

# Investigating the Dose-Response Relationship Between Cannabis Use and the Onset of Schizophrenia: A Hazy Link

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## ABSTRACT

**Research Question:** Is there a dose-response association between the use of cannabis and the subsequent development of schizophrenia?

**Methods:** A structured literature review was conducted in SCOPUS, resulting in 11 pertinent articles.

**Results:** Upon analysis, 9 articles presented a strong association between cannabis use and the onset of schizophrenia. A strong dose-response relationship was present in 5 of the articles, while the remaining 6 articles showed weak or inconclusive evidence.

**Conclusion:** A strong association between cannabis use and the development of schizophrenia was established. There was little consensus within the articles attributing schizophrenia development to the dosage of cannabis use. In order to formulate a definitive dose-response relationship, further research must be conducted.

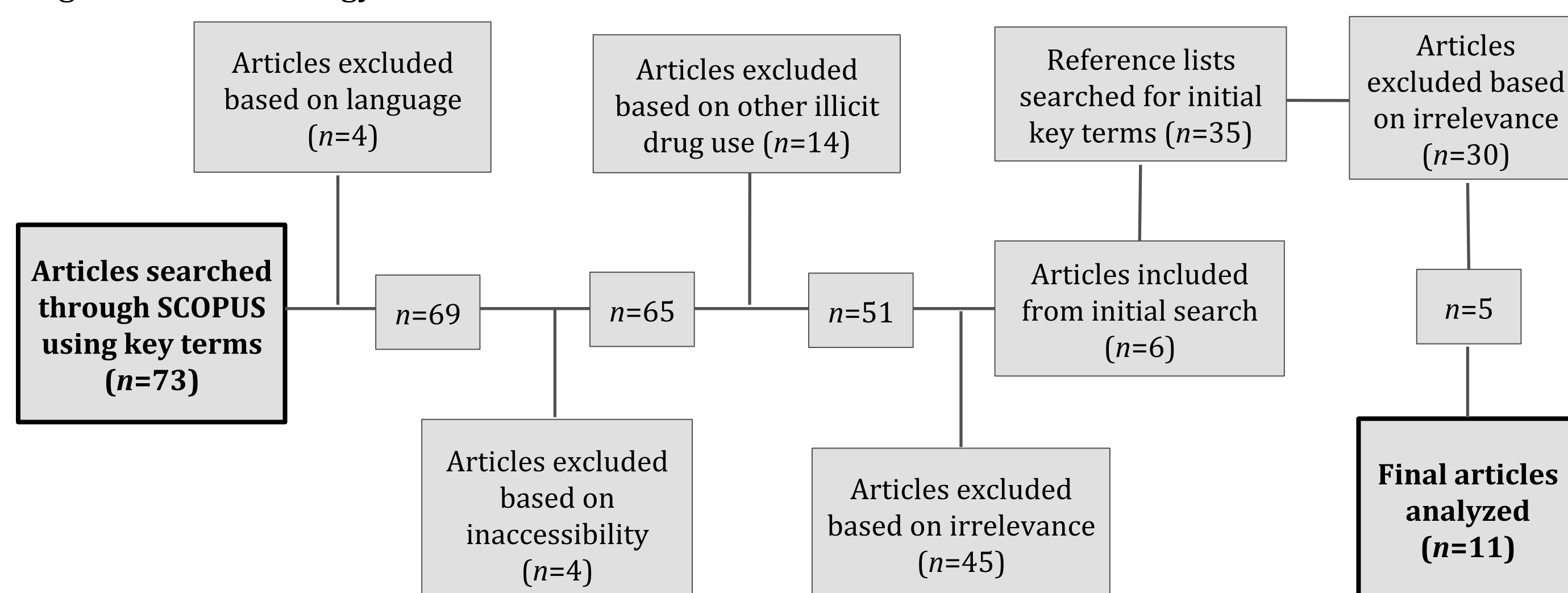
## BACKGROUND

Cannabis is the most commonly used illicit drug in the world; 2.7-4.9% of the global population aged 15-65 reported having used cannabis recreationally in 2015.<sup>1</sup> Cannabis use is particularly popular among adolescents aged 15 or older, with approximately 13% of North American and European's reporting use of cannabis regularly.<sup>2</sup> Cannabis contains a psychoactive substance, tetrahydrocannabinol (THC), which is responsible for adverse effects on memory, cognition, and other physiological functions.<sup>3</sup> Schizophrenia is a psychological disorder that 21 million individuals suffer from globally.<sup>4</sup> This disorder has been speculated to have both biological and environmental origins.<sup>5</sup> Cannabis use has been investigated as a potential risk factor for the development of schizophrenia in a dose-response relationship. Distinct features of schizophrenia include a variation of delusions, hallucinations and disorganized speech.<sup>6</sup> Symptoms typically begin between ages 15 to 30 and the prevalence rate severely declines after age 45.<sup>7</sup> Current literature continues to show strong evidence for an association of cannabis use on the development of schizophrenia, with little research focusing on dose-response. Investigating this dose-response relationship is essential to understanding the etiology of schizophrenia and to enhance interventions and improve prevention strategies.

