Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meiera,b,1, Avshalom Caspia,b,c,d,e, Antony Amblera,1, Honalee Harringtonb,c,d, Renate Houtsb,c,d, Richard S. E. Keefef, Kay McDonald1, Aimee Ward1, Richie Poulton1, and Terrie E. Moffitto,b,c,d,e

aDuke Transdisciplinary Prevention Research Center, Center for Child and Family Policy, bDepartment of Psychology and Neuroscience, and cInstitute for Genome Sciences and Policy, Duke University, Durham, NC 27708; dDepartment of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710; *Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King’s College London, London SE5 8AF, United Kingdom; and bDunedin Multidisciplinary Health and Development Research Unit, Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin 9054, New Zealand

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Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants were members of the Dunedin Study, a prospective study of a birth cohort of 1,037 individuals followed from birth (1972/1973) to age 38 y. Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38 y. Neuropsychological testing was conducted at age 13 y, before initiation of cannabis use, and again at age 38 y, after a pattern of persistent cannabis use had developed. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. Informants also reported noticing more cognitive problems for persistent cannabis users. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users. Findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents.

marijuana | longitudinal | cognition

Cannabis, the most widely used illicit drug in the world, is increasingly being recognized for both its toxic and its therapeutic properties (1). Research on the harmful and beneficial effects of cannabis use is important because it can inform decisions regarding the medicinal use and legalization of cannabis, and the results of these decisions will have major public-health consequences. As debate surrounding these issues continues in the United States and abroad, new findings concerning the harmful effects of cannabis on neuropsychological functioning are emerging.

Accumulating evidence suggests that long-term, heavy cannabis use may cause enduring neuropsychological impairment—impairment that persists beyond the period of acute intoxication (2). Studies of long-term, heavy cannabis users fairly consistently show that these individuals perform worse on neuropsychological tests (2–5), and some (6–8) but not all (9) studies suggest that impairment may remain even after extended periods of abstinence. The magnitude and persistence of impairment may depend on factors such as the quantity, frequency, duration, and age-of-onset of cannabis use (2), as more severe and enduring impairment is evident among individuals with more frequent and prolonged heavy use and a younger age-of-onset (3, 6, 8, 10–16).

The extant evidence base draws on case–control studies of recruited cannabis users and comparison subjects. These studies screen participants for potential confounding factors, such as alcohol and drug dependence, and compare them on neuropsychological test performance after a period of abstinence from cannabis. There are two commonly cited potential limitations of this approach. One is the absence of data on initial, preabstinence-use neuropsychological functioning. It is possible that differences in test performance between cannabis users and controls are attributable to premorbid rather than cannabis-induced deficits (17–20). A second limitation is reliance on retrospectively reported quantity, frequency, duration, and age-of-onset of cannabis use, often inquired about years after initiation of heavy use.

A prospective, longitudinal investigation of the association between cannabis use and neuropsychological impairment could redress these limitations and strengthen the existing evidence base by assessing neuropsychological functioning in a sample of youngsters before the onset of cannabis use, obtaining prospective data on cannabis use as the sample is followed over a number of years, and readministering neuropsychological tests after some members of the sample have developed a pattern of long-term cannabis use. To our knowledge, only one prospective, longitudinal study of the effects of cannabis on neuropsychological functioning has been conducted (21), and, in this study, the sample was small and the average duration of regular cannabis use was only 2 y.

In the present study, we investigated the association between persistent cannabis use—prospectively assessed over 20 y—and neuropsychological functioning in a birth cohort of 1,037 individuals. Study members underwent neuropsychological testing in 1985 and 1986 before the onset of cannabis use and again in 2010–2012, after some had developed a persistent pattern of cannabis use. We tested six hypotheses. First, we tested the “cognitive decline” hypothesis that persistent cannabis users evidence greater decline in test performance from childhood to adulthood than nonusers. By examining within-person change in neuropsychological functioning, any effect of premorbid deficits on later (postcannabis-initiation) test performance was nullified. Second, we tested the “specificity” hypothesis to address whether impairment is confined to specific neuropsychological domains or whether it is more global. To test this hypothesis, we administered multiple tests for each of five specific domains, as different tests may be differentially sensitive to cannabis-associated neuropsychological impairment. In conducting our analyses, we tested alternative explanations for the association between per-
sistent cannabis use and neuropsychological functioning by ruling out potential confounding effects of (i) acute or residual can-
babis intoxication, (ii) tobacco dependence, (iii) hard-drug de-
pendence (e.g., heroin, cocaine, amphetamines), (iv) alcohol de-
pendence, and (v) schizophrenia. Third, we tested the “edu-
ca tion” hypothesis that persistent cannabis users experience neuropsychological decline simply because they have eschewed
academics and other opportunities for learning. Recent evidence
suggests that staying in school can boost one’s intelligence quo-
tient (IQ) (22), and cannabis users tend to receive less schooling
than nonusers (23). Therefore, we tested whether the association
between persistent cannabis use and neuropsychological decline
remained after controlling for years of education. Fourth, we
queried third-party informants to test the “everyday cognition”
hypothesis that cannabis-induced neuropsychological impair-
ment translates into functional problems in daily life. Fifth, we
tested the “developmental vulnerability” hypothesis that indi-
viduals who begin cannabis use as adolescents are particularly
vulnerable to the effects of persistent cannabis use on neuro-
psychological functioning, as evidence suggests that cannabis has
e especially toxic effects on the developing brain (24–31). Sixth, we
tested the “recovery” hypothesis that former persistent users who
quit or reduce their cannabis use may be able to restore their
neuropsychological health.

