



DANNY LENNON:

Brendon, welcome to the podcast. Thank you for taking the time to come and talk to me today.

BRENDON STUBBS:

Oh absolute pleasure, Danny, really looking forward to our conversation.

DANNY LENNON:

We have a lot to get through. But before I get to that, for people listening, can you maybe give them some context of your work up to this point, both in practice and in academia, and anything else you think might be relevant for today's discussion?

BRENDON STUBBS:

Sure, yeah. So I'll keep this bit quite brief, because it's probably the most boring, when it is the most boring part. But I'm a physiotherapist and an academic. I predominantly, well, I work in mental health services as a clinician, helping people with various different types of mental illness. I've previously been head of a clinical service, but now I'm predominantly an academic, and I do honorary clinical work, which is great. And over the last 10 years, particularly, I focused on research that's focused on two core topic areas, and one cross cutting area, one is looking at how movement and physical activity and different types of exercise can help possibly prevent mental ill health and help us keep us

happy in the moment, and possibly prevent mental illness in the future, and also be used as an intervention for people who do have a mental illness diagnosis. The other area is looking at the relationship between the mind and the body, and how those are sort of interlinked between each other, and across cutting that, really is sort of like meta research. So research and research to try and understand how good is the evidence on any particular topic, how reliable is it, and that's my sort of three key areas of interest. And just to give a bit of academic sort of caliber, quantity doesn't mean quality, quality is more important, but I've published 650 plus academic publications, ranging from, I don't know, lots of big medical journals, leading nutrition journals, leading sports, science journals to lots of random other journals. I've led Lancet guidelines on topics of fields, and I've written European guidelines. I do policy work, I advised the World Health Organization about managing mental health and research priorities during COVID. And yeah, since 2019, I've been a highly cited researcher by Reuters, so that means I'm in the top, I think they'd tell you, top 8000 researchers in the world, specifically within mental health. So people cite what I write for good or for bad reasons, frequently. So that's probably the most boring bit.

DANNY LENNON:

Fantastic. And I think, yeah, anyone who looks up your publication record, in addition to those various other things around your background, can't help but be impressed. But I won't kind of ponder on that and try and embarrass you with this long list of accolades, which I can mention, and we'll dive into some of that work. So on the, if we start broad, and we maybe can narrow down, if we're thinking about movement or physical activity, and how that plays a role as a risk factor in depression – you mentioned there that there's kind of two areas that therefore we can look at. We can look at what is the impact of physical activity as a preventative measure, and then we could have a kind of separate discussion around physical

activity as an actual intervention or treatment with someone with preexisting depression. Just as maybe a very broad question on the prevention, how do we go about investigating that as a type of research question giving as we're looking at something that doesn't currently exist. So for maybe people that aren't familiar, how we might investigate a question like that, how do we go about that?

BRENDON STUBBS:

Yeah, so there's different ways that you can do that, and some types of research methods are better than others. The most natural way to do this, and the way that you get larger numbers of people, when it's much more economically feasible to do is to do observational research, where we measure people over time. We call this prospective cohort studies. So you get a group of representative people. It could be, for instance, a few thousand adolescents or children we've looked at in some research, or UK Biobank data where you're looking at hundreds of thousands of people. And then at baseline, what you're doing is you're doing a comprehensive evaluation of all people's physical and mental health, and then if you wanted to look at the exposure as being physical activity, in this instance, and then the outcome being depression, at the start, if anybody had symptoms of depression, history of depression, recurrent diagnosis, they would be excluded from the analysis. And then, what you would do is you'd follow those people up over time, you would look at people with physical activity in the most simple sense, you would adjust for what we call, quote-unquote, confounded as best as possible other factors that could contribute to the risk of depression. You'd follow those people up over time, and that could be a few months to a year, obviously, the longer the better, and then you would see what is the relationship between how active people are at baseline compared to the risk of depression in the future, in advance. And then you try and adjust in this natural environment for all of these other things as best as you can. And I should say, and we've studied this across

all risk factors for depression, depression is a really complex condition, it's a very heterogeneous cluster of symptoms and conditions, and experts often struggle despite having diagnostic guidelines about what are the sort of true symptoms of depression. So it's not like I don't know, for instance, you may look at cancer, where you've got specific markers, and you can clearly look at a tumor, depression's actually, you know, and many mental illnesses are much more difficult to identify and diagnose. So we have a tricky time doing this, and it's complex. We can never just say, often, it's due to one risk factor, very, very rarely, often, it's a build-up of many different factors, but we do our best to try and account for those and understand the relationships. Another way would be a better way to understand this, but it would be really expensive, really difficult to do, particularly over a long period of time, because depression over a population happens, you know, doesn't happen often, in eight weeks for most people; it happens over a period of time, would be to do a massive, randomized controlled trial, and following up people in a randomized controlled trial over many, many years, but that would be enormously expensive, and that would be a way to sort of look at causal inferences.

DANNY LENNON:

Fantastic. I think that sets up a couple of things that I want to put a pin on, and come back to later. One relates to that kind of heterogeneity we may see, and that might also get into our discussion around meta-analyses, I think as well. But to start off, you mentioned that when we're looking at this kind of prospectively, or when we look at prospective cohort studies, when we get into some of that, I know one of your publications, I think was it a 2018 paper, was a meta-analysis of these prospective cohort studies. From a kind of Overview level, can you maybe outline to people a bit about that paper and kind of some of its implications?