## METHODS

A structured literature review was conducted in the SCOPUS database, using the following key search terms: (schizophrenia) and ((cannabis) or (marijuana)) and (dose-response). A total of 73 articles were retrieved, however, after the exclusion criteria was applied, 6 pertinent articles remained. To ensure the literature was representative, a secondary search was conducted using the reference lists of the original 6 articles. The reference lists were searched using the key terms (schizophrenia) and (cannabis), leading to 35 new articles. These articles were subjected to the same exclusion criteria, resulting in the discovery of 5 additional articles. A total of 11 articles were analyzed, furthermore a quality rating was assigned to each of the 5 primary studies, in order to assess and rank according to quality (see figure 1).

Figure 1. Methodology



## RESULTS

Table 1. Editorials, Literature and Structured Reviews

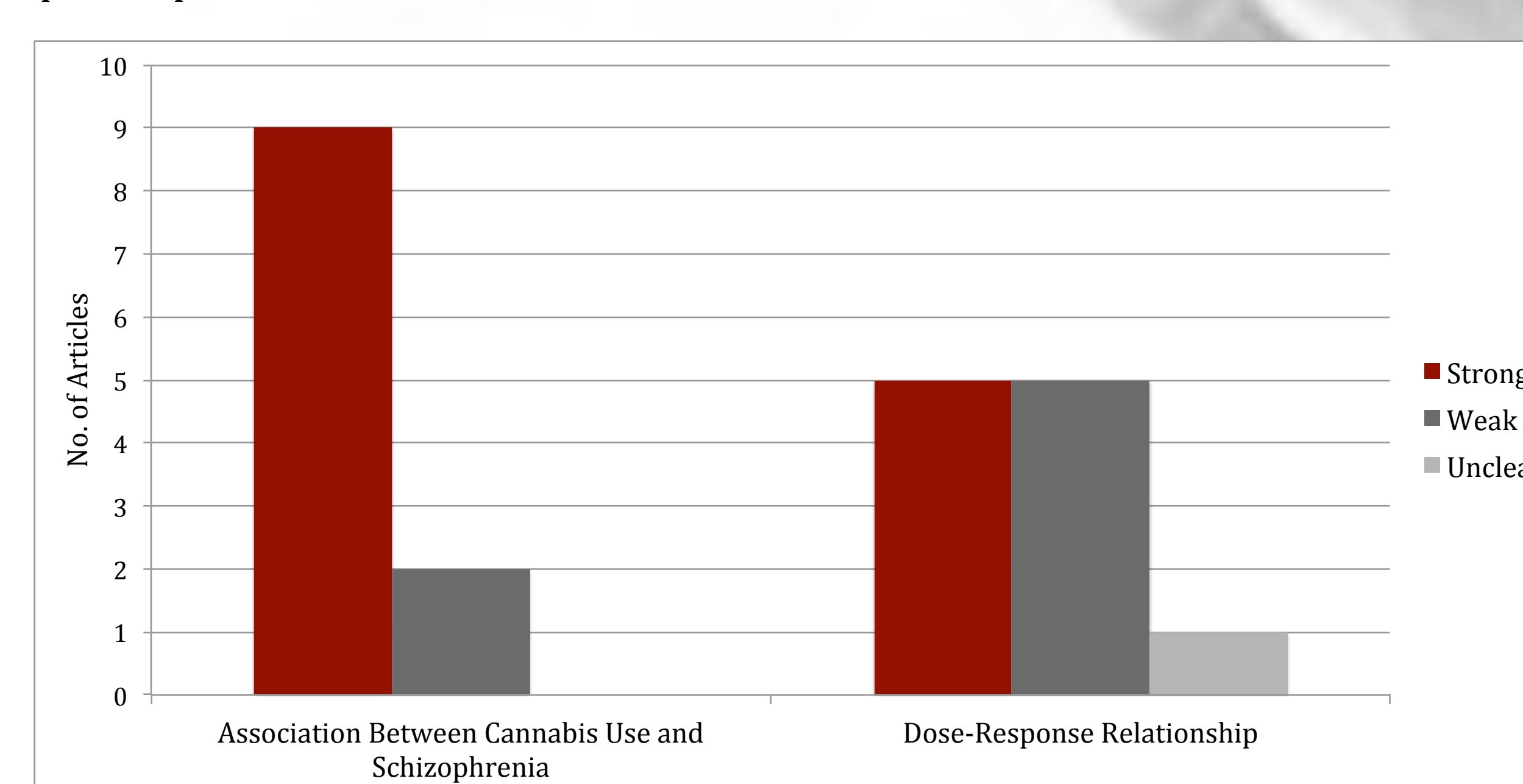
Study, Author & Date	Methodology & Primary Outcome	Association	
		Cannabis Use & Schizophrenia	Dose-Response
Cannabis use and cognitive dysfunction Shrivastava et al., 2011	<b>Methodology:</b> Editorial <b>Primary Outcome:</b> Heavy marijuana use causes a decline of neurocognitive performance, which is associated with schizophrenia in a dose-response relationship.	Strong	Strong
Is cannabis responsible for early onset psychotic illnesses? Dervaux et al., 2011	<b>Methodology:</b> Editorial <b>Primary Outcome:</b> Chronic cannabis use increases the risk for psychotic disorders (particularly schizophrenia) and likely in a dose-response fashion.	Strong	Weak
Cannabis and psychosis/schizophrenia: human studies D'Souza et al., 2009	<b>Methodology:</b> Literature Review <b>Primary Outcome:</b> Heavy use of cannabis increases the likelihood of developing schizophrenia, however cannabis is not the only factor in the development of this disease.	Strong	Weak
Cannabis as a risk factor for psychosis: systematic review Semple et al., 2005	<b>Methodology:</b> Systematic Review <b>Primary Outcome:</b> There is a notable consistency between cannabis use and schizophrenia, specifically in a dose-response relationship.	Strong	Strong
Cannabis use and the risk of later Schizophrenia: a review Smit et al., 2004	<b>Methodology:</b> Literature Review <b>Primary Outcome:</b> Cannabis use does indeed increase the risk of schizophrenia, in a dose-response relationship.	Strong	Strong
Cannabis use and psychosis: a review of clinical and epidemiological evidence Hall et al., 2000	<b>Methodology:</b> Literature Review <b>Primary Outcome:</b> Cannabis use may precipitate schizophrenia in a dose-response relationship, but it is unlikely to account for more than a minority of cases.	Weak	Weak

