Good afternoon, Mr. Chairman and members of the Caucus. Thank you for inviting me to contribute my knowledge about adolescent vulnerability to cannabis effects on cognitive functioning.

Summary

What We Know:

1. Cannabis use is associated with cognitive deficits that persist beyond the period of acute intoxication
2. Cannabis-related cognitive deficits are subtle
3. More frequent, persistent, and earlier-onset cannabis use is associated with larger cognitive deficits

What We Still Need to Know:

1. What are the mechanisms underlying cannabis-related cognitive deficits?
2. What are the parameters of cannabis use that determine the magnitude and persistence of cognitive deficits (quantity, frequency, age-of-onset, duration, THC content)?
3. Does cognitive functioning recover with abstinence?
4. Are there individual differences in susceptibility to cannabis-related cognitive deficits?

Cannabis Effects on Cognitive Function

Cannabis intoxication results in temporary cognitive impairment,[1-3] but it is less clear if cannabis use results in enduring cognitive impairment – impairment that persists beyond the period of acute intoxication. Studies comparing heavy cannabis users with nonusers have collectively shown that heavy cannabis users, even when not intoxicated by cannabis, perform worse on cognitive tests, including tests of learning and memory, attention, and other executive functions.[4-6] The magnitude of cognitive deficits in these heavy cannabis users is small,[4-6] though some evidence suggests that cognitive deficits might be larger among more frequent, chronic, and earlier-onset cannabis users.[3,7-12] Some evidence suggests that cognitive deficits might resolve with prolonged abstinence.[5,6,13]

The extant evidence base draws largely on studies that compared heavy cannabis users with nonusers on cognitive test performance, and these studies have two commonly cited limitations. First, the studies lack information on initial cognitive functioning before the onset of cannabis use. Therefore, the studies do not address the possibility that cognitive differences between cannabis users and comparison individuals represent pre-existing rather than cannabis-induced deficits. Second, the studies rely on cannabis users' retrospective reports of their frequency, quantity, age-of-onset, and duration of cannabis use, with reports often obtained years after initiation of heavy use. Therefore, retrospective reports of cannabis use might not be accurate.

To redress these limitations, prospective longitudinal studies are needed. Prospective longitudinal studies assess cognitive functioning in youth before the initiation of cannabis use, obtain prospective information about cannabis use as the sample is followed over a number of years, and then reassess cognitive functioning again, after some individuals in the sample have developed a persistent pattern of cannabis use. The most comprehensive prospective longitudinal study of cannabis use and cognitive functioning was published by our group in 2012 (Meier et

al., 2012).[14] Our study found that persistent cannabis use was associated with IQ decline from childhood to adulthood, and IQ decline was concentrated in adolescent-onset persistent cannabis users. Here I (1) describe our 2012 study and explain the findings, (2) address questions about whether cannabis-associated IQ decline could be accounted for by factors such as low socioeconomic status and poor childhood self-regulation, and (3) explain why the study is unique and why we need more studies like it.

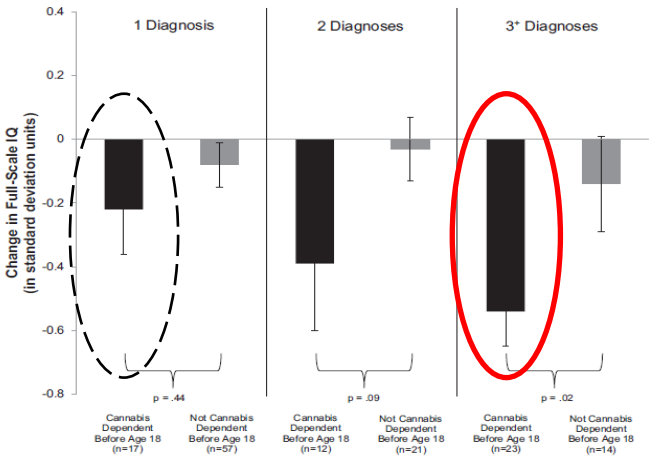
Cannabis and IQ (Discussion of Meier et al., 2012)

The Findings: We studied the association between persistent cannabis use and IQ decline and asked whether IQ decline was concentrated among adolescent-onset cannabis users. Findings come from the Dunedin Multidisciplinary Health and Development Study. The Study has followed a group of 1,037 children, who were born in 1972-73 in Dunedin, New Zealand, from birth to age 38 years, with 96% of the sample taking part at age 38. IQ was tested at age 13, before cannabis use, and again at age 38, after some study members had used cannabis for years.