Results

Do Study Members with More Persistent Cannabis Use Show Greater IQ Decline? Table 1 (far right column) shows effect sizes for within-
person IQ change from childhood to adulthood as a function of
persistent cannabis dependence. In this analysis, each study
member served as his or her own control; given that the groups
were not equivalent on childhood IQ, we accounted for premorbid
IQ differences by looking at IQ change from childhood to age 38 y.
Study members with more persistent cannabis dependence
showed greater IQ decline. For example, study members who
never used cannabis experienced a slight increase in IQ, whereas
those who diagnosed with cannabis dependence at one, two, or
three or more study waves experienced IQ declines of −0.11,
−0.17, and −0.38 SD units, respectively. An IQ decline of −0.38 SD
units corresponds to a loss of ~6 IQ points, from 99.68 to 93.93.
Results of analyses for persistent cannabis dependence and per-
sonal regular cannabis use were similar (Table 1). Table 2 expands the analysis by showing results for the sub-
tests of different cognitive abilities that constitute the IQ. Per-
sistent cannabis dependence was associated with greater decline
on the majority of the subtests.

IQ decline was most pronounced among the most persistent
cannabis-dependence group (i.e., the 3+ group; n = 38), but the
effect of persistent cannabis dependence on IQ decline was not
solely attributable to this group. For example, the association
between persistent cannabis dependence and full-scale IQ de-
cline was still apparent after excluding the study members with
3+ cannabis-dependence diagnoses from the analysis (t = −2.94,
P = 0.0034). Table S1 shows parallel results for persistent reg-
ular cannabis use and persistent cannabis dependence.

Is Impairment Specific to Certain Neuropsychological Domains or Is It
Global? Table 3 shows the effects of persistent cannabis de-
pendence on five different areas of mental function assessed at
age 38 y. Effects represent mean neuropsychological test per-
formance at age 38 y, adjusted for childhood IQ. Across
different areas of mental function, study members with more
persistent cannabis dependence generally showed greater
neuropsychological impairment. Inspection of the means sug-
gests that the greatest impairments were for the domains of
executive functioning and processing speed. To test whether
impairment was relatively greater for certain domains, we
compared cannabis-associated neuropsychological impairment
across the four Wechsler Adult Intelligence Scale-IV (WAIS-
IV) indexes (i.e., working memory index, processing speed in-
dex, perceptual reasoning index, and verbal comprehension
index), which share psychometric properties (i.e., reliability)
important for such a test. Using a model-fitting approach, we
fitted (i) a model allowing the association between persistent
cannabis dependence and age-38 neuropsychological impair-
ment, adjusted for childhood IQ and sex, to vary across the four
WAIS-IV indexes and (ii) a model equating this association
across the four WAIS-IV indexes. Results showed that associ-
ations between persistent cannabis dependence and all four
WAIS-IV indexes could be equated without a resultant de-
terioration in model fit (Δχ2 = 2.13, df = 3, P = 0.55), which
suggests that impairment was not statistically significantly dif-
ferent across neuropsychological domains.