BRENDON STUBBS:

Yeah, sure. So this is a paper we did in the American Journal of Psychiatry, which is a

credible psychiatric journal. We did something very simple, which is what I briefly described there is, we look to people of all ages and immediate subgroups for young people, for people of working age, and for older age, and looked at all of the cohort studies, combined them together, and that is a point of meta research. And a point of good research is we never really believe one study on its own, we're always saying we need independent replication. So if I do one study, it's no good me just sort of saying this is the answer. We want independent research groups to verify my hypothesis, and my research to disprove it. And that's one of the good things about meta-analysis is often studied, you can combine them together, in as good way as possible and account for that variation, and you can get a much better answer of our research question. And when you're looking at smaller studies, that may or may not be representative, and you can combine and say what is the totality of the evidence come with that, they're imperfect, because all research is imperfect. For every research paper that's ever written, it's got a limitation section and every limitation section is always shorter than it should be. So that is another important point to consider. So in this paper, we looked at physical activity levels at baseline, people who are free from depression or depressive symptoms, or any other mental health comorbidity, followed them up for an average of seven and a half years. And people measured physical activity in various different ways, so it's messy in terms of looking at our exposure, and then looked at depressive symptoms or a clinical diagnosis of depression in the future. We adjusted for these other confounders, these risk factors which I mentioned at the beginning, as best as we could, you know, nutritional intake and other environmental exposures such as trauma, other medical conditions, etc. And broadly, the headline message is we found that people who were more active, were around 22% less likely to develop depression in the future compared to people who were less active. And because of

the heterogeneity in terms of how physical activity was measured, it was difficult to sort of make recommendations about, should it be X minutes, or should it be Y minutes. But what we did find within a subgroup is that people who met 150 minutes of moderate or 75 minutes of vigorous physical activity were around 30 to 35% less likely to have depression in the future, compared to those who didn't meet those guidelines, and that held true across all geographical continents, in young people, in people of middle age, and people of old age. This is a prospective cohort study. We can only look at the direction the relationships, we can't prove a causal relationship within that. And as I mentioned earlier on, depression is really, really complex. We're trying to look at one risk factor just to try and understand but that is a sort of brief headline message.

DANNY LENNON:

And I do want to continue down that route, but if we just, again, embark on some of the methodology here, I think this is kind of a really interesting example where you've mentioned how a meta-analysis can be really powerful, because we can combine several studies, so we can have a bit more confidence, but it's almost a double-edged sword. And I know this is something you talked about as well that a well done meta-analysis is extremely powerful, a poorly done meta-analysis almost compounds any errors that you're doing along the way. And it seems, with something like you just described, where we have different exposures in terms of exercise, but then we also have perhaps differences in endpoints across various studies, presuming because of how one paper may evaluate it, can maybe just talk to that challenge or some of the best practices that might be useful in conducting a meta-analysis?

BRENDON STUBBS:

Yeah. So it's interesting, because if you look at the evidence based hierarchy pyramid and say what is the best form of evidence, you'll often see, I think it's been recently updated to say someone who looks good with their top off, is the top of the evidence hierarchy, but just

underneath that is meta-analysis, particularly meta-analysis of randomized controlled trials, but we're talking about prospective cohort studies here. And really with any meta-analysis, if you put rubbish in, you're going to get rubbish out, and so, you've got to be quite careful about what you put in, in terms of meta-analysis. And all studies are imperfect, all studies are different, all studies include different people, and you have to be very, very careful within this, literally, mathematically, you can meta-analyze anything. You can pull and combine data, and you can get numbers out in terms of an effect size, and you can get measures of heterogeneity, and you can try and explain that. But it's really up to the discretion of the authors or coauthors who go to the individual studies to say, are they sufficiently homogeneous enough, similar enough to make a meaningful story. And the important thing is that that is considered in terms of the exposures, like, in this instance, physical activity, and also in terms of endpoints and also populations, and also comparatives, if you're comparing it to other groups. So you need to consider all of those individual factors, then you need to statistically adjust for those. So if we considered, if we're worried, for instance, that these are really different, we can do different types of analyses within a meta-analysis.

So we could just broadly categorize this into like a fixed effect analysis, or a random effect analysis, and using a random effects analysis, theoretically accounts for heterogeneity or differences between studies and participants. But it is not a panacea to getting rid of all of the issues within differences, within participants, but it is common practice. And then, what you will tend to do when you get, you do a meta-analysis at the end is you will get two measures of heterogeneity and how different they are. So we get something called the I squared statistic, and this is a measure of heterogeneity or difference between the studies and participants. And this ranges on a percentage

from naught to 100%, and generally, the higher the in score, the more heterogeneous your sample is. And good practice within this in heterogeneity, is trying to understand that heterogeneity with subgroup analysis. So, for instance, I mentioned physical activity, looking at children, working age adults, looking at older adults would be a very sensible thing to do, to reduce clinical and population heterogeneity, looking at people with and without medical conditions would be another really sensible thing, which we did in that example, to reduce clinical and population heterogeneity. And then for each of these subgroup analyses, you should see the dropping of this in statistic. The other one commonly used is something called the Cochran's Q statistic, and it's a bit more difficult to interpret. So I probably won't go into the statistics of that, but essentially, again, it's another measure, not as limiting to naught to 100% to look at how different are these studies in populations within that.