We found that:

1. Persistent cannabis use was associated with IQ decline from childhood to adulthood, and IQ decline was concentrated among adolescent-onset persistent cannabis users. For example, individuals who began using cannabis in adolescence (before age 18) and used it for years thereafter showed an average 8-point IQ decline from childhood to adulthood (circled in red in the figure). Individuals who used cannabis short-term in adolescence showed only weak evidence of IQ decline (3-point IQ decline; circled in black dashes in the figure). Individuals who began using cannabis in adulthood (after age 18) did not show IQ decline (gray bars), even when they used persistently.

   In the figure below, 1 diagnosis = the study member met criteria for cannabis dependence at only one of the five assessment phases (ages 18, 21, 26, 32, 38); 2 diagnoses = the study member met criteria for cannabis dependence at two of the five assessment phases.; 3+ diagnoses = the study member met criteria for cannabis dependence at three or more of the five assessment phases. More diagnoses = greater persistence.



Adolescent vulnerability. Shown is change in full-scale IQ (in SD units) from childhood to adulthood among study members with 1, 2, or 3+ diagnoses of cannabis dependence as a function of age of onset of cannabis dependence. Individuals with adolescent-onset cannabis dependence (black bars) experienced greater IQ decline than individuals with adult-onset cannabis dependence (gray bars). IQ decline of approximately −0.55 SD units among individuals with adolescent-onset cannabis dependence in the 3+ group represents a decline of 8 IQ points. Error bars = SEs.

2. Quitting or reducing cannabis use did not appear to fully restore intellectual functioning among adolescent-onset former persistent cannabis users.
3. IQ decline could not be explained by alcohol or other drug use or by reduced years of education among persistent cannabis users.
4. IQ decline could also not be explained by low childhood socioeconomic status or poor childhood self-regulation.[15]
5. Third-party informants (e.g., friends, relatives) reported noticing more attention and memory problems in everyday life among persistent cannabis users (e.g, losing focus when they should be paying attention, forgetting to do errands, return calls, pay bills).

Why are these findings important? *The importance of "before and after" IQ testing.* Previous studies have suggested that adolescents may be particularly vulnerable to the effects of cannabis on cognitive functioning.[8-10,16-18] However, until our study, research had not been able to rule out the possibility that poorer cognitive test performance among adolescent-onset cannabis users predates cannabis use initiation. We showed that regardless of their initial (pre-cannabis) test performance, adolescent-onset persistent cannabis users performed worse than non-users and adult-onset cannabis users on cognitive tests in adulthood.

What is the size of the IQ decline? The extent of IQ decline among adolescent-onset persistent cannabis users (8 IQ points) is non-trivial. For example, an average person has an IQ of 100, placing them in the 50th percentile for intelligence compared to their same-age peers. If this average person loses 8 IQ points, they drop from the 50th to the 29th percentile for intelligence.

Why is an 8-point decline in IQ significant? Research has shown that IQ is a strong predictor of a person's access to a college education, their lifelong total income, their access to a good job, their performance on the job, and even early death.[19,20] Individuals who lose 8 points may be disadvantaged, relative to their same-age peers, in many important aspects of life. In fact, the adolescent-onset persistent cannabis users from the Dunedin Study experienced downward social mobility. That is, they ended up in occupations that were less prestigious, less skilled, and less well paid than their parents' occupation.[21]

How many people does this affect? Only approximately 2% of the 1,037 individuals born in one year in Dunedin became adolescent-onset persistent cannabis users. Thus, any effect of cannabis on IQ is confined to a relatively small segment of the population. Nonetheless, findings are concerning given that fewer adolescents today believe that regular cannabis use presents a serious health risk.[22]

What should we do? We should direct efforts toward delaying the onset of cannabis use in young people and encourage cessation, particularly for cannabis users who began using in adolescence.