Table 2. Case-Control and Cohort Studies

Study, Author & Date, Sample Size	Population, Design & Primary Outcome	Association		Quality Rank*
		Cannabis Use & Schizophrenia	Dose-Response	
Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study Zammit et al., 2002 n=50,087	<b>Population:</b> Swedish male conscripts <b>Design:</b> Historical Cohort Study <b>Primary Outcome:</b> A relationship between cannabis and schizophrenia exists in a dose-response fashion.	Strong	Strong	1
White matter fractional anisotropy over two time points in early onset schizophrenia and adolescent cannabis use disorder: A naturalistic diffusion tensor imaging study Epstein et al., 2014 n=156	<b>Population:</b> Children and adolescents <b>Design:</b> Longitudinal Cohort Pilot Study <b>Primary Outcome:</b> Cannabis use disorder may be associated with alterations on white matter development, which is shown to influence the development of schizophrenia. It is unclear whether this is a dose-response relationship.	Weak	Weak	2
Cannabis and Schizophrenia: A Longitudinal Study of Swedish Conscripts Andreasson et al., 1987 n=45,570	<b>Population:</b> Swedish male conscripts <b>Design:</b> Cohort Study <b>Primary Outcome:</b> There is a strong relationship between the dosage of cannabis exposure and the future development of schizophrenia.	Strong	Strong	3
Schizophrenia in users and nonusers of cannabis: A longitudinal study in Stockholm County Andreasson et al., 1988 n=21	<b>Population:</b> Swedish male conscripts <b>Design:</b> Longitudinal Cohort Study <b>Primary Outcome:</b> Cannabis use is associated with an increased risk of schizophrenia, with little evidence suggesting a dose-response relationship.	Strong	Weak	4
Cannabis use and genetic predisposition for schizophrenia: a case-control study Veiling et al., 2008 n=163	<b>Population:</b> Non-Western immigrants in the Netherlands <b>Design:</b> Case-Control Study <b>Primary Outcome:</b> Cannabis use was found to be a risk factor for schizophrenia, however the evidence of a dose-response relationship is unclear.	Strong	Unclear	5

\* Quality ranking measured using "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" published by the National Heart, Lung, and Blood Institute.<sup>8</sup>

Graph 1. Representation of Results



## DISCUSSION

### Limitations

Structured literature reviews have inherent limitations that influence the strength of the results. The articles obtained in our review were restricted to those available on the SCOPUS database. Several potentially appropriate articles were inaccessible due to database restrictions. Foreign language exclusion bias further limited the quality of evidence that was evaluated in this structured literature review. Due to likely publication biases, it was not surprising that our review did not offer articles opposing the association between cannabis use and schizophrenia development. Also, due to the widespread illegal status of cannabis, it is likely that cannabis use is underreported in these studies, thus leading to less significant results that would otherwise suggest a dose-response relationship.

