligned with going back to the day social routines and behaviors. And so, that means potentially things like thinking about the meal timing on the days and across the days that nightshifts are being worked, thinking about light exposure, thinking about the timing of sleep, thinking about stimulant use in terms of caffeine, and all of these things, trying to kind of basically do the best one can, to mitigate the effects. And like you said, unless someone's working on an oil rig or in Antarctica, adapting to nights generally is not likely to happen.

So yeah, I think it's difficult because a lot of the advice still is very generic – even from a dietary perspective, it's just like, eat a general healthy, balanced diet; okay, well, that probably lacks some of the precision that someone working nightshifts might need. But that said, we don't really have any good evidence for any more precise strategies. We have evidence of negative effects, and you form recommendations based off what those negative effects have shown, i.e., trying to avoid it. But unfortunately, and I feel the frustration of shift workers in this respect, there's scant literature on positive steps that could be taken or positive interventions that could be taken to assist the pattern of nightshift work. But yeah, so I think, generally, considering meal timing, light exposures, and stimulant use, and all of that over the course of a period of nightshift work might be the best that we can do right now.

DANNY LENNON: And it's interesting, there's, in one of the papers that I'll link to, I think the ones I sent you, Lee and colleagues, they kind of use this term compromise phase position, essentially trying to get the idea of how can we like delay their circadian clocks to a position that is basically compatible with nighttime shift work and sleeping during the day, but is also at the same time not incompatible with the days off where they're going to be doing nighttime sleep, so this kind of compromise position of not trying to fully adjust to one or the other. And in that particular study, basically, they took people in, had them sleep from 11:00 p.m. to 7:00 a.m. for three weeks, did a series of nightshifts then that were 11:00 p.m. to 7:00 a.m. and had some days off. And so, they had the experimental group where they're trying to essentially get them to this compromise phase position using a number of those strategies you just outlined. So they gave them intermittent bright light pulses once per hour during the nightshifts, and they had them wear blue blocking glasses as they traveled home after work, and they had them sleep in pitch black room from 8:30 a.m. to like 3:30 p.m. the following day, whereas the controls kind of didn't do those things. So they stayed in a very dim lit room, they wore sunglasses that weren't actually blue blockers, so it didn't really attenuate as much of that light; they slept whenever they wanted to after the shifts, as opposed to kind of getting to early morning time. And so, at least in that study, you see that phase shift that occurred, I think they looked at body temperature as well as melatonin, so basically, that minimum body temperature being a sign of when sleep is deepest. So that is at least one case where if we're thinking about strategies that can be used, and then how practical some of them are, for everyone it may be different, but at least there are strategies here to try and think about, okay, how can I get myself into this zone where I can't completely adapt to one or the other but I'm putting myself

in a position where moving back and forth, it's not going to be as big of a phase shift.

ALAN FLANAGAN: Yeah, absolutely. That's exactly what we mean by mitigation, so it's not going to abolish any effects of the shift. And that's really well described, because it does appear that the shift in when someone's going to sleep and if they're sleeping in a dark room is going to cause a shift anyway, because that's going to have the strongest effect on the circadian system. But it can be controlled to an extent in terms of being consistent with those signals over the course of those couple of days. So the wearing of blue light blockers on the way home is one that I think is potentially quite helpful, because it allows someone to transition into their sleep phase, which may be say from 8:00 a.m. or whenever they're back, 8:30, into the early afternoon, it does seem like the early sleep morning and into afternoon napping is the most beneficial way to go rather than to kind of like continue to stay up and to maybe try to sleep from late morning to kind of later afternoon, and that may be just related to the actual magnitude of the phase shift itself, how far it kind of goes.

But also, there's some evidence that inflammatory markers and stuff like that are reduced more with a kind of morning and afternoon, so I think that strategy is also helpful. And then it can be helpful to try and maintain for kind of peripheral clocks, hypothetically helpful to try to maintain a meal timing that is relatively consistent with the normal day to day. And there could be – this is where we get more hypothetical – there could be a role for protein in this regard as a macronutrient that has kind of less deleterious effects on some of these processes like glucose tolerance and homeostasis. So having a kind of high protein like breakfast before going to sleep, when someone's back, allows them to then say, wake up from the afternoon in the early afternoon from that sleep, have a kind of light lunch meal and then a dinner meal and

then return to the nightshift. So actually, when they return from the nightshift period, when the nightshift period is over, they slip back more to a similar meal timing and they haven't drastically altered their meal timing as a result of nightshifts.

