Episode 56: Cannabis and Heart Health - Unpacking the Evidence Behind Cardiovascular Risk

Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week, we're gonna be taking a bit of a look at cannabis and specifically whether or not cannabis can cause cardiovascular disease. There has been a lot of data coming out recently on this subject.

We thought we'd dive in and have a look at some of this. Before we dive into the specifics of cannabis and cardiovascular disease, I wanted to have a little bit of a look at cannabis in general and how it interacts with medical conditions because the cannabis landscape is complicated, isn't it? Particularly in terms of scientific literature, unbiased literature is actually quite hard to find when it comes to cannabis. So I've done a little experiment.

Okay. This isn't very scientific, but I have generated a list of medical conditions. Yep. I want you to tell me if there is a study that supports cannabis as a treatment, or if there is a study that shows cannabis makes it worse.

Okay. Okay, understand? Yes, yep. Right, so the first one, this was completely random, sciatica.

Treatment? There is papers that support cannabis as a treatment for sciatica. There is also papers that show, apparently, that cannabis can make sciatica worse. Oh, okay.

Rheumatic disease and arthritis. I feel like there are definitely papers on cannabis being used as a treatment. Yes, but there are also papers that show cannabis can make rheumatic disease worse. I'm sensing a theme.

Meniere's disease and vestibular disorders. I feel like there will be papers for either side. You've understood where this is going. You're absolutely right.

For virtually every medical condition, someone has published a paper that says cannabis can help. Similarly, someone has published a paper that says cannabis makes it worse. Picking through that literature can be really, really challenging. So we're gonna dive into some of that literature this week.

Health warning. We don't necessarily have all the answers here. There may well be counterpoints to what's raised here, and we're okay with that. Do get in touch if you've got thoughts.

Before we jump into today's episode, if you want to stay up to date with our content, you can find us on Instagram at @the_tox_lab. We also have a page on LinkedIn and we're fairly active on there. And for those of you who don't use social media, but still want to get in touch with episode suggestions or comments about our episodes, you can email us at thetoxlab@gmail.com. Let's set the scene a little bit.

Cannabis has been around for a long time. Earliest archeological reports indicate THC being used in braziers thousands of years ago, I'm told. But it's a drug that's really undergone an awful lot of changes within my lifetime in terms of both the nature of the beast, the nature of cannabis itself, but also how society has moved from the 1970s and 80s where it was broadly illegal to changing legal trends in terms of medicinal use and recreational use. Focusing in the UK, back in the 80s, 90s, most cannabis

was in hash form.

Most of it had relatively low THC content, typically sub 5%. We don't have good prevalence statistics, but I think it was a drug that a lot of people used occasionally, but regular use was less common. And then in the 90s and the 2000s, there was a move towards homegrown within country skunk. Potency started to climb.

There was that weird policy zigzag in the mid 2000s. Not sure if you remember this, Rebecca. In 2004, cannabis was reclassified as a class C drug. In 2009, it became a class B drug again.

So there was that weird five-year window where it was downgraded. And then in 2018, we had medicinal cannabis finally being approved. And originally within a very narrow window as to what it could be prescribed for. And now here we are where medicinal cannabis seems to be on the increase.

Recreational use is still banned in the UK, of course, but its prevalence and its potency do seem to be increasing. And we've seen different pictures across the world, haven't we? Some countries have completely decriminalized and allowed recreational use freely. Other countries have moved towards a mixed hybrid medicinal theme.

The US is complex because it still varies by state to state, but certainly in a very different world than we were in the seventies and the eighties. And so our question today, isn't, is cannabis helpful for all these various medical conditions or is it harmful? I think there's so much debate there surrounding specific conditions, but more generally, is the use of cannabis associated with cardiovascular disease? So Rebecca, why don't we dive into the first study that we wanna talk about?

This was a study that I think originally got me thinking about this as an episode idea. It came up earlier this year. So this first paper is a systematic review and metro analysis of data collected between the 1st of January, 2016 to the 31st of January, 2023. And they were looking at major adverse cardiovascular events which included acute coronary syndrome, stroke, composite outcomes of acute coronary syndrome or stroke and cardiovascular mortality.