Is Impairment Attributable to Persistent Cannabis Use or Are There
Alternative Explanations? We ruled out six alternative explana-
tions for the observed effects of persistent cannabis use on
neuropsychological functioning, namely that these effects could
be explained by (i) past 24-h cannabis use, (ii) past-week can-
nabis use, (iii) persistent tobacco dependence, (iv) persistent
hard-drug dependence, (v) persistent alcohol dependence, and
(vi) schizophrenia. We recalculated the mean change in full-

<table>
<thead>
<tr>
<th>Persistence of cannabis dependence</th>
<th>N</th>
<th>% male</th>
<th>Age 7–13 full-scale IQ</th>
<th>Age 38 full-scale IQ</th>
<th>Δ IQ effect size*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never used, never diagnosed</td>
<td>242</td>
<td>38.84</td>
<td>99.84 (14.39)</td>
<td>100.64 (15.25)</td>
<td>0.05</td>
</tr>
<tr>
<td>Used, never diagnosed</td>
<td>479</td>
<td>49.48</td>
<td>102.32 (13.34)</td>
<td>101.25 (14.70)</td>
<td>−0.07</td>
</tr>
<tr>
<td>1 diagnosis</td>
<td>80</td>
<td>70.00</td>
<td>96.40 (14.31)</td>
<td>94.78 (14.54)</td>
<td>−0.11</td>
</tr>
<tr>
<td>2 diagnoses</td>
<td>35</td>
<td>62.86</td>
<td>102.14 (17.08)</td>
<td>99.67 (16.11)</td>
<td>−0.17</td>
</tr>
<tr>
<td>3+ diagnoses</td>
<td>38</td>
<td>81.58</td>
<td>99.68 (13.53)</td>
<td>93.93 (13.32)</td>
<td>−0.38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Persistence of regular cannabis use</th>
<th>N</th>
<th>% male</th>
<th>Age 7–13 full-scale IQ</th>
<th>Age 38 full-scale IQ</th>
<th>Δ IQ effect size*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never used</td>
<td>242</td>
<td>38.84</td>
<td>99.84 (14.39)</td>
<td>100.64 (15.25)</td>
<td>0.05</td>
</tr>
<tr>
<td>Used, never regularly</td>
<td>508</td>
<td>50.59</td>
<td>102.27 (13.59)</td>
<td>101.24 (14.81)</td>
<td>−0.07</td>
</tr>
<tr>
<td>Used regularly at 1 wave</td>
<td>47</td>
<td>72.34</td>
<td>101.42 (14.41)</td>
<td>98.45 (14.89)</td>
<td>−0.20</td>
</tr>
<tr>
<td>Used regularly at 2 waves</td>
<td>36</td>
<td>63.89</td>
<td>95.28 (10.74)</td>
<td>93.26 (11.44)</td>
<td>−0.13</td>
</tr>
<tr>
<td>Used regularly at 3+ waves</td>
<td>41</td>
<td>78.05</td>
<td>96.00 (16.06)</td>
<td>90.77 (13.88)</td>
<td>−0.35</td>
</tr>
</tbody>
</table>

Means (SDs) are presented for child and adult full-scale IQ as a function of the number of study waves between ages 18 y and 38 y for
which study members met criteria for cannabis dependence or reported using cannabis on a regular basis (at least 4 d/wk). The last
column shows that study members with more persistent cannabis use showed greater IQ decline from childhood to adulthood.

This coefficient indicates change in IQ from childhood to adulthood, with negative values indicating decreases in IQ. These change
scores are in SD units, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large changes, respectively.
scale IQ as a function of persistent cannabis dependence, excluding each of the aforementioned groups. We elected to show results just for full-scale IQ for this analysis as well as all subsequent analyses because full-scale IQ captures overall intellectual functioning. Fig. 1 shows that excluding each of these groups of study members did not alter the initial finding; effect

### Table 2. IQ subtest changes

<table>
<thead>
<tr>
<th>IQ test/subtest</th>
<th>Never used, never diagnosed, n = 242</th>
<th>Used, never diagnosed, n = 479</th>
<th>1 diagnosis, n = 80</th>
<th>2 diagnoses, n = 35</th>
<th>3+ diagnoses, n = 38</th>
<th>Linear trend</th>
<th>t test*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-scale IQ</td>
<td>0.05</td>
<td>−0.07</td>
<td>−0.11</td>
<td>−0.17</td>
<td>−0.38</td>
<td>−4.45</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>0.02</td>
<td>−0.05</td>
<td>−0.13</td>
<td>−0.19</td>
<td>−0.31</td>
<td>−4.15</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Information subtest</td>
<td>0.05</td>
<td>−0.08</td>
<td>0.02</td>
<td>−0.25</td>
<td>−0.15</td>
<td>−2.40</td>
<td>0.0168</td>
<td></td>
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<tr>
<td>Similarities subtest</td>
<td>0.03</td>
<td>−0.05</td>
<td>−0.03</td>
<td>−0.19</td>
<td>−0.44</td>
<td>−2.78</td>
<td>0.0056</td>
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<tr>
<td>Vocabulary subtest</td>
<td>0.07</td>
<td>−0.05</td>
<td>−0.16</td>
<td>−0.16</td>
<td>−0.45</td>
<td>−3.67</td>
<td>0.0033</td>
<td></td>
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<tr>
<td>Arithmetic subtest</td>
<td>−0.05</td>
<td>−0.07</td>
<td>−0.05</td>
<td>0.00</td>
<td>0.06</td>
<td>−0.73</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Performance IQ</td>
<td>0.08</td>
<td>−0.08</td>
<td>−0.09</td>
<td>−0.08</td>
<td>−0.42</td>
<td>−2.84</td>
<td>0.0046</td>
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<tr>
<td>Digit symbol coding subtest</td>
<td>0.15</td>
<td>−0.09</td>
<td>−0.17</td>
<td>−0.23</td>
<td>−0.62</td>
<td>−5.60</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Block design subtest</td>
<td>−0.03</td>
<td>−0.07</td>
<td>−0.01</td>
<td>−0.11</td>
<td>0.02</td>
<td>−0.55</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Picture completion subtest</td>
<td>−0.01</td>
<td>−0.08</td>
<td>0.08</td>
<td>0.05</td>
<td>0.15</td>
<td>1.18</td>
<td>0.24</td>
<td></td>
</tr>
</tbody>
</table>

