

Cannabis Use and Chronic Kidney Disease (CKD): Epidemiological Evidence, Biological Mechanisms, and Mendelian Randomization Analysis

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Abstract. Chronic kidney disease, also known as CKD, has always been a major global health issue with a rising prevalence and substantial cardiovascular risks. With this introduced, cannabis use has increased in many countries due to social environments, medical uses, and policy pressures. This allows people to question its potential renal consequences, while its effect on kidney health is controversial. This paper will be using a literature review as the analysis method in order to explore the association between cannabis exposure and CKD-related outcomes, such as the association between cannabis and CKD, and also the casualty of these association. In order to further more strengthen research observations, the paper would review Mendelian randomization (MR) studies that use genetic proxies for cannabis initiation, lifetime use, or cannabis use disorder to estimate the effect of this substance on kidneys functions. Overall, the reviewed evidence suggests that all observations are mixed and they tend to be sensitive towards the difference in social factors, while MR findings have provided limited support for evidence of a strong causal effect, although power and phenotype specificity are challenged. The paper will highlight the considerations of method and future research directions to clarify whether cannabis use contributes to the risk of CKD.

Keywords: Cannabis use, Chronic Kidney Disease (CKD), epidemiology, Mendelian Randomization

1. Introduction

Chronic Kidney Disease (CKD) is a progressive health issue that is characterized by decreasing kidney function over time. It affects millions of people worldwide and can lead to end-stage kidney disease, cardiovascular complications, and increasing mortality. Due to the fact that DKS has major health and economic consequences, being able to identify the modifiable risk factors is very important.

As the research stated, cannabis is one of the most widely used psychoactive substances in the world, and its use has increased massively in recent years for both recreational and medical purposes. This trend has raised concerns about the potential long-term health effects of cannabis use, including the possible impacts on kidney function. Some researchers have suggested that cannabis

may influence kidney health through influencing blood pressure, inflammation, metabolic regulation, or dehydration symptoms. However, there is still more evidence required while existing findings tend to be inconsistent.

There are many observational studies that examine cannabis and the kidney, which have limited outcomes due to confounding factors such as tobacco use, obesity, diabetes, and social factors. In addition, self-reported cannabis use and reverse causation make it even more difficult to come to a causal conclusion. Mendelian randomization (MR) offers an alternative approach by using genetic variants associated with cannabis use, helping reduce confounding or any potential unknown data. Therefore, this paper reviews both types of observed evidence to evaluate whether cannabis use is associated with CKD and identifies any possible future research directions to further explore the topic.

2. Literature review

2.1. Epidemiological studies

First, looking into large-scale epidemiological studies. DellePiane et al. have examined the association between cannabis use and CKD by using the All of US cohort (N=223,354), investigating lifetime cannabis use and frequency of use [1]. The study has found that long-term usage, such as less than monthly, monthly, and lifetime cannabis use, was not significantly associated with CKD. However, weekly use was associated with higher odds of CKD (OR=1.28), and daily use also showed increased odds (OR=1.25), after adjusting for multiple confounders, including age, sex, BMI, smoking, hypertension, diabetes, education level, and insurance status. Other studies have reported similar mixed findings. Some cohort analyses have shown no significant relationship between cannabis use and kidney function decline, while others have suggested that heavy or long-term use may be associated with increased CKD risk [2, 3]. These inconsistencies may be explained by differences in study design, population characteristics, and measurement of cannabis exposure. A key limitation of epidemiological studies is the presence of residual confounding. Cannabis users may differ from non-users in terms of lifestyle, diet, and health behaviors. In addition, individuals with chronic illness may be more likely to use cannabis for symptom management, which introduces reverse causation. These factors make it difficult to determine whether cannabis use directly contributes to CKD.