So good meta-analyses are preregistered upfront, so it's not like a post hoc thing which people do. It's clearly evident how people have sourced, gathered the data. It's clearly evident what the primary objective is within the meta-analysis is clearly evident how the data has been analyzed, it's clearly evident how heterogeneity is there, how it's been investigated, has it been rolled out. Another way, which I didn't mention is something which we call meta-regression, and essentially, this is looking at other variables across multiple studies to say, can these individual variables influence the effect size, and sort of increase it or dial it down. So one example just really commonly, that we used in that example was body mass index, within the relationship between how active you are and the risk of depression in the future. We know there's a relationship between body mass index and physical activity, and we know there's a bidirectional relationship between depression. So you can look at body mass index across



studies, and how does it influence your outcome. And the issue with meta-analyses is you're always dependent upon what is published and how good that is by the original authors. So if they don't publish data on BMI, you have to go and ask them for it. If they don't give it to you, then you just don't know, so meta-analyses are a good way to understand things, but they're imperfect, they can be wrong, and people do over stretch the mark, and people do tend to overdo them. And another thing which will probably feed into this meta research discussion is the issue of publication bias more broadly.

So I'll just introduced publication bias more broadly before I talk about it in the context of meta-analyses. So research is flawed for a number of different reasons, but one of the reasons is that published findings are much, much more likely to be published than what we call, quote-unquote, negative findings, i.e., an intervention that doesn't work. So if I go and do like an exercise study, or if I go and do a pharmaceutical study or a nutrition study as an investigator, we should publish them all, but I'm much more likely to have that submitted, research shows that. And if I go to the leading journals, you think about that in the nutrition field, or the BMJ or New England Journal of Medicine, they are much, much more likely, and people have looked at this in academic papers to publish positive findings, and it's very difficult to publish negative results. So when you look at research out there, you get, all of us, we get this distorted view because negative findings are missing, most negative findings are missing. So we've got this huge distortion of what really does and does not work, and what really is a true relationship because it's hard to publish negative findings. So that is just a sort of broad, meta topic about publication bias, and how this perpetually feeds into what we know about individual topics. So what we tend to do within meta-analyses is we investigate this through a number of different statistical tests. There's a

couple where we look, is there an evidence of publication bias, and then there is one particular test, where we can look at how many studies, mathematically it's very, very clever, how many studies do we think are missing from the literature based on the statistical analysis. And that can give you a number to say how true this effect and how many studies may be missing on any given topic, say, physical activity and a risk of depression in the future. So I know that was a lot and I hope it was interpretable.

DANNY LENNON:

Yeah, no, no, fantastic. And there's, I suppose, at least two or three points that I think actually I want to dive into a bit further, certainly on this kind of big idea around science, even as a system, maybe we will circle back to later. One, I want to get into some of the stuff around causality. But first, if we kind of round this off on meta-analysis, briefly, as a really useful example, I think for people that illustrates just what you said of how different findings may be if something is done poorly versus done more appropriately, let's say, is, I think you gave a recent example of a meta-analysis that had been done on depression and inflammation, if I'm remembering correctly, and you and some of your colleagues did a kind of reanalysis of that. So essentially, working with the same research question, and still doing a meta-analysis, but finding these kind of big differences. Can you maybe give people an overview, because I think that works as a really good example of how different our kind of interpretation of that data may end up being?

BRENDON STUBBS:

Yeah, sure. So I know a lot of geeks, and I'll include myself in that. So we question everything, including our own research. So we've published, in this instance, two meta-analysis on relationship between depression and inflammation, and what we like to understand is how true are results out in the academic field. So meta-analysis, typically, most people, and why wouldn't you, you just read a meta-analysis, perhaps read the

abstract, maybe read a bit more and think this is the results. So we wanted to go a step further in this particular example, and it really highlights some of the issues and the nuances around meta-analyses to say, how true is a relationship between depression, inflammation, and how well has this been done previously. And essentially, what we did is we found 15 meta-analyses over recent time periods that have looked at the relationship between depression and inflammation, lots has been written about this, some great books out there that have been written on this, and we wanted to have a look at this. And what we found was across these 15 meta-analyses, and many individual studies, and hundreds of thousands of people is that 14 out of 15 of the meta-analyses had errors within them. So when we went back – so we didn't just look at the meta-analysis, we found these 15, we went back to all of the original studies, we went back to all of the original participants, we went back to all of the original results, we looked at the means, the standard deviations, the participant numbers, all of that granular detail from the original meta-analysis, and we found that 14 out of 15 had errors within them. So people, when they've been doing these meta-analysis, not saying there's any misconduct or anything like that, it just, you know, it just happens in terms of, so some of the examples where people had extracted the wrong numbers of participants, people had extracted the wrong standard deviations for some inflammatory markers, people had extracted the wrong information on a range of different factors. So that just goes to illustrate, whilst science and meta-analyses are good, they're not perfect. It's much better than just someone giving an expert opinion, so I just want to be clear on that, or, someone giving their opinion, but while science is our best way to understand things, this clearly gives an example that science and meta-analyses are not perfect. We analyzed and meta-analyzed everything, and found these errors, but fundamentally, we found that it wasn't many major differences in