Mean change in IQ subtest scores from childhood to adulthood is presented in SD units as a function of the number of study waves between ages 18 y and 38 y for which a study member met criteria for cannabis dependence. These change scores can be interpreted as effect sizes, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large effects, respectively. Persistent cannabis dependence was associated with IQ decline for the majority of IQ subtest

### Table 3. Five areas of mental function

<table>
<thead>
<tr>
<th>Age 38 y neuropsychological tests</th>
<th>Never used, never diagnosed, n = 242</th>
<th>Used, never diagnosed, n = 479</th>
<th>1 diagnosis, n = 80</th>
<th>2 diagnoses, n = 35</th>
<th>3+ diagnoses, n = 38</th>
<th>Linear trend</th>
<th>t test*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS-IV Working Memory Index</td>
<td>0.01</td>
<td>0.03</td>
<td>−0.16</td>
<td>−0.03</td>
<td>−0.16</td>
<td>−2.16</td>
<td>0.0311</td>
<td></td>
</tr>
<tr>
<td>Wechsler Memory Scale Months of the Year Backward</td>
<td>0.24</td>
<td>0.01</td>
<td>−0.38</td>
<td>−0.23</td>
<td>−0.63</td>
<td>−5.24</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Trail-Making Test B Time†</td>
<td>−0.04</td>
<td>−0.03</td>
<td>0.16</td>
<td>0.08</td>
<td>0.19</td>
<td>1.15</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>CANTAB Rapid Visual Information</td>
<td>0.05</td>
<td>0.01</td>
<td>−0.02</td>
<td>−0.04</td>
<td>−0.45</td>
<td>−2.58</td>
<td>0.0100</td>
<td></td>
</tr>
<tr>
<td>Processing A Prime (Vigilance)</td>
<td>−0.02</td>
<td>0.01</td>
<td>0.06</td>
<td>0.04</td>
<td>−0.14</td>
<td>−0.05</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>CANTAB Rapid Visual Information</td>
<td>−0.02</td>
<td>0.01</td>
<td>0.06</td>
<td>0.04</td>
<td>−0.14</td>
<td>−0.05</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Processing Total False Alarms†</td>
<td>−0.02</td>
<td>0.01</td>
<td>0.06</td>
<td>0.04</td>
<td>−0.14</td>
<td>−0.05</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Total Recall</td>
<td>0.11</td>
<td>0.06</td>
<td>−0.26</td>
<td>−0.22</td>
<td>−0.48</td>
<td>−2.65</td>
<td>0.0081</td>
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<tr>
<td>Rey Auditory Verbal Learning Delayed Recall</td>
<td>0.14</td>
<td>0.02</td>
<td>−0.22</td>
<td>−0.28</td>
<td>−0.31</td>
<td>−2.11</td>
<td>0.0348</td>
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<tr>
<td>Wechsler Memory Scale Verbal Paired Associates Total Recall</td>
<td>0.07</td>
<td>0.06</td>
<td>−0.21</td>
<td>−0.21</td>
<td>−0.12</td>
<td>−1.48</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Wechsler Memory Scale Verbal Paired Associates Delayed Recall</td>
<td>0.07</td>
<td>0.06</td>
<td>−0.19</td>
<td>−0.15</td>
<td>−0.14</td>
<td>−1.07</td>
<td>0.29</td>
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</tr>
<tr>
<td>CANTAB Visual Paired Associates Learning First Trial Memory Score</td>
<td>0.09</td>
<td>0.01</td>
<td>−0.06</td>
<td>−0.36</td>
<td>−0.10</td>
<td>−2.22</td>
<td>0.0270</td>
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<tr>
<td>CANTAB Visual Paired Associates Learning Total Errors†</td>
<td>−0.07</td>
<td>−0.03</td>
<td>0.17</td>
<td>0.33</td>
<td>−0.06</td>
<td>1.41</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Tests of processing speed</td>
<td>WAIS-IV Processing Speed Index</td>
<td>0.14</td>
<td>0.03</td>
<td>−0.21</td>
<td>−0.05</td>
<td>−0.61</td>
<td>−3.64</td>
<td>0.0003</td>
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<tr>
<td>CANTAB Rapid Visual Information</td>
<td>−0.13</td>
<td>0.04</td>
<td>0.06</td>
<td>−0.20</td>
<td>0.25</td>
<td>1.92</td>
<td>0.06</td>
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<tr>
<td>Processing Mean Latency†</td>
<td>0.19</td>
<td>−0.11</td>
<td>−0.13</td>
<td>−0.01</td>
<td>0.18</td>
<td>−0.38</td>
<td>0.71</td>
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</tr>
<tr>
<td>CANTAB Reaction Time 5-Choice Reaction Time†</td>
<td>0.19</td>
<td>−0.11</td>
<td>−0.13</td>
<td>−0.01</td>
<td>0.18</td>
<td>−0.38</td>
<td>0.71</td>
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<tr>
<td>Tests of perceptual reasoning</td>
<td>WAIS-IV Perceptual Reasoning Index</td>
<td>0.08</td>
<td>−0.02</td>
<td>0.07</td>
<td>−0.18</td>
<td>−0.12</td>
<td>−2.33</td>
<td>0.0202</td>
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<tr>
<td>Tests of verbal comprehension</td>
<td>WAIS-IV Verbal Comprehension Index</td>
<td>0.10</td>
<td>−0.01</td>
<td>−0.03</td>
<td>0.02</td>
<td>−0.23</td>
<td>−3.04</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