After narrowing down the papers available across this period, they had 24 studies available for review, 17 were cross-sectional studies, six were cohort studies, and one was a case control study. It's important to note participants within the study may have overlapped. 14 of these studies were using data from three different databases, including the National Inpatient Sample, the Behavioral Risk Factor Surveillance System and the National Health and Nutrition Examination Survey. So there's a chance that patients participated in multiple surveys or that the studies crossed the same sort of time period.

So in total, it was estimated that 432,245,972 patients were included with ages ranging from 19 to 59. In the 14 studies where data was available, cannabis users were predominantly male. It's important to note that four of the studies may have had bias that these authors identified and these were due to uncontrolled confounding factors and possible misclassification of cannabis exposure. In terms of what these studies looked at, 14 studies evaluated the risk of stroke, seven focused on acute coronary syndrome, three focused on cardiovascular mortality, and two focused on composite endpoint of acute coronary syndrome and stroke.

And overall, the findings suggested there was a positive association between cannabis and adverse cardiovascular events. So breaking it down a bit further, the studies looking at cerebrovascular disorders did show divergent results as to whether or not there was an association between cannabis use and stroke. Some papers saw a positive association, others saw no association at all. When looking at cardiac disorders, seven studies were included in this with five focused on acute MIs.

And again, some of the studies showed an association even after adjustment of other factors such as tobacco smoking, and there seemed to be a trend that was a higher risk in younger patients. And when looking at cardiovascular mortality, there was a significantly increased all-cause mortality and cardiovascular mortality in patients with a previously diagnosed MI use cannabis. But it is important to remember that with this large dataset, there are quite a few limitations that I think are important to discuss. So there aren't many patients that are included in this and often in a lot of these surveys, cannabis exposure was poorly reported.

There was potential for bias due to lack of information regarding missing data and medical databases may result in misclassification as to whether people are using cannabis. Again, some of these were patient-led surveys, so patients may not necessarily be so forthcoming with whether or not they're using cannabis and may bend the truth a little bit when looking at other confounding factors like how much physical activity they're taking part in and how much they drink during the week, et cetera.

And as we've already talked about, there was the potential for lots of data overlap with these studies using the same databases covering the same sort of time period. So this was a large meta-analysis, wasn't it? So it was a study that looked at studies and found a number of different types of study to include in its assessment of studies. So some of these were cross-sectional studies and a cross-sectional study is really a snapshot of the population at a given time.

And you take a population, you ask them a survey, hundreds of questions probably, but one of those questions is, have you ever used cannabis and how frequently? And the other question is, have you ever suffered from cardiovascular disease? And these studies found an association. The second type was a cohort study.

And these are where groups of people are followed over a period of time. And these generally tend to be better studies, don't they, because you get more data points throughout the course of the study. But again, a lot of these were still self-reported, weren't they? They were self-reported over a period of time.

And the other type is a case-controlled study whereby people with cardiovascular disease are paired with people of a similar demographic, but without cardiovascular disease and look at differences between them. So it's kind of backwards. All of these studies have got limitations, haven't they? And a lot of this in particular relies on self-reported cannabis use.

So why don't we dive into one of these studies and have a little bit of a more detailed look at some of the methodology used to generate some of this data. So this next study looks at the association between cannabis use and cardiovascular outcomes among US adults. And they used the Behavioral Risk Factor Surveillance System data, which is a national cross-sectional survey performed by the Centers for Disease Control and Prevention. And within the survey, they added an optional cannabis module in 2016.

So they combined the data taken between 2016 and 2020 from 27 American states and two territories who participated in the cannabis module in at least one of these years. They then further narrowed it down to look at those aged between 18 and 74 who answered the question during the past 30 days on how many days did you use marijuana or hashish. And they excluded less than 1% of people who responded don't know or refuse to answer the question. So they quantified cannabis use as a continuous variable as the days of use in the past 30 days, which they then divided by 30.

So those who used every day had a score of one and those who used less than this had a score of less than one. And they looked at demographic variables, including age, sex, self-identified race and ethnicity. They also looked at socioeconomic status, which was represented by education levels, either

like high school, college graduate, et cetera. Cardiovascular risk factors included tobacco cigarette use, which they categorised as never used, former user or current user, nicotine e-cigarette use, current alcohol consumption, which they again split into non-use, non-daily use and daily use.