the actual outcomes in terms of the relationship between various inflammatory cytokines and depression. We found that one of the interleukins was not associated with depression, but the general story didn't change. But some of the effect sizes that had been extracted were substantially different ranging from an effect size of 0.1 to sort of like 1. So many of the effect sizes which had been reported previously were watered down quite substantially, and that's what we tend to see is an overestimation and a correction within this, and this is what science should be, it should continually be self-correcting, and trying to improve itself, and this is where science is good, because we don't just take anything that's published and think this is gospel. We like to look at it further, and we like to analyze and understand in much more detail.

DANNY LENNON:

Fantastic. If we return again to the evidence based on studies looking at movement or exercise, and that, and in terms of a preventative measure for depression, and we've talked already about prospective cohort studies and their value there, and then the meta-analysis of those prospective cohort studies that you published, and you mentioned a really important point around how that can be really, really useful, but it may be we have to stop a bit short of looking at causality when we're doing that. One of the things that has garnered a lot of attention, at least in nutrition science, and I think in other fields as well in recent years has been the use of Mendelian randomization as a kind of tool to get us towards causality in lieu of randomized control trials, and I know you've talked about that there started to be MR studies published in this area as well. Can you maybe give an overview of what they have tended to show and maybe what they've added to the evidence base on this particular question?

BRENDON STUBBS:

Yeah, sure. So Mendelian randomization studies are quite hot at the moment, in terms of people who are really interested in looking at

these, and looking at the relationship between specific genetic markers, and an outcome of interest, so depression in this instance. We've had a couple of really important Mendelian randomization studies, which have added some further weight and confidence to their prospective relationships. So Karmel Choi is a researcher at Harvard University, and she's done two really important Mendelian randomization studies using the UK Biobank data, and this addresses some of the concerns, both methodologically and conceptually, that we have around our meta-analysis, for example. So Karmel looked at objective accelerometry derived physical activity and sedentary behavior. We have much more confidence in the accuracy of this, and if you ask me what I've done over the last week, I'm going to have a good guess, but it's not anywhere near as accurate as direct measurement. So Karmel looked at that in a few hundred thousand people, and the causal relationship between depressive symptoms and does it go the other way, you know, is there a causal relationship between being depressed and being less active. And essentially, what she found in this big study, Mendelian randomization study is there is a causal pathway between being more active and reducing your risk of depression in the future. But that relationship didn't go the other way around, interestingly, which is one of the things that people often say to me, and, isn't it the other way around, and it's reverse causality even though you've ruled out people in prospective cohorts who don't have depression at baseline. So Karmel really helpfully published that paper in JAMA Psychiatry in 2018. She did another study, which really built upon that, and was really, really interesting. She looked at, again, the UK Biobank, 60,000 people who were all genetically equally predisposed of having depression. So we've talked about depression being complex, multifaceted, and there's a core genetic component, the proportion of which is yet to be determined. But I think we all fundamentally

agree there is a genetic predisposition for some people, and some genetic candidates are particularly strong. So she looked at 60,000 people, all have had these genes that predispose them to potentially developing depression in the future. She looked at accelerometry derived physical activity and said, if you are equal genetic weighting, of having depression in the future, and you're more active in these Mendelian randomization observational studies, can you reduce your risk of depression or genes determine your risk. And she found the people who were more active with accelerometry derived physical activity of equal genetic weighting were less likely to have depression in this MR study compared to those who were less active. So that adds further confidence to our observational data, and I think that's a really nice addition to literature.

DANNY LENNON:

That's incredibly important. So as a kind of summary, we're saying, therefore people that do have a genetic predisposition, and we take all those people that have that say, similar level of high genetic risk, those with the higher levels of physical activity have lower risk of actually developing depression or depressive symptoms into the future.

BRENDON STUBBS:

That's it. That's correct. And I do want to caveat that again that depression is complex and multifactorial, and it's all good. And when looking at this in MR studies and everything else, and it's helpful to understand the issue, but that's what it's saying, but it is complex.

DANNY LENNON:

Yeah, we're certainly talking about levels of risk as opposed to 100% certainty on anything, and also then with this issue of looking at what we're actually talking about with changes in outcomes, I want to bring that up when we get to the intervention studies. But to kind of round out this idea of exercise in prevention of depression, what do we know, mechanistically, that might explain why we're seeing this reduced risk? Is it something that's purely

physiological? Is it something that there's psychological benefits to doing? Is it a combination? Have we been able to work that out from the research? What kind of evidence do we have around, mechanistically, what's going on?