What additional research is needed? Additional research is needed to answer the following questions:

1. *What are the mechanisms underlying cannabis-related IQ decline?*
   One hypothesis is that cannabis use causes brain changes that result in IQ decline. Further, adolescents might be particularly vulnerable to the effects of cannabis because

cannabis use might disrupt critical neuromaturational processes (e.g., synaptic pruning [culling of weak/unused synapses, which might result in more efficient information processing] and white matter development [which is important for efficient brain signaling]) that occur during adolescence.[13,18] Our 2012 study on cannabis and IQ lacked brain imaging data, and so we could not test this hypothesis. Findings from extant brain imaging studies of cannabis users and comparison individuals have been somewhat inconsistent,[23] but functional imaging studies have found evidence of altered brain activity in cannabis users in at least some brain regions,[23,24] and structural imaging studies have consistently found that cannabis users have lower hippocampal volume.[23,25,26] The consistent finding of lower hippocampal volume among cannabis users is interesting because the hippocampus has a high density of cannabinoid receptors and is involved in learning and memory. Nonetheless, most brain imaging studies lack data from before cannabis initiation, leaving open the possibility that differences between cannabis users and non-users in terms of brain structure or function reflect pre-existing differences. Overall, there is a clear need for large-scale longitudinal studies to follow youth from before to well after cannabis initiation and to combine cognitive testing with brain imaging. The Adolescent Brain and Cognitive Development Study (ABCD Study) was launched, in part, to meet this need.

Although adolescence is receiving attention as a developmental period of heightened vulnerability to cannabis effects, there are likely other sensitive periods in development. For example, cannabis exposure during prenatal development is receiving increased attention, and evidence suggests that the children of mothers who used cannabis during pregnancy show poorer cognitive functioning.[27] Another example is that cannabis use in older adulthood might be associated with serious cognitive consequences. With continued follow-up of the Dunedin Study cohort, who are now age 45, our team can answer new questions about cannabis effects on the aging brain.

2. *What are the parameters of cannabis use that determine the magnitude and persistence of cognitive deficits?*
   Additional work is needed to identify the frequency, quantity, age-of-onset, and duration of cannabis use that is sufficient to produce cognitive deficits. Findings from our 2012 study on cannabis use and IQ suggest that cannabis use that begins before age 18 and continues for many years is associated with IQ decline from childhood to adulthood, but short-term cannabis use in adolescence might not be associated with IQ decline (see above Figure). Several recent longitudinal studies,[28-30] including a study from our group using data from a different cohort,[31] found little evidence of cannabis-related IQ decline in adolescence. Importantly, these studies do not conflict with our 2012 study. Rather, the studies collectively suggest that short-term cannabis use in adolescence might not be associated with IQ decline, but long-term cannabis use from adolescence onward might. A caveat is that the adolescents in these recent longitudinal studies had relatively low levels of cannabis use. For example, adolescents were classified as cannabis users if they had ever used cannabis or if they had used cannabis 50+ times. It is possible that

cannabis-related IQ decline in adolescence might only become apparent after heavier use. Consistent with this, an earlier longitudinal study of youth followed to adolescence found evidence of IQ deficits among heavy adolescent cannabis users (>5 joints per week) but not lighter uses.[32]

One parameter of cannabis use that has received almost no research attention is cannabis potency, which refers to the THC content of cannabis. (THC is the main psychoactive constituent of cannabis.) In our 2012 study on cannabis and IQ, the cannabis users had access to low-potency cannabis -- 3.5% THC.[33] Today's teenagers have access to cannabis with much higher potency. For example, the average THC content of confiscated marijuana (flower) in the US was 12% in 2014,[34] and the average THC content of marijuana sold in US dispensaries is now ~20%.[35,36] In addition, work from my group showed that nearly 1 in 4 adolescents have used cannabis concentrates,[37] which are cannabis plant extracts with unprecedentedly high THC content.[38,39] Cannabis concentrates have estimated average THC content of ~40-70%,[38] but THC content of concentrates can exceed 80%. Because THC has been shown to have dose effects on drug reinforcement (e.g., liking of the drug), cognitive impairment, and psychotic-like experiences,[40-43] there is speculation that use of cannabis with higher THC content might increase risk for addiction, cognitive deficits, psychosis, and other adverse consequences.[41,44-49] However, an alternative hypothesis is that higher THC cannabis might not pose greater risks, because cannabis users might titrate their use (use less cannabis when THC content is high). My recent work showed that cannabis users who used concentrates had higher rates of physiological dependence (symptoms of addiction) on cannabis than cannabis users who did not use concentrates.[50] However, additional research on this topic is needed. Moreover, research is needed to ascertain if cannabidiol (CBD), another constituent of cannabis, might attenuate the negative effects of THC.[51,52]

To summarize, research is needed to understand how cannabis frequency, quantity, duration, age-of-onset, and potency impact cognitive functioning. To do this work, cannabis researchers must work together to develop standardized measures of each of these cannabis parameters.