They also looked at BMI, diabetes and physical activity. Individuals were also asked if they have had angina or coronary heart disease or heart attack or a stroke. So overall there were 434,104 individuals that were included, 4% reported daily cannabis use, non-daily use included 7.1% of people and there was a median use of five days per month. 74% of users who used cannabis reported that they smoked it and the mean age of respondents overall was 45.4 years with 51% being women.

Looking at some other demographics, 60% of individuals were white, 11.6% were black, 19.3% were Hispanic and 9% reported as other race and ethnicity. 61% of individuals had never used tobacco cigarettes, 4.3% reported daily alcohol use and 75% of individuals reported physical activity. Although it's important to mention that there was no information on the level of physical activity and what sort of activity this was, so there's lots of room for like personal interpretation. So quite a lot of information was collected on potential confounding risk factors.

We've talked about alcohol, we've talked about diabetes, we've talked about tobacco use, but quite a lot of data that's also not captured in this survey. For example, we're saying daily cannabis use, but is that one joint daily or is that 10 joints daily? Similarly, is that very high potency extracts or is that low potency, maybe even CBD containing hemp? And as well, it's only capturing use within the last 30 days so individuals could have been very heavy users of cannabis, like up to 31 days prior to the study.

But when asked that question and they're not currently using, that's gonna sway potentially the outcome. So already focusing just on the cannabis use, there's a lot of potential nuance being lost. But similarly, looking at some of the other factors, as you say, how much exercise counts as good exercise, that's gonna be open to so much interpretation. Yeah, and as well, people self-reporting alcohol use, like it's known that people generally downplay how much they drink, so that's again something to be aware of.

So the prevalence of coronary heart disease in this day set was 3.5%. 3.6% of people had experienced MI and 2.8% of people had experienced a stroke. And overall, there were significant differences in demographics, outcomes, and tobacco and alcohol use between adults who use cannabis daily, non-daily, and not at all within the last 30 days. Current tobacco use and daily alcohol use was more prevalent in individuals who reported daily cannabis use versus not at all.

And what was interesting was that cannabis use has had a lower prevalence of obesity, diabetes, had a higher education level, and were younger than those who didn't use. Looking at outcomes, there was no significant association between daily cannabis use and coronary heart disease, but there was a significant association between cannabis use and MI, and they reported there was a 25% increase in odds of MI among adults using cannabis daily compared to those who weren't using.

So MI, myocardial infarction, the classic heart attack that people might think of, whereby a coronary artery is blocked and it reduces the blood supply to the heart muscle itself. Breaking this data down even further, they looked at those who'd never used tobacco cigarettes and never used e-cigarettes, and cannabis use was not associated with coronary heart disease or MI, but was associated with stroke. When looking at adults at a risk of premature cardiovascular disease, that's men aged less than 35 and women aged less than 65.

It showed that cannabis use was significantly associated with cardiovascular disease, MI, and stroke, and it did appear overall that cannabis and tobacco smoking had an independent association with cardiovascular outcomes. In other words, it wasn't just that there was overlap between cannabis users

and tobacco users. They were thought to be actually independent of one another. Yeah, rather than just the risks of smoking.

So there did seem to be some association between cannabis use and different types of cardiovascular disease. That said, very, very messy data, a lot of potential confounders. And crucially, none of this indicates causation, does it? This is purely an association.

It's entirely possible, reverse causations at play here, that cardiovascular disease is more likely to cause people to use cannabis. Mechanisms, maybe we don't understand, but there is potential from this data alone. That's what this data is telling us. Only that there is an association.

It's also important to mention that a large proportion of users within the study were younger people. And obviously, a lot of these disease processes do take time to develop. So the effects might not be truly captured. I feel like we need some more long-term monitoring studies to see whether these individuals do go on to develop cardiovascular disease.

Yes, but to pour petrol on the fire, cannabis has been used a long time. True. Another point the study brought up was that if you do stop smoking cannabis, are the risks of developing cardiovascular disease reversible? Like it sort of is when you quit smoking tobacco and you can kind of reduce your risk.