BRENDON STUBBS:

Yeah, so before I talk about mechanisms, I'll just briefly mention that we've talked about physical activity. Now, we've recently looked in the UK Biobank sedentary behavior as a risk factor as well as independence, so that's not moving around, sitting down, and during the day, we've also looked at the importance of cardiorespiratory fitness. Again, that seems to be really important to how your heart and lungs function, and your risk of depression and anxiety in the future and also strength. So we've looked at resistance training in large cohorts of studies. Aaron Kandola is the first author of those papers in BMC Medicine, being active, having good heart and lung fitness and strength is, you know, all appear to be nudging the cards in your favor. When we get around to sort of mechanisms about why this may have an impact, the short answer, and probably the most honest answer is we're still finding out, and we don't know that's the truth. And if you know of anybody who knows more than me, I'd like to meet them, and they can tell me that it's slightly longer, but I'll try and keep it as short as I can, is that we realize it's a multi system, multifaceted, complex reason. The onset of depression is very complex and multifaceted. So to say that the mechanism is down to hormone X or hormone Y, or psychological factor X would be completely reductionist. But I'll very briefly touch upon some of the mechanisms which we've looked at, and we brought together.

Aaron Kandola did a really nice paper in Neuroscience & Biobehavioral Reviews in 2019, bringing together all of these different topics, great PhD candidate who recently finished at UCL. And essentially, we know that when you move around neck size, you get immediate

changes in important areas within the brain, such as the hippocampus, reduced in depression and other mental disorders, you know, areas of the brain called the anterior cingulate cortex too, that's been shown in observational studies, also randomized controlled trials. We've done randomized controlled trials, showing you get an increase in BDNF, for instance, in people with clinical depression. BDNF is really important for brain fertilization, increases in neuroplasticity, and connections between nerve pathways. There's also changes in cortisol, stimulation of the endocannabinoid system, reductions in inflammation which we've talked about in terms of depression, and keep going on about neurobiological mechanisms, but there's a number that all interact at any particular given time. And these are all really important, and clearly, none of them work in isolation, they all work concurrently and together. And the psychological and social mechanisms are equally really important, so if you go out and do some physical activity and exercise, and you don't have depression, or you do have depression, then you feel a sense of achievement, you've done something, you feel good, your self-esteem can improve; if you go out and socialize with a group of friends, you get a sense of social connection. You go outdoors, there's benefits to being in green space, blue space. So these are some of the other types of psychosocial mechanisms, which also contribute to why physical activity and movement may protect us against the emergence of depression in the future, and also, as an actual intervention, some of the mechanisms through which it may work.

DANNY LENNON:

Fantastic. One thing you just raised there was beyond just thinking of movement per se, thinking about cardiorespiratory fitness, and then things like strength, and I wanted to ask about that, because clearly, it seems that being generally active relative to sedentary is a good idea for a number of reasons. But are there additional benefits then to not just being active,



but actually having a higher level of fitness or strength or whatever performance marker we mentioned? And, of course, those two things influence each other, you're probably more likely to be fitter if you do physical activity more often, but there's still some disconnect there that can occur. So is there an additional benefit from having those higher levels of fitness and/or of strength? And, if so, is that more potent than just being more physically active per se, if that makes sense?

BRENDON STUBBS:

Yeah, it does make sense. And I think this is just another methodological conceptual, really important issue, just to say that these, as you say, these are all really highly correlated in terms of how active you are, how good your heart and lung fitness is, and perhaps less so, in terms of how strong your muscles are. So, the short answer is, and the honest answer is that we don't know how much added value specifically each of them give above each other. Probably the best answer to address the specific question again is a paper which Aaron published in BMC Medicine earlier this year, where he looks again in the UK Biobank, 100,000 people. And he wanted to understand when we adjusted physical activity and sedentary behavior, what happens if we look at the risk of anxiety and depression in the future, over a seven-year period, and we look at people's cardiorespiratory fitness levels, and we put people typically into tertiles or quartiles within that, because it's a very heterogeneous outcome. So we sort of slice it into those categories, and then also, when we look at resistance training, and previous studies have found that cardiorespiratory fitness is good, but we want to see what happens when you compare these separately, and then when you compare them combined in terms of cardiorespiratory fitness, resistance training. And Aaron found, you know, reaffirmed what was known, in terms of high levels of cardiorespiratory fitness, protective against depression, not much is done on anxiety, so he made a novel contribution there. But he also

found that resistance training and having strong muscles was protective against anxiety and also depression; and he found that you get the best bang for your buck in terms of protection when you have both. So you are adjusting for physical activity and sedentary behavior, and you're also having good heart and lung fitness, cardiorespiratory fitness, and also good strength. So that is about as much as we know at the moment, we can't make specific recommendations around added value of one over the other. But again, I'd be welcome for anyone to tell me that I'm wrong, and they know on that than me.

DANNY LENNON:

Yeah, no, fantastic. So with that, and kind of going along that theme, if we look at actual interventions, first, if we consider maybe depression as one outcome, and we can maybe talk about some of the others, I'm happy to, do we see differences or a relatively similar picture emerge when we look at exercise as an actual intervention when someone has depression?