Neuropsychological test scores at age 38 y are shown as a function of the number of study waves between ages 18 y and 38 y for which study members met criteria for cannabis dependence. Scores are standardized means adjusted for baseline (childhood) full-scale IQ assessed before the onset of cannabis use. These means can be interpreted as effect sizes, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large effects, respectively. Persistent cannabis dependence was associated with impairment in each of the five areas of mental function. CANTAB, Cambridge Neuropsychological Test Automated Battery; WAIS-IV, Wechsler Adult Intelligence Scale-IV.

*To test for a dose-response effect, we conducted an ordinary least-squares regression, estimating the linear trend controlling for childhood full-scale IQ and sex.

†Higher score indicates worse performance.
sizes, representing within-person IQ change as a function of persistent cannabis dependence, remained virtually the same and remained statistically significant (see Table S2 for IQ subtests).

Furthermore, a multivariate regression of the effect of persistent cannabis dependence on full-scale IQ decline, controlling for past 24-h cannabis use, persistent substance dependence (the number of study waves for which study members diagnosed with tobacco, hard-drug, or alcohol dependence), and schizophrenia remained statistically significant ($t = -2.20, P = 0.0282$).

Is Impairment Apparent Even After Controlling for Years of Education?
The linear effect of persistent cannabis dependence on change in full-scale IQ was significant before controlling for years of education ($t = -4.45, P < 0.0001$; Table 2, top row) and remained

Mean change in full-scale IQ from childhood to adulthood is presented in SD units as a function of the number of study waves between ages 18 y and 38 y for which a study member met criteria for cannabis dependence. Change scores can be interpreted as effect sizes, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large effects, respectively. Change scores are presented for the full sample and for the sample of study members with a high-school education or less. Persistent cannabis dependence was associated with IQ decline in the full sample and the sample of study members with a high-school education or less.

To test for a dose–response effect, we conducted an ordinary least-squares regression, estimating the linear trend controlling for sex.

### Table 4. IQ decline after holding education constant

<table>
<thead>
<tr>
<th>Sample</th>
<th>Never used, never diagnosed</th>
<th>Used, never diagnosed</th>
<th>1 diagnosis</th>
<th>2 diagnoses</th>
<th>3+ diagnoses</th>
<th>Linear trend $t$ test*</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full sample</td>
<td>0.05 ($n = 242$)</td>
<td>-0.07 ($n = 479$)</td>
<td>-0.11 ($n = 80$)</td>
<td>-0.17 ($n = 35$)</td>
<td>-0.38 ($n = 38$)</td>
<td>-4.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High-school education or less</td>
<td>-0.03 ($n = 59$)</td>
<td>-0.14 ($n = 130$)</td>
<td>-0.16 ($n = 43$)</td>
<td>-0.25 ($n = 20$)</td>
<td>-0.48 ($n = 26$)</td>
<td>-3.36</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

*To test for a dose–response effect, we conducted an ordinary least-squares regression, estimating the linear trend controlling for sex.
significant after controlling for years of education (t = −3.41, P = 0.0007). Moreover, although fewer persistent cannabis users pursued education after high school (χ² = 63.94, P < 0.0001), among the subset with a high-school education or less, persistent cannabis users experienced greater IQ decline (Table 4).