So that is potentially something that can help, and then I think from coming back to just the sleep standpoint, I think it's important to think of nightshifts, not just as the acute period of say three nights in a row, but kind of macro it out over the longer term. And in that regard, there is good evidence for the effect of, shall we say, kind of sleep extension and adding say two hours to sleep on nights in that after shift period can be helpful to essentially somewhat mitigate some of the factors influencing adverse effects of sleep curtailment. So that can be addressed by having some period of maybe three nights of sleep extension after that period of kind of curtailed sleep and sleep loss.

And I think that kind of brings us then to the potential for kind of more advanced strategies, maybe in terms of from a dietary intake. We've just highlighted all of the psychosocial reasons as to why people eat during nightshifts. So it's the purest point that does not take any of those factors into account, would say, well, the easiest thing to do is to maintain, roughly, maintain the meal timing that one might have on their normal day, active days, and don't eat or consume calories during the biological night. And while that's the best laid plans of mice and men, it may not for all the reasons we've highlighted be in any way something that someone, even if they wanted to, may not be something that they're really able to. There's the chrono group that Monash published a paper last year looking at high protein evening meal, and we know that that can, you know, high protein diets can have beneficial impacts on blood glucose regulation, and that was the outcome in this study, lower overnight postprandial glucose levels or postprandial glucose levels extending overnight or into the

early hours, I think they measured three hours afterwards. But that study dinner was at 8:00 p.m., so it's difficult to extrapolate that to suggest that will that be the case if a high protein kind of snack type meal to keep someone going was consumed at 1:00 a.m., we don't know, I think that research really should be done. There's suggestive evidence from – I think we touched on this yesterday actually, even from Jorn Trommelen and Luc van Loon's research group that have looked at overnight high protein feeding, nasogastric feeding.

So there's proof in concept that the gut functions for protein digestion during the biological night. Now, what effect might that have in terms of protein rich, low calorie snacks during biological night? We don't know. We literally just don't have that data. So there is still potential room for more research to find some potentially beneficial strategies. I would say that it is kind of unavoidable as a conclusion that energy dense foods, particularly foods that are rich in carbohydrate and fat during the biological night, it's just not conducive to metabolic health. Good time restricted feeding provides a kind of helpful strategy for people doing nightshift work. We don't really have any evidence specific to that question. We obviously have other TRF studies where they're trying to align food intake to the opposite of this really, to the point in the day in the early part of the day when metabolism is kind of more optimal.

So time restricted feeding could be beneficial, but it comes back to then you're deliberately using TRF to restrict energy away from the nightshift phase. And for a myriad reasons that may not be something that's necessarily possible, but between trying to control the period as best as possible from finishing a nightshift to getting home, minimizing light exposure at that time, because it's daytime, so the reason that the suggestion for the blue light blockers on the way home from work is if you come out of your hospital at 8:00 a.m. in the

morning, and it's a bright blue sky in May day, now your system is getting the signals, you'll perk up and feel awake because your rhythms are still aligned to that part of the day. So that suggestion is to keep that signal blocked, so to speak, until you get home, blacked out room, put eye mask, go to bed, sleep to the early... but try to not oversleep necessarily, try to maintain a consistent enough meal timing. I would say that if someone is going to prepare to eat during the nightshift, then the best strategy that we could hypothesize at this point would be to try to keep it to kind of more protein rich snacks that are lower in overall energy. And maybe that has a satiating effect as well, that kind of dampens the hedonic food seeking behavior that can kind occur during nightshifts. But yeah, we're clutching at straws with a lot of it.

DANNY LENNON: Yeah, so like you say, there's not much in the way of very clear evidence based recommendations of actually what to do from a nutrition standpoint. It's more based on, like you say, we can, as we've discussed here, and actually previously on the podcast, some of the stuff we know mechanistically that goes on during biological night, and it's influenced then on how certain nutrients are metabolized, we can hypothesize better and worse things to be doing. So, for example, based on that, as a kind of summary of what Alan just said, because we know that the metabolism of carbohydrate and fat during biological night is worse, then it might be a good idea, can we avoid large, high fat high carbohydrate meals during that biological night period. One way to do that would be to focus on high protein snacks or meals potentially; another way would be to fast through that danger zone, quote-unquote, of, I don't know, 1:00 a.m. to 4:00 or 5:00 a.m., something like that, where things are definitely going to be screwed up. So there's kind of with the nutrition stuff, there's kind of two components here. It's like, what can we eat based on how we know certain biological functions are going to run. In other words,

what we've just said, that avoiding that period of time where carbohydrate and fat metabolism isn't going to be great. But also we can think of the other side of when do we eat in terms of how food acts as a cue on those circadian rhythms.