BRENDON STUBBS:

We've got good evidence now that when you offer exercise to standard care, whether that be aerobic, and also resistance training for people with mild to moderate and less evidence, but emerging evidence for more severe depression, that it can be effective in terms of reducing people's depressive symptoms, compared to your standard usual care, whether that be seeing your GP, perhaps being on or off medication, whatever best practice may be on that. There's lots of randomized controlled trials that have looked at that. There's various meta-analyses that have confirmed that that is good evidence. But most of the evidence in the context of depression has been relatively short term in terms of follow-up. So that's been one of the sort of main lagging issues in terms of getting much traction and getting much people to sort of implement this into guidelines, often 12, perhaps 24 weeks. And again, within exercise studies with randomized controlled trials, we've had limited study numbers often, you know, 100 people, maybe 150 people; and

to make big broad changes and convince lots of people, we want big groups, adequately powered samples, and we want long term follow-up to say, is this really working over the long run. So highlight one, randomized controlled trial, which is really good, and really beneficial in terms of swaying the evidence base and convincing people how important exercise can be for some people as part of their menu of options. I'm by no means saying that is a panacea and will work for anyone. I don't think there is a panacea for depression. Full stop. Certainly, it's just part of the menu of options. But what Mats did was a three armed randomized controlled trial in Sweden, and he had 330 people in each arm. So around a 1000 people with mild moderate depression, and Mats followed them up for 12 months. So we've got big sample sizes, three groups, long term follow-up. All of the groups had usual care, so best practice within each group. One, and this is a randomized, one group was in randomized to have cognitive behavioral therapy delivered via the internet, which again, is a fantastic treatment and recognized and guidelines around the world as being really helpful for people; and the other group had structured exercise delivered over a comparable period; interventions were for 24 weeks, and in people who followed it for 12 months. And what Mats found after this 12 months, and it's really well powered trial is at the end exercise and CBT were equally as good as each other, and they were just as good as each other, but they were both clinically and significantly better than just usual care. So adding both of these on was really helpful for people in significant terms in sort of a research sense, but also in terms of looking at the clinical importance of scales. So that gives you some indication about the benefits of exercise, and we know the physical health benefits of exercise beyond that as well. And CBT is widely regarded as being helpful for people – that's not the sort of comparisons in saying people should have one or the other. I mean, it's just to say bring to the table, exercise is a viable option for people and it should be

considered as a serious option for helping some people.

DANNY LENNON:

I want to touch on a point you just raised there, when we're thinking about something that might be clinically meaningful as a result, as opposed to just seeing this statistical difference, and obviously, there's going to be a correlation there, but when we're looking and trying to deem, what is a, quote-unquote, success from an intervention in this regard, probably because most of the time we're looking at these kind of suite of symptoms, or we're trying to get a reduction in those symptoms as maybe, as opposed to a complete amelioration of them. What is typically, in your mind, success if we take a certain intervention, and what type of reduction are we going to see, and what translates to actually something that in the real world as clinically meaningful, if that's not too broad of a question?

BRENDON STUBBS:

Yeah, I can fill the rest of the time talking about that. So it really depends on the scale that people are using, because when we're talking in the context of depression, really helpfully people have developed lots of different scales to measure depressive symptoms and validate them against clinical diagnosis. So what is, quote-unquote, clinically meaningful has been tested across lots of different scales. So the clinical meaning depends upon the sort of scale that which people have used and, of course, you know I'd say, really, rather than the operating symptoms on a scale, it should be asking the individual person, in addition to looking at the score, essentially, you know, do you feel that you've benefited and feel better as a result of taking part in this intervention your symptoms have improved in a more structured way than that. I think that would be a really nice addition to some of these symptom metrics. But generally, if we see an improvement looking across scales, bearing in mind, they're all different, they've got different measures, reduction, sort of 20%, 30% of people's reductions in symptoms up to 50%, then that

would be considered a success for people, but that does vary across individual studies. Now, you could see, for example, and this would be just really, really silly, and people do this, and I read a paper earlier in the week, where there was an improvement in an odds ratio of 1.03 with a confidence intervals all over one for an improvement in this intervention, and what does 1.03 mean. I mean, it just, in terms of clinical meaning, it means nothing, you've got a P value less than 5. But, I mean, that's just a classic example of you found something which didn't happen by chance through a P value, but it means nothing.

DANNY LENNON:

Yeah, and that actually brings me on to a topic that I want to ask about, of both the reporting and phrasing of some research findings, both in maybe author's conclusions, but then also within medium press releases that come from those papers, and it relates to how we actually start phrasing, again, success or what is meaningful in this. And the reason why I ask is because it actually relates to something I remember seeing recently in relation to some of the published literature in relation to psychedelics, which are obviously a very hot topic now, and there's obviously a lot of hype around, but there's also some really interesting work done, probably most predominantly Johns Hopkins, Imperial College, UCSF. But with some of the publications that are coming out in different places now, you tend to see very kind of positive reporting of those, positive conclusions, but there's one particular example where the phrasing had been a remission from depression, and this was a kind of intervention trial that had like a follow-up period of, I believe, seven days, maybe it was 14, but it was something like that, for people with treatment resistant depression, which is, I think the average time that these people had had their symptoms was like 11 years, this is something that wasn't responding to treatment. And now we're seeing kind of headlines of now there's a remission from this one intervention where someone I think it was an Ayahuasca trial,

which contains Dimethyltryptamine or DMT, and I think to get to a point of we are seeing a remission from depression, when we're having a seven-day follow-up for something that's an 11-year chronic disease, seems like that's causing a bit of angst amongst other researchers, which are saying maybe this is not the best way to report things, versus as you just said a moment ago, a reduction in symptoms is accurately what we're saying. Can you just touch on, do we see that in other areas related to depression research, and how should we view the importance of phrasing and what conclusions we're coming to off the back of certain interventions, particularly, if there are acute interventions?