**Does Cannabis-Associated Neuropsychological Impairment Translate into Functional Problems in Daily Life?** Informant reports of study members’ neuropsychological functioning were also obtained at age 38 y. Study members nominated people “who knew them well.” These informants were mailed questionnaires and asked to complete a checklist, including whether the study members had problems with their attention and memory over the past year. Table 5 shows mean informant-reported cognitive problems, adjusted for childhood IQ, as a function of persistent cannabis dependence. Informants reported observing significantly more attention and memory problems among those with more persistent cannabis dependence.

**Are Adolescent Cannabis Users Particularly Vulnerable?** Adolescent-onset users, who diagnosed with cannabis dependence before age 18 y, tended to become more persistent users, but Fig. 2 shows that, after equating adolescent- and adult-onset cannabis users on total number of cannabis-dependence diagnoses, adolescent-onset users showed greater IQ decline than adult-onset cannabis users. In fact, adult-onset cannabis users did not appear to experience IQ decline as a function of persistent cannabis use. Because it might be difficult to develop cannabis dependence before age 18 y, we also defined adolescent-onset cannabis use in terms of weekly use before age 18 y [the correspondence between cannabis dependence before age 18 y and weekly use before age 18 y was not perfect (κ = 0.64)]. Results of this analysis (Fig. S1) were similar.

**What Is the Effect of Cessation of Cannabis Use?** Given that adolescent-onset cannabis users exhibited marked IQ decline and given speculation that this could represent a toxic effect of cannabis on the developing brain, we examined the cessation effect separately within adolescent-onset and adult-onset cannabis users. Fig. 3 shows that, among adolescent-onset persistent cannabis users, within-person IQ decline was apparent regardless of whether cannabis was used infrequently (median use = 14 d) or frequently (median use = 365 d) in the year before testing. In contrast, within-person IQ decline was not apparent among adult-onset persistent cannabis users who used cannabis infrequently (median use = 6 d) or frequently (median use = 365 d) in the year before testing. Thus, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset former persistent cannabis users.

**Discussion** Persistent cannabis use over 20 y was associated with neuropsychological decline, and greater decline was evident for more persistent users. This effect was concentrated among adolescent-onset cannabis users, a finding consistent with results of several studies showing executive functioning or verbal IQ deficits among adolescent-onset but not adult-onset chronic cannabis users (8, 10, 14, 15), as well as studies showing impairment of learning, memory, and executive functions in samples of adolescent cannabis users (11–13, 32).

The present study advances knowledge in five ways. First, by investigating the association between persistent cannabis use and neuropsychological functioning prospectively, we ruled out premorbid neuropsychological deficit as an explanation of the link between persistent cannabis use and neuropsychological impairment occurring after persistent use. Second, we showed that the impairment was global and detectable across five domains of neuropsychological functioning. Third, we showed that cannabis-associated neuropsychological decline did not occur solely because cannabis users completed fewer years of education. Fourth, we showed that impairment was apparent to third-party informants and that persistent cannabis use interfered with everyday cognitive functioning. Fifth, we showed that, among adolescent-onset former persistent cannabis users, impairment was still evident after cessation of use for 1 y or more. Collectively, these findings are consistent with speculation that cannabis use in adolescence, when the brain is undergoing critical development, may have neurotoxic effects.

The study’s results must be interpreted in the context of its limitations. First, although we were able to rule out a set of plausible alternative explanations for the association between persistent cannabis use and neuropsychological functioning, such as premorbid neuropsychological deficit and hard-drug and alcohol dependence among persistent cannabis users, our data cannot definitively attest to whether this association is causal. For example, there may be some unknown “third” variable that could account for the findings. The data also cannot reveal the mechanism underlying the association between persistent cannabis dependence and neuropsychological decline. One hypothesis is that cannabis use in adolescence causes brain changes that result in neuropsychological impairment. Several lines of evidence support this possibility (24–31, 33, 34). First, puberty is a period of critical brain development, characterized by neuronal maturation and rearrangement processes (e.g., myelination, synaptic pruning, dendritic plasticity) and the maturation of neurotransmitter systems (e.g., the endogenous cannabinoid system), making the pubertal brain vulnerable to toxic insult (33). Second, cannabis administration in animals is associated with structural and functional brain differences, particularly in hippocampal regions, with structural differences dependent on age and duration of exposure to cannabinoids (33). Third, studies of human adolescents have shown structural and functional brain differences associated with cannabis use (26, 29, 35).

