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

Fallon Melville, Bronte Patterson, Erika Rudnicki, and Crystal Usher

### 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. Cannabis use is particularly popular among adolescents aged 15 or older, with approximately 13% of North American and European reporting use of cannabis regularly. Cannabis contains a psychoactive substance, tetrahydrocannabinol (THC), which is responsible for adverse effects on memory, cognition, and other physiological functions. Schizophrenia is a psychological disorder that 21 million individuals suffer from globally. This disorder has been speculated to have both biological and environmental origins. Cannabis use has also 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. Symptoms typically begin between ages 15 to 30 and the prevalence rate severely declines after age 45. Current literature continues to show strong evidence for an association between cannabis use and 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) 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, furtherly a quality rating was assigned to each of the 5 primary studies, in order to assess and rank according to quality (see figure 1).

### RESULTS

<table>
<thead>
<tr>
<th>Study, Author &amp; Date</th>
<th>Population</th>
<th>Design</th>
<th>Primary Outcome</th>
<th>Population</th>
<th>Design</th>
<th>Primary Outcome</th>
<th>Population</th>
<th>Design</th>
<th>Primary Outcome</th>
<th>Association</th>
<th>Quality Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semple et al., 2004</td>
<td>Population: Australian youth</td>
<td>Cross-sectional study</td>
<td>Cannabis use increases the risk for schizophrenia.</td>
<td>Population: Australian youth</td>
<td>Cross-sectional study</td>
<td>Cannabis use increases the risk for schizophrenia.</td>
<td>Population: Australian youth</td>
<td>Cross-sectional study</td>
<td>Cannabis use increases the risk for schizophrenia.</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Zammit et al., 2004</td>
<td>Population: Australian youth</td>
<td>Cross-sectional study</td>
<td>Cannabis use is associated schizophrenia.</td>
<td>Population: Australian youth</td>
<td>Cross-sectional study</td>
<td>Cannabis use is associated schizophrenia.</td>
<td>Population: Australian youth</td>
<td>Cross-sectional study</td>
<td>Cannabis use is associated schizophrenia.</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Rudnicki et al., 2004</td>
<td>Population: Canadian youth</td>
<td>Cross-sectional study</td>
<td>Cannabis use is associated with schizophrenia.</td>
<td>Population: Canadian youth</td>
<td>Cross-sectional study</td>
<td>Cannabis use is associated with schizophrenia.</td>
<td>Population: Canadian youth</td>
<td>Cross-sectional study</td>
<td>Cannabis use is associated with schizophrenia.</td>
<td>Strong</td>
<td>Strong</td>
</tr>
</tbody>
</table>

* Quality rating awarded using “Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies” published by the National Heart, Lung, and Blood Institute.

### DISCUSSION

**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 increasing legalization of cannabis use, future 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.

### 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

40% OF CANADIANS HAVE USED CANNABIS
10% OF CANADIANS HAVE USED CANNABIS IN THE PAST YEAR
20% OF CANADIANS AGED 15-24 YEARS HAVE USED CANNABIS IN THE PAST YEAR
70% OF CANADIAN CANNABIS USERS ARE AGED 23 OR OLDER

---

* Graph 1: Methodology

* Table 1: Editorial, Literature, and Structured Reviews

* Figure 1: Methodology

* Table 2: Case-Control and Cohort Studies

---

* DOI: 10.1093/eurpub/ckv032

---

* References

---

* Footnotes