Yeah, that's a really good point. And this study won't capture that, will it? Because again, it is just a snapshot study, but that's a really good point. If there is an association between cannabis and cardiovascular disease, does stopping the cannabis bring you back to a baseline risk or not?

And you could say, okay, well, this is just one study, and that's true. But in the context of the wider meta-analysis, this was one of 20-something studies that were all included. So the epidemiological data, the public health data does seem to suggest there is an association between cannabis use and cardiovascular disease of various forms. Crucially, we can't prove one causes the other.

And secondly, this data is really dirty. There is an awful lot of potential confounding factors. The big one I guess is, is it just the effect of smoking in general? We know that smoking tobacco increases your risk.

Does smoking cannabis increase your risk? Not just because it's cannabis, but actually because smoking anything increases your risk. There are a handful of studies looking at gummies and edibles and things like that, which maybe we could look at at another time. It'd be interesting to see how that data stacks up.

So if cannabis is associated with cardiovascular disease, by what mechanism? And this is a question that scientists have been trying to answer for some time. And there's a whole host of potential mechanism studies out there. We're just going to dive into just one of those this week and have a look at some proposed mechanisms and pathways that might be at play.

So THC has been previously identified as a mediator for cell cycle arrest, cell apoptosis, inhibition of cell migration, and is a modulator of F-actin integrity in urethhelial cell carcinoma models. Cannabis is also known to increase heart rate by approximately 20 to 100% with an increase in blood pressure as a result. And this can contribute towards acute coronary syndrome. So the aim of this next study was to look at the effects of THC at its metabolites in in vitro conditions on cardiac myocytes to try and work out the role of cannabinoids on fibrogenesis and like the development of acute coronary syndrome.

So there's a few proposed models of cannabis potentially having an impact on cardiovascular disease, isn't there? You've touched on two there. The first is the fact that it's known that cannabis can affect your heart rate and that potentially can lead to alterations in blood pressure. And anything that

changes your heart rate could potentially lead to cardiac arrhythmia.

And so the hypothesis here is that cannabis acts to increase the risk of things like myocardial infarction by influencing heart rate and blood pressure. One of the other mechanisms being proposed is endothelial dysfunction. Cannabis having an effect on the inside of blood vessels leading to inflammation and inflammatory cascades. So one of the first things they looked at was how THC or THC metabolites affect cell migration.

So basically they grew cells on a plate and then created a wound and then saw how the cells moved across that gap to close it. So 250 nanograms per millilitre of hydroxy THC or carboxy THC potentiated cell migration into the wound space within 24 hours and the migration distance was significantly increased compared to controls. However, the same effect was not seen when 100 nanograms per millilitre of THC was used which suggests that THC does not alter cytoskeletal dynamics. So this is a model of repair effectively and how this data showed that cannabis metabolites, THC metabolites altered wound repair.

So the next thing they looked at was whether there were changes to cell proliferation. So they used a BRDU incorporation assay. BRDU is a thymidine analog which is used to detect DNA synthesis as a marker of cell proliferation. So cells treated with 100 nanograms per millilitre of THC showed no change in proliferation in this assay but hydroxy THC and carboxy THC treated cells did show a statistically significant increase in cell proliferation and also mediated time dependent increases in expression of ERK1, P44 and ERK2, P42 which are markers of cell proliferation.

And again, interesting in this case, the cannabis metabolites seem to lead to increases in cell proliferation, THC didn't. So extracellular matrix protein deposition is a key indicator of the pathogenesis of fibregenolysis and during this you get upregulation of key matrix proteins such as alpha-SMA and collagen-1. So the cardiac myocytes when treated with 250 nanograms per millilitre of hydroxy THC or carboxy THC showed a statistically significant increase in the expression of alpha-SMA within 48 hours before returning to baseline and collagen-1 expression was also significantly increased within 24 to 48 hours.

This suggests that the cannabinoid metabolites increase the production of matrix proteins in these cardiac myocytes in vitro. They also looked at alterations in the microstructure of cardiac myocytes by using scanning electron microscopy and treatment with THC showed no significant change to morphology compared to the control whereas hydroxy THC and carboxy THC at low doses increased cell polarization and there was pronounced stress fiber formation. They also acquired a star-like shape and showed changes in cell adhesion which are changes consistent with an increase in cell motility.