And in that respect, Alan discussed, trying to keep food timing as similar as possible to normal daytime eating, and this is kind of this compromise phase position that we just mentioned that we want to have as minimal disruption when we're moving back and forth. So if those times are going to have to change to some degree, but can be relatively similar, that would be preferential. And maybe as a hypothetical example for people, let's consider someone's doing a shift from 8:00 p.m. to 8:00 a.m., here what we're talking about is you'd probably have a meal before you go in, then throughout the kind of night the next kind of access you to food, focusing on high protein foods, trying to avoid high carb, high fat meals, maybe even fasting during that middle part of the night, and then after finishing the shift, having again maybe another high protein meal before going to sleep. And then in terms of some of the other aspects to light dark exposure, this would be during that nightshift or even just before, for people who really want to go at it, maybe they can get access to a blue light box, for example, that would kind of mimic what we just mentioned in that study.

But even without that, going through that nightshift on finishing the nightshift, wearing a pair of blue blocking glasses, which are these kind of orange tinted glasses you probably would have seen that block out certain wavelengths of light that disrupt your melatonin production; and so wearing them when you are leaving your shifts on the way home, therefore, is not going to lead to essentially you sensing that is daytime, and getting to sleep as soon as is feasibly possible rather than extending your wakefulness out multiple hours after getting home from that

shift. So trying to get to bed early, those things seem to confer a benefit because again that phase shift isn't going to be as severe as it otherwise would.

So it kind of seems like that's generally where we're at with some things that people could potentially try. If we were to talk maybe more pragmatically, from a behavioral standpoint in terms of nutrition, I would probably say, knowing that there's going to be a decreased opportunity to get access to good quality foods typically as time, we don't have full control over what's going to be available during those working hours, maybe this is where planning ahead of time, having some food prepared, if that's possible, and knowing when you're going to have these meals, having a time set ahead of time, all this kind of behavioral/habit based stuff is going to be useful.

ALAN FLANAGAN: For such a ubiquitous part of daily life. We have 24-hour societies. It would really be nice to see more research, look at strategies that could have benefits. But yeah, like I said, most of it is making recommendations of things we know go wrong or adverse effects.

DANNY LENNON: Maybe the only thing I thought is with caffeine timing, seeing as people are going to be using caffeine, again, probably just using the same standard thing of trying to leave some period of time before you attempt to sleep while you haven't consumed caffeine just beforehand. So again, just timing that to earlier at the start of your shift, as opposed towards the tail end, if at all possible.

ALAN FLANAGAN: Yeah, and if it needs, you know, caffeine can be very useful chronotherapeutic. It could be useful even for everyday kind of later day wakefulness prior to the shift, if someone wants to avoid just kind of oversleeping to the early evening, and then having to get up and go for a shift, have that sleep period wake, use some caffeine and the kind of mid-afternoon, and, like, yeah, as Danny said, maybe frontload

that caffeine then on the nightshift, so that you're not having another double espresso at 4:00 a.m., and then coming home and trying to sleep. So I think, yeah, I think timing caffeine can be a really important part of not just facilitating wakefulness when tired, but getting through the shift in such a way that combines being alert and awake with not, hopefully, eating into the ability to kind of put the head down the next morning.

DANNY LENNON: And in terms of people that are changing across shifts that are alternating or moving from a certain block of shifts to another, perhaps the use of supplemental melatonin could be useful, again, to reestablish a phase shift...

ALAN FLANAGAN: I think, yeah, the reason I tend to sometimes not end up saying anything about melatonin is just because I know that it has oddly various legal, as in availability status in different countries.

DANNY LENNON: So we're only talking to our US citizens.

ALAN FLANAGAN: Yeah, go to Whole Foods. So yeah, melatonin can be very useful for resetting. So I think melatonin can be useful in the recovery phase. So once someone, say, worked three nights in a row, then it could be useful to time melatonin at a normal – their normal bedtime for the next couple of nights in order to help to reestablish that melatonin rhythm, that anchor of the daily circadian rhythm around that, I guess, normal day and night cycle for that individual. So yes, supplemental melatonin can be very useful, I think, give or take in the range of one to three milligrams before bed. So yeah, that can be helpful too. I think it's available in the UK, I don't know, I know in Ireland it's not, you can't get it anywhere. But yeah, that can be useful to help to reset in the post nightshifts, a couple of nights, hopefully in conjunction with some sleep extension as well on those nights.

DANNY LENNON: For the moment, I think, yeah, that I think does us on this topic.

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