3. *Does cognitive functioning recover with abstinence?*
In our 2012 study, we found that adolescent-onset persistent cannabis users performed worse in adulthood than in childhood even after they had quit or reduced their use in the year leading up to cognitive testing in adulthood. This suggests that quitting or reducing use might not fully restore functioning among adolescent-onset persistent cannabis users, but longer-term follow-up is needed. In general, the evidence on recovery with abstinence is mixed. Some studies have found evidence of cognitive deficits among cannabis users who were abstinent for approximately a month or more.[53-56] Yet, studies that compared heavy cannabis users with comparison individuals have collectively found little evidence of cognitive deficits among longer-term abstinent cannabis users.[5,6] Carefully designed studies are needed to understand the extent and time course of recovery associated with

quitting cannabis, and to understand if recovery depends on age-of-onset of use, duration of use, or other cannabis use parameters.

4. *Are there individual differences in susceptibility to cannabis-related cognitive deficits?* One intriguing possibility is that some individuals are less likely than others to experience negative effects of cannabis. Research is needed to identify these individuals and to isolate the factors that offer them protection. For example, evidence suggests that some people might be genetically less susceptible than others to experiencing cannabis-related cognitive deficits.[57,58] This could have significant implicants for prevention. Relatedly, research is needed on sex differences in vulnerability to cannabis effects on cognitive function.[40] For example, one recent study found that an earlier age of onset of cannabis use was associated with poorer memory in women but not men.[59]

Appendix

Supporting Details for Meier et al., 2012: *How we measured cannabis use.* We measured cannabis use in two ways: cannabis dependence and regular cannabis use. Persistence of cannabis dependence was defined as the total number of study waves out of five (ages 18, 21, 26, 32, and 38) at which a study member met DSM criteria for cannabis dependence. Study members were grouped according to their number of dependence diagnoses: (a) those who never used cannabis at any study wave and thus could not have become dependent; (b) those who used cannabis at least once at one or more study waves but never diagnosed; (c) those who diagnosed at one wave; (d) those who diagnosed at two waves; and (e) those who diagnosed at three or more waves.

Cannabis dependence is a substance use disorder as defined in the Diagnostic and Statistical Manual of the American Psychiatric Association (known as DSM-IV). The purpose of the DSM-IV diagnosis is to predict a patient's future prognosis, and to identify which patients are most in need of treatment. A diagnosis of cannabis dependence generally reflects an individual's continued use of cannabis despite experiencing significant health, social, and/or legal problems related to cannabis use.

Persistence of regular cannabis use. Because some people use cannabis on a regular basis but never develop problems, we also examined IQ decline as a function of persistent regular cannabis use. This was defined as the total number of study waves out of five at which a study member reported using cannabis four or more days per week (the majority of days in a week). Study members were grouped as those who: (a) never used cannabis; (b) used but never regularly; (c) used regularly at one wave; (d) used regularly at two waves; and (e) used regularly at three or more waves.

Results were similar for persistent cannabis dependence and persistent regular cannabis use.

How we defined adolescent-onset cannabis use. We defined adolescent-onset cannabis in two ways: 1) cannabis dependence before age 18 or 2) weekly cannabis use before age 18. Results were similar across both definitions.

How we measured IQ. We assessed intelligence in childhood (ages 7, 9, 11, and 13) and again in adulthood at age 38 using standard tests for the field.

How we measured everyday life cognitive functioning. Study members nominated people "who knew them well." These informants were mailed questionnaires and asked to complete a checklist, including whether the study member had problems with their attention (e.g., "can't concentrate, mind wanders) and memory (e.g., forgets to do errands, return calls, pay bills) over the past year at age 38.

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