Alternatively, persistent cannabis users may experience greater neuropsychological decline relative to nonusers because they receive less education. Our results suggest that cannabis-associated neuropsychological decline in childhood and adolescence may be associated with lower education, highlighting the need for continued research on the long-term effects of cannabis use on cognition.

**Table 5. Cognitive problems outside the laboratory**

<table>
<thead>
<tr>
<th>Age 38 y informant reports</th>
<th>Never used, never diagnosed, n = 228</th>
<th>Used, never diagnosed, n = 457</th>
<th>1 diagnosis, n = 71</th>
<th>2 diagnoses, n = 31</th>
<th>3+ diagnoses, n = 35</th>
<th>Linear trend</th>
<th>t test*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informant-reported attention problems</td>
<td>−0.21</td>
<td>−0.07</td>
<td>0.31</td>
<td>0.64</td>
<td>0.96</td>
<td>7.74</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Informant-reported memory problems</td>
<td>−0.27</td>
<td>−0.03</td>
<td>0.38</td>
<td>0.78</td>
<td>0.75</td>
<td>7.65</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Shown are informant reports of cognitive problems at age 38 y as a function of the number of study waves between ages 18 y and 38 y for which study members met criteria for cannabis dependence. Scores are standardized means adjusted for baseline (childhood) full-scale IQ assessed before the onset of cannabis use. These means can be interpreted as effect sizes, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large effects, respectively. Cognitive problems among persistent cannabis users were apparent to the “naked-eye.”

*To test for a dose-response effect, we conducted an ordinary least-squares regression, estimating the linear trend controlling for childhood full-scale IQ and sex.

Higher score indicates worse everyday problems.
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.

Fig. 2. 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.
Meier et al. | PNAS Early Edition | 7 of 8

Adolescent-Onset (Used Cannabis Weekly Before Age 18)

![Graph showing Full-Scale IQ for Inpatient and Adult IQ for each group.

Adolescent-Onset (Did Not Use Cannabis Weekly Before Age 18)

![Graph showing Full-Scale IQ for Inpatient and Adult IQ for each group.

Fig. 3. Postcessation IQ among former persistent cannabis users. This figure is restricted to persistent cannabis users, defined as study members with two or more diagnoses of cannabis dependence. Shown is full-scale IQ in childhood and adulthood. IQ is plotted as a function of (i) age of onset of at least weekly cannabis use and (ii) the frequency of cannabis use at age 38 y. Infrequent use was defined as weekly or less frequent use in the year preceding testing at age 38 y. Median use among infrequent and frequent adolescent-onset cannabis users was 14 (range: 0–52) and 365 (range: 100–365) d, respectively. Median use among infrequent and frequent adult-onset cannabis users was 6 (range: 0–52) and 365 (range: 100–365) d, respectively. IQ decline was apparent even after cessation of cannabis use for adolescent-onset former persistent cannabis users. Error bars = SEs.

2010–2012. The Otago Ethics Committee approved each wave of the study. Study members gave informed consent before participating.

Because individuals with missing data at one wave tend to return to the study at some later wave(s), the attrition in the Dunedin Study has not been cumulative, and reasons for missing assessments seem to be idiosyncratic rather than systematic. There was no evidence of differential attrition for cannabis-dependent individuals. For example, the 4% of study members who did not participate at age 38 y were no more likely to have been cannabis dependent at age 18 y than study members who did participate (F = 2.22, P = 0.14).

Measures. Cannabis use. Past-year cannabis dependence was assessed with the Diagnostic Interview Schedule (43, 44) at ages 18, 21, 26, 32, and 38 y following criteria for the Diagnostic and Statistical Manual of Mental Disorders (DSM) (45, 46). Cohort members having missing data from three or more of the five study waves (ages 18, 21, 26, 32, and 38 y) were excluded when we defined our cannabis-exposure variables: 97% of living cohort members were studied, composed of 83% of living study members with no missing data points, 11% with one missing data point, and 3% with two missing data points. Our main exposure, persistence of cannabis dependence, was defined as the total number of study waves out of five at which a study member met criteria for cannabis dependence. Study members were grouped according to their number of dependence diagnoses: (i) those who never used cannabis at any study wave and thus could not have developed dependency, (ii) those who used cannabis at least once at one or more study waves but never diagnosed, (iii) those who diagnosed at one wave, (iv) those who diagnosed at two waves, and (v) those who diagnosed at three or more waves.