2.2. Cannabis and metabolic risk factors

Cannabis use may influence CKD risk indirectly through metabolic pathways. Evidence suggests that cannabis exposure can affect glucose metabolism, lipid profiles, and blood pressure regulation [4, 5]. These metabolic factors are well-established contributors to CKD development. For example, hypertension is one of the leading causes of CKD, and cannabis use has been associated with changes in vascular tone and blood pressure regulation. Similarly, alterations in insulin sensitivity and glucose metabolism may increase the risk of diabetes, which is another major risk factor for CKD.

In addition, cannabis use may influence body weight and lipid metabolism, which are linked to cardiovascular and renal health. Although some studies suggest that cannabis users may have a lower body mass index, others indicate an increased risk of metabolic abnormalities under certain conditions. These findings suggest a complex relationship between cannabis use and metabolic health.

Overall, a potential pathway can be described as: cannabis exposure → metabolic changes (hypertension, diabetes, dyslipidemia) → increased CKD risk. This indirect mechanism may partly explain the associations observed in epidemiological studies.

2.3. Biological mechanisms

From a biomechanical point of view, the endocannabinoid system plays an important role in kidney physiology. Cannabinoid receptors CB1 and CB2 are expressed in kidney tissues, including glomerular and tubular cells. Preclinical studies suggest that CB1 receptor activation may promote inflammation, oxidative stress, and fibrosis, which contribute to kidney damage [6, 7]. CB2 receptors, on the other hand, may have protective effects by modulating immune responses and reducing inflammation. However, the overall impact of cannabis use on these pathways depends on the balance of different cannabinoids and their interactions with these receptors. Cannabis may also influence renal hemodynamics, oxidative stress pathways, and inflammatory signaling. For example, increased oxidative stress may damage renal cells, while chronic inflammation may lead to fibrosis and functional decline. Despite these findings, direct evidence in human populations remains limited, and further research is needed to clarify these mechanisms.

2.4. Acute kidney injury (AKI)

Plenty of recent evidence suggests that cannabis use may be associated with acute kidney injury (AKI). Clinical reports have documented cases of AKI following cannabis use, particularly with synthetic cannabinoids, which may have stronger and more unpredictable effects than natural cannabis [8, 9]. AKI is an important risk factor for CKD, as repeated episodes of acute injury can lead to permanent structural damage and progressive loss of kidney function. This suggests that cannabis use may contribute to CKD indirectly through recurrent AKI.

Although evidence is still limited due to the scope of research, this pathway highlights the importance of considering both acute and chronic effects when evaluating the impact of cannabis on kidney health.

3. Evidence synthesis and Mendelian randomization

3.1. Observation evidence

Observational evidence on cannabis use and CKD remains uncertain. Most studies have reported that there was no significant association for occasional use, while frequent use may be associated with an increase in the risk of CKD [1-3]. However, these associations are often weakened after adjusting for the confounding variables.

The magnitude of the observed associations between cannabis use and CKD is generally small, suggesting that cannabis use may not be a major component of the risk factor for CKD. However, the presence of residual confounding and measurement limitations reduces confidence in these findings.

3.2. Mendelian randomization

Due to the fact that observational data are limited, Dellepiane et al. also conducted a two-sample Mendelian randomization (MR) analysis using genetic instruments that are associated with cannabis use disorder (CUD) [1]. Within the MR analysis, evidence showed that genetic liability to cannabis

use disorder was not associated with CKD; the OR was 1.00 (95% CL 0.99-1.01), and $P = 0.96$. The analysis used multiple MR techniques, including MR-RAPS, inverse-variance-weighted methods, and sensitivity analysis. However, MR studies have limitations. Genetic instruments for cannabis use may not fully capture exposure patterns, such as frequency, dosage, or type of cannabis product. In addition, statistical power may be limited, particularly for detecting small effects. Therefore, the absence of a significant association does not completely rule out a causal relationship.

4. Discussion

The study aimed to investigate the relationship between cannabis use and the effect on kidney function or health risks (such as CKD), and the findings indicate that the association between these factors remains uncertain. Observational studies suggest a very weak correlation under some conditions, but these results are often diminished after adjusting for confounders. MR evidence, on the other hand, does not support a strong causality, although methodological limitations exist. From a clinical perspective, healthcare providers should still be aware that cannabis use should be considered when assessing CKD risk, especially among individuals with existing risk factors, for example, diabetes or hypertension.