### Strengths

In order to access the most relevant articles, no restrictions were set on publication dates. The articles found in this review were not limited geographically, as numerous international studies were evaluated. Additionally, our review did not exclude any population groups based on sex, age or ethnicity. Therefore the conclusions of this review can be applied to general populations.

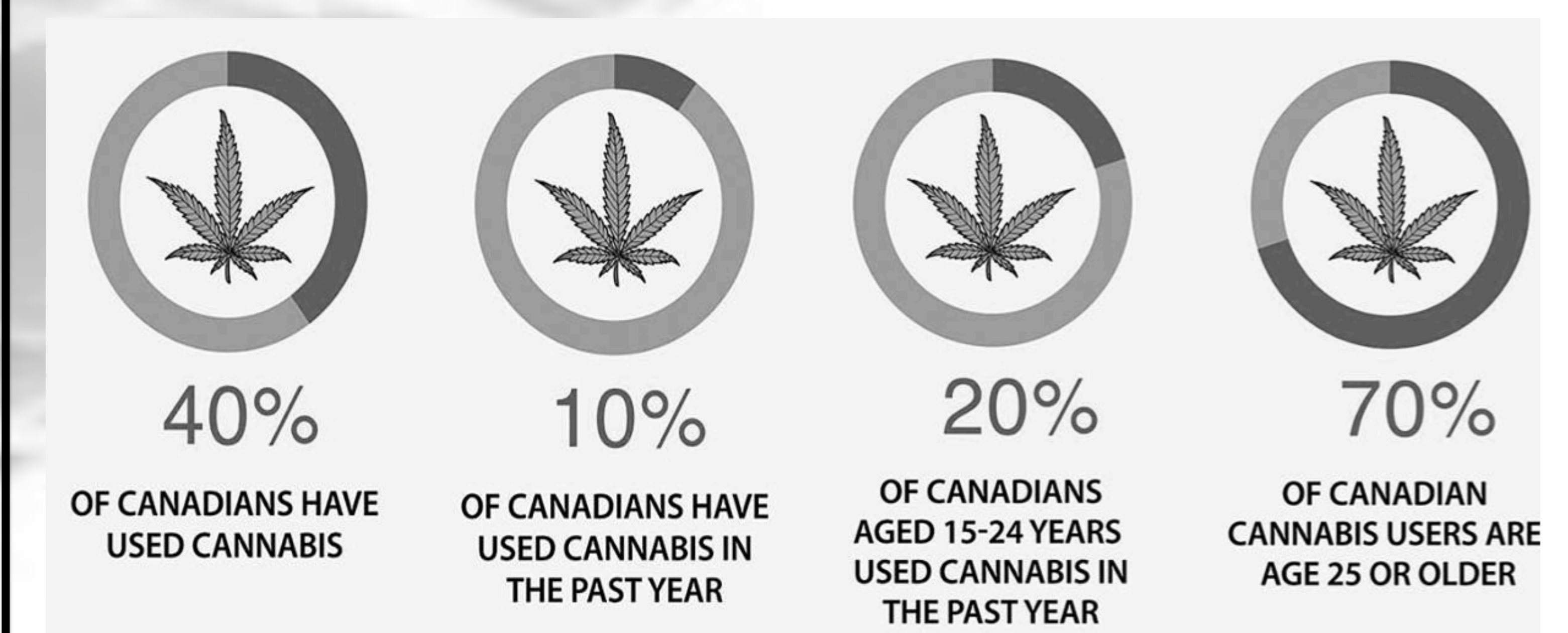
### Future Research

This structured literature review indicated that future research is necessary to target the dose-response relationship of cannabis use and the development of schizophrenia. Ideally, prospective longitudinal studies with large sample sizes should be conducted in order to determine if a specific threshold of cannabis use exists in the pathways to schizophrenia development. Considering the upcoming legalization of cannabis use, Health Canada must have conclusive evidence on this topic in order to disseminate the necessary information to their citizens. Increasing awareness of the severe adverse effects of cannabis should be a primary responsibility of Canada's government. Further research should be conducted to determine other risk factors of schizophrenia, given that environment, genes and brain development are currently the only known risk factors.<sup>4</sup>

## CONCLUSION

A strong association between cannabis use and the development of schizophrenia was established. There was little consensus within the articles attributing schizophrenia development to the dosage of cannabis use. In order to formulate a definitive dose-response relationship, further research must be conducted.

Figure 2. Prevalence of Cannabis Use Across Canada<sup>9</sup>



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