BRENDON STUBBS:

Yeah, so it's a great point, and it's really, really important, and, I'm not familiar with that particular study. But certainly for treatment resistant depression, and I've met lots and lots of people with treatment resistant depression, it sounds like a miracle cure, and I'm not sure if seven days – I mean, normally to be diagnosed, you have to have symptoms for a long period of time, so to have your symptoms go in seven days would seem a bit premature. So yeah, I don't know the details about that. So with the greatest respect to the colleagues that published that, yeah, it doesn't sound like it's – it seems as reliable as has been reported. What I would do is I'd just frame this within a few broader sort of research ideas is the, again, we know that most published findings are much more likely to be positive, most negative findings are not published. We also know that from John Ionnidis has done a lot of work on this. If you look at the abstracts of medical literature, which is like the shop window of research, which most people read, sometimes myself at any particular time, over time, we are seeing a significant and substantial reporting of increasing of P value reporting, of increasing of positive results, and even have increasing of positive statements of results, which don't have appropriate effect sizes going alongside it. So P value on its own means nothing really. It just

shows you the probability of rejecting your null hypothesis. So we've got this distortion within the literature, we've got an overwhelming majority of published findings, which are published; loads of negative findings, which are not published; then when we've got reporting in abstracts, we're seeing this overwhelming majority of positive statements and cherry-picking of the positive P value results being reported in the abstracts and statements, and people are not including effect sizes within that. So P value on its own means nothing.

So combined with that, and the fact that most people read that when you go into, I don't know, if you're going to be a journalist, for instance, and you don't read the full text, and you look at this abstract, and you see the result section that may be three lines, and you see there was a significant reduction in symptoms or improvement in remission, and a P value was less than 0.01, you may think, wow, this is absolutely fantastic. But really, it's just a short window, and it's a short window to where you show the best particular results, and it's biased, abstracts are biased, don't read abstracts. I typically tend to start articles within the message section, and then look at how people have analyzed the data, and then look at the limitation section, and then go into the results. So I would say we've got a distortion within what's published, we've got a distortion within abstracts, then we've got a distortion which is translated into media articles as a result. And that's not all the fault of researchers, I've certainly been on the end of some unhelpful reporting, where we think we did the science pretty well. And interestingly, my not so positive experiences around research findings are in the field, when I'm with colleagues, delved into the field of nutritional research, so I'm aware of how things can get twisted along the process.

DANNY LENNON:

Yeah, there's so much we could talk about along that line, I think there's a phrase you had put in one of your posts previously, where I

think you referred to science as a “broken business”. I think that, again, can open up a huge topic of going forward, and where we're currently at, how do we make the whole system better of like, not only getting good quality research done, but the peer review process of getting it out to people, there's all these intricate parts. And if you talk to most people doing academic research, there's a significant amount of frustration with that. So I don't know if that's something we have time to get into here, but if there's any immediate thoughts on that, before we finish, I'd love to hear some.

BRENDON STUBBS:

Sure. Yeah, so science and academia is a multi-billion industry, publishing is a multi-billion industry, so it's broken on a on a reward scale. So most research is funded by government agencies, taxpayers across the world, who will fund research to do ideas, and that's awarded through a fair process. And then if you as a taxpayer wants to look at research, or even I want to look at my own research, you publish it to academic publishers, who then charge exorbitant fees. And I said, if not, it's hidden behind a pay wall and taxpayers who've paid for this research can't access it. And universities are awarding millions and millions of pounds worth of contracts to make research accessible to more broad people. So the system around publishing is completely broken, and it's a very, very profitable industry. The margins in the research are very, very high, and fundamentally, it's not accessible to the people who are paying for it, and the people who need to hear it, and it's obviously written in complete language, which is not accessible to most people. And it's there to sort of confuse people, and then on top of that, when you put on the publication bias issues and all of the methodological issues, and the fact that there's a lot of mistakes, and a lot of it's not true, it makes thing even more murkier, so that's just a slight skeptic in me. And what I would say in terms of improving research practices more broadly is there's a lot of initiatives and great work going on, so like Ben Goldacre at



University of Oxford is doing a lot of open science based research. John Ionnidis been championing this for a long period of time. Doug Altman, who sadly passed away, the Oxford Clinical Trials Unit, a couple of years ago has done a lot. And this really starts at the beginning is, before we do any research, and before we even start, we need to have a clear hypothesis about what we're doing, what are the aims of this research, and what is going to be our primary outcome.