When these metabolites were given up high doses a deterioration of membrane integrity was seen with the carboxy THC and it's also showed visible perforations in the cell. High dose hydroxy THC exacerbated stress fiber formation. They also looked at how cannabinoids modulate regenerative capacity of poly-cells is nigra which are planarian flatworms and you can decapitate these flatworms and they have the ability to regenerate which I thought was really, really cool.

So when looking at low and high doses of THC which was a hundred nanograms per millilitre and a thousand nanograms per millilitre, THC did not alter the structure or regenerative capacity compared to the control worms. There was increased cellular deposition at the wound site suggested the amplification of tissue deposition and rapid wound healing which occurred with 250 nanograms per millilitre of THC hydroxy and carboxy THC. But when using 2,500 nanograms per millilitre of hydroxy THC and carboxy THC this resulted in a significant incidence of lethality with a decreased rate of regeneration of tissue and a slow response to stimuli in surviving organisms.

So it seems that a low dose does increase wound healing and upregulates the extracellular matrix deposition but high doses result in cell toxicity and death. So we've gone from one end of the spectrum to the other, haven't we? We've looked at large population studies and now we're looking at single cells and flatworms in a petri dish. I found some of this data really interesting but there's a few thoughts that I don't think I quite understand.

Firstly, that it seems that a lot of these effects are being mediated by the metabolites. Hydroxy THC is active at CB1. Carboxy is generally considered inactive. So this isn't at least at first glance a pharmacological effect.

This could be a mechanistic effect. They are quite fat soluble compounds. Could this be fat soluble, small molecules interfering with cell membranes and things like that. But interestingly, the THC which is also quite fat soluble didn't seem to do the same thing.

So I think there's quite a few unanswered questions here. I think the other thought I've got regarding this data that we need to be really clear about is the concentrations that they were using are way, way higher than what we tend to see in blood following cannabis use, right? Yeah, for the metabolites they were using 250 nanograms per millilitre of those metabolites and 100 nanograms per millilitre of THC for their low dose. Then really, really high for their high dose.

It does show some interesting data though, doesn't it? At least in cell models, there is some possible effects. Does this answer the epidemiological effect that we've seen? That I don't know.

I'm not convinced. At least this particular study in isolation doesn't mean it doesn't add to the broader literature of course. So all in all then, we've not really answered that question, have we? We've looked at some associations.

We've looked at some potential mechanisms. I'm left more confused than I was. Yeah, me too. Before we started.

There's so much work going on out there to try and understand cannabis. It is one of the more investigated. Drugs of misuse and inverted commas, although as I said at the start, that's now considered a medicine as well. Also, we do need to look at the magnitude of the risk that the epidemiological paper pulled out, right?

It wasn't huge. No. There was a very small modest risk. It's not zero, but it wasn't also huge.

So what's your takeaway from this, Rebecca? That cannabis is really complicated. I think that's fair. Yeah, I think that's really fair.

I think I'm going to go out and try and do a bit more reading around some of the mechanisms, because I think the biochemistry behind it's really complex, isn't it? We know that cannabis interacts with the CB1 receptor and the CB2 receptor, and CB2 receptor being involved in immune responses. And it does look like the endocannabinoid pathways in general might be involved in some cardiovascular pathways somehow. This data doesn't suggest it's direct agonism because the inactive metabolite was doing something too.

So I think there's a lot potentially to further explore here. In terms of the broader epidemiological risk, other than saying it looks like there's an association, I'm not sure we can say much more than that. It will be interesting to see where things go. Cannabis from 40 years ago isn't the same as cannabis today.

Potency keeps going up. It's becoming increasingly accepted by society. And so prevalence is possibly increasing or maybe reported prevalence is increasing because people feel more comfortable

admitting it if it's not illegal, maybe. So I think it will be interesting to see where we go in the next 20 years, to see whether there is a trend towards more cardiovascular disease or not.

This could just be noise. So I hope you've enjoyed listening to us this week. Please do give us a like, give us a follow, and share us with your friends. Hope you have an amazing week and we'll see you next time.

Bye.