4.1. Differences between observational evidence and Mendelian randomization findings

The findings in this review show that observational studies and Mendelian randomization (MR) studies do not give the same conclusion. In observational studies, some results suggest that cannabis use, especially frequent or long-term use, may be related to a higher risk of CKD. However, these associations are usually not very strong, and in many cases, they become weaker after adjusting for confounding factors like smoking, obesity, diabetes, hypertension, and socioeconomic background. This means the relationship seen in observational studies may not be fully caused by cannabis itself, but also by other health and lifestyle differences between users and non-users.

On the other hand, MR evidence did not support a strong causal relationship between cannabis use disorder liability and CKD. This is important because MR is less affected by reverse causation and some confounding problems. So, compared with observational studies, MR can give stronger evidence when discussing causality. But MR also has its own limitations. For example, the genetic instruments may not fully reflect real cannabis exposure, such as how often a person uses it, how much they use, or what type of cannabis product they use. Also, MR studies may not have enough statistical power to detect very small effects. Because of this, the difference between observational and MR findings suggests that the current evidence is still uncertain, and the observed association may be influenced by study limitations instead of a clear and direct causal effect.

4.2. Policy implications

Even though current evidence does not prove that cannabis has a strong causal effect on CKD, the findings still have some important policy and clinical implications. First, healthcare providers should still pay attention to cannabis use when they assess people who already have CKD risk factors, such as diabetes, hypertension, obesity, or other metabolic problems. In these groups, cannabis use may still be relevant as part of a broader health risk profile, even if it is not confirmed as a major direct cause of CKD. Second, in places where cannabis legalization is increasing, public health messages should be careful and balanced. It is not accurate to say that cannabis clearly causes CKD, but it is also not safe to say that cannabis has no kidney risk at all. A better policy approach is

to give cautious health education, especially for heavy users and people who already have existing metabolic or cardiovascular risk factors. In addition, cannabis use can also be included in routine screening and counseling in kidney-related healthcare settings. Overall, current evidence suggests that policymakers and clinicians should take a careful but not extreme position when discussing cannabis and kidney health.

4.3. Future possible directions

Future research should focus on improving both the measurement of cannabis exposure and the strength of causal analysis. First, observational studies need more detailed information about cannabis use, such as frequency, duration, dosage, route of use, and the difference between natural cannabis and synthetic cannabinoids. Better exposure data may help explain why current epidemiological findings are mixed. MR studies should be improved by using stronger genetic instruments, larger sample sizes, and more multi-ancestry populations. This can increase statistical power and also help researchers study more specific cannabis-related traits, instead of only using broad measures like cannabis use disorder liability. Finally, future studies should combine epidemiological evidence, genetic evidence, and biological mechanism research together. By doing this, researchers can better understand whether cannabis use contributes to CKD risk directly, indirectly, or maybe only under some specific conditions.

5. Conclusion

This study aimed to investigate the relationship between cannabis use and chronic kidney disease through the method of literature review of epidemiological and Mendelian randomization evidence. The findings indicate that even though observational studies suggest an association between frequent cannabis use and CKD, Mendelian randomization analyses still do not support a causal relationship.

This research contributes to the existing body of knowledge by combining observational and genetic evidence, helping to clarify inconsistencies in previous findings. The study is significant for public health risk communication and clinical counseling, especially for the areas that have problems with cannabis legalization.

However, this study is limited by reliance on existing data, potential heterogeneity across study designs, and the limited availability of quantitative exposure data in the analysis of genetics. Future studies should focus mainly on obtaining more detailed exposure measurements, multi-ancestry genetic samples, and long-term kidney outcomes.

Overall, this study provides new insights into the relationship between cannabis use and CKD, and highlights the importance of using multiple methods in analyzing data for epidemiological research.

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