Because there were some study members who used cannabis on a regular basis but never met full criteria for a diagnosis of cannabis dependence, we repeated analyses using persistent regular cannabis use as the exposure. At each of the five study waves between ages 18–38 y, study members self-reported the total number of days (0–365) they used cannabis over the preceding year. Persistence of regular cannabis use was defined as the total number of study waves out of five at which a study member reported using cannabis 4 d/wk or more (the majority of days in a week). Study members were grouped as those who (i) never used cannabis, (ii) used but never regularly, (iii) used regularly at one wave, (iv) used regularly at two waves, and (v) used regularly at three or more waves. Correspondence between cannabis dependence and regular cannabis-use groups was high but not perfect (weighted κ = 0.77).

The Dunedin Study uses past-year reporting to maximize validity and reliability of recall. A potential consequence is that individuals could have experienced dependence only during a gap between the Study’s five 12-mo assessment windows and gone uncounted. Our “net” of 1-y assessments at ages 18, 21, 26, 32, and 38 y captured all but four of the cohort members who reported receiving treatment for a drug-use problem between assessment windows. Three of the four were hard-drug and alcohol dependent, and the remaining person sought counseling for cannabis use only as part of a child custody dispute. As these four cohort members reported cannabis use but not dependence, they were classified as “used but never diagnosed.”

Neuropsychological functioning. Intelligence was assessed in childhood at ages 7, 9, 11, and 13 y, before the onset of cannabis use (only seven study members reported trying cannabis by age 13 y), and again in adulthood at age 38 y. We report comparison of the Wechsler Intelligence Scale for Children-Revised (WISC-R) (47) and the WAIS-IV (48), both with M = 100 and SD = 15. At age 38 y, additional neuropsychological tests were administered, including the Wechsler Memory Scale-III (WMS-III) (49), the Trail-Making Test (50), the Cambridge Neuropsychological Test Automated Battery (CANTAB) (51), and the Rey Auditory Verbal Learning Test (52). Because the sample is a representative birth cohort, it formed its own norms. Table S3 provides further details about each test. Each study member attended the research unit for an 8-h day of assessments. All testing occurred in the morning in two 50-min counterbalanced sessions.

Informant reports of study members’ neuropsychological functioning were also obtained at age 38 y. Study members nominated people who knew them well. These informants were mailed questionnaires and asked to complete a checklist, including whether the study members had problems with their attention and memory over the past year. The informant-reported attention problems scale consisted of four items: “is easily distracted, gets sidetracked easily,” “can’t concentrate, mind wanders,” “tunes out instead of focusing,” and “has difficulty organizing tasks that have many steps” (internal consistency reliability = 0.79). The informant-reported memory problems scale consisted of three items: “has problems with memory,” “misplaces wallet, keys, eyeglasses, paperwork,” and “forgets to do errands, return calls, pay bills” (internal consistency reliability = 0.64).
Control variables. Past 24-h cannabis use and past-week cannabis use were assessed at age 38 y on the day of neuropsychological testing. Persistent DSM (45, 46) tobacco, hard-drug, and alcohol dependence were assessed over the same 20 y period during which cannabis dependence was assessed, and the number of study waves during which study members diagnosed was counted and used as covariates. For Fig. 1, persistent dependence was defined as having been diagnosed at three or more study waves. Research diagnoses of lifetime schizophrenia (53) are also reported.

Statistical Analysis. First, for the IQ test and subtests (47, 48) administered in both childhood and adulthood, change scores were created by subtracting the precannabis childhood IQ averaged across ages 7, 9, 11 and 13 y (or, for the seven members who reported trying cannabis by age 13 y, ages 7, 9, and 11 y) from postcannabis adulthood IQ. Negative scores indicate IQ decline. Ordinary least-squares linear regression was used to test whether persistent cannabis use (entered as a five-level independent variable, with each study member receiving a score ranging from 1 to 5) predicted amount of IQ change. Second, for the neuropsychological tests administered only in adulthood, ordinary least-squares linear regression was used to test whether persistent cannabis use predicted neuropsychological test performance in adulthood (i.e., rescaled change scores).

Tables 2–5 present the t tests associated with the regression coefficient testing the linear effect of persistent cannabis use on change in neuropsychological functioning, including the hypothesis that more persistent cannabis use predicts greater decline in neuropsychological functioning. Change scores are presented in SD units as a function of persistence of cannabis use. These scores can be interpreted as effect sizes, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large change, respectively (54). Sex was included as a covariate in all statistical tests.

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12. Meier et al.