So clear research question, clear objective, and then clearly defined in the public domain, so people can do it. Because what you don't want is you're seeing some cohort studies. I've done this too. So I'm talking to myself, it's within these cohort studies NHANES, for example, is one of the common ones or the World Health Survey, we've used a lot. These were designed to do population surveillance around specific issues. And then what happens is you get authors, myself included, I've done this, so I'm openly being hypocritical is going back and analyzing data and exposures and outcomes that were measured, but they weren't really intending that purpose. And when you do that, you are going to get spurious findings, so you're going to get spurious findings, findings which are not real, but may show up as real within your results. So we need less of that in terms of going forward, so we need clear reporting of research, we need clear directions, we need better controls on salami slicing and retrospective analysis of that. We need clear reporting of results, open access to data, which people have got, open access of sharing of people's results, in an anonymous and confidential way, and following clear reporting guidelines. So whatever type of study you are doing, whether it was a systematic review or meta-analysis, a cohort study, a randomized controlled trial, there are recommended guidelines, which, once you've registered, you should follow in order to ensure that you're doing research within good practice. So we need better adherence to these individual

guidelines, and then we need much better translation of the research findings into the public domain, and then also into sort of clinical practice, because we've got this huge gap. We publish findings as academics, and before the main findings are out, we're applying for funding, and we're looking at other things before we have time to implement what we've done, and we move on, and that's it. And for me, that just seems like a completely broken thing on another level. We find something which is good, but part of our role is to go and get funding and do more research. So before we can really implement it and make real good changes, unless you've got lots and lots of time, it's really, really difficult, and it's doing the whole process a disservice. So we need less research, we need better quality research, we need better reporting of research, and we need better implementation of research.

DANNY LENNON:

Fantastic. Like I said, this could be a topic we could spend hours talking about alone, so that's maybe for another time. So just maybe to wrap up, if we circle back to the discussion we've had around physical activity, and depression, or maybe other mental health issues as well, if you want to include that, for the kind of key points that you would most like people to leave this conversation with when they think about, okay, what do we actually know from current evidence, and in lieu of future research questions we would love to answer, given that a lot of people maybe want to be able to take steps either as practitioners or as individuals, what are kind of some of the things that will be the most reasonable conclusions that we could come to now based on where we are?

BRENDON STUBBS:

Sure. I'll give you a balanced answer to that. So there's no panacea for any mental health or mental illness condition at all that I'm aware of, physical activity and exercise is no exception. We broadly have faith that prospectively, being more active and keeping your muscles strong and having good

cardiorespiratory fitness, is protective against the emergence of depression and anxiety; and this is backed up by some Mendelian randomization, and also some randomized controlled trials that have enforced sedentary behavior, small randomized controlled trials which reinforce this sort of causality picture. So we've got confidence to a reasonable degree, that physical activity and muscle strength and cardiorespiratory fitness are important within a broader context of the risk of common mental disorders. We're less certain about other complex mental health conditions such as schizophrenia. When it comes to interventions, we've got good reasonable evidence of good quality, the structured exercise, whether that be aerobics combined with resistance or resistance alone, we've also recently looked at high intensity interval training. There's also evidence around some yoga, Pilates can be an effective intervention versus usual care for the treatment of common mental health symptoms, anxiety, depression, improve people's physical health, and there's evidence in other conditions such as schizophrenia, emerging evidence around bipolar disorder. Two important future research questions, I would say, part of me is tempted to say it'd be great to look at mechanisms, but then another part of me is like that's really interesting and academically important. But really, it's just, I don't know how relevant that is to the public, that'd be great for us to sort of know and understand. But really, we need to know how can we implement that prevention level, and also a treatment level, what we know already to help the health of the population, because we've got good evidence, we're in guidelines now within Europe. And in the UK, the NICE guidelines were updated last week to say that exercise should be part of the treatment for people with depression or part of the menu of options for people first presenting. We really need to move to implementation and evaluating that and saying, how do we best do this in practice to engage people, and improve people's mental health symptoms in the future.

And then also just population level interventions to say, how can we help people live healthier lives to help people be, you know, live healthy and happy for longer.

DANNY LENNON:

Brendon, before I get to the very final question to wrap up, for people who are looking to find more about you on social media, on the internet, and if your publications, that type of stuff, where are some places you would send them?

BRENDON STUBBS:

If you're really sad, then go and put my name in PubMed, or there's another website called ResearchGate, where I think we give most of our publications open access. And then, perhaps if you're even more bored, I publish research, mainly research and my sort of musings around methodological biases and areas of research, that's sort of interesting to me. On Instagram, I think my tag is brendon.stubbs, so I can also be found there.

DANNY LENNON:

Brilliant. And for everyone listening, I will link to that in the show notes as well as any of the specific papers that we made reference to throughout this conversation today, so you can go and check out those. Brendon, that brings us to the final question I always end this podcast on, and it can be to do with anything even outside of what we've discussed today. And it's quite simply: if you were to advise people to do one thing each day that would have a positive impact on any area of their life, what might that one thing be?

BRENDON STUBBS:

Good question. Well, I'll give an example about what's important for me. For me, it's a sense of gratitude, and I know that's a bit sort of, well, there is science behind it, but for me, practicing gratitude is really, really helpful, because I can very quickly find myself drifting off into being ungrateful, particularly, when I get a bit depressed about the state of science and academia. So practicing gratitude for all of the great things I have in my life really helps keep me grounded.

DANNY LENNON:

I love it. Perfect way to finish. And with that, I want to say thank you so much for taking the time to do this, I really appreciate the conversation, really enjoyed it, but more so, for the work that you've done over an extensive period that's really a help not only for me, but I'm sure, many, many others. So thank you for all that you've done.

BRENDON STUBBS:

Thank you.

[00:58:42]