The purpose of this study was to investigate possible adverse effects of cannabis use on cognitive decline after 12 years in persons under age 65 years. This was a follow-up study of a probability sample of the adult household residents of East Baltimore. The analyses included 1,318 participants in the Baltimore, Maryland, portion of the Epidemiologic Catchment Area study who completed the Mini-Mental State Examination (MMSE) during three study waves in 1981, 1982, and 1993–1996. Individual MMSE score differences between waves 2 and 3 were calculated for each study participant. After 12 years, study participants’ scores declined a mean of 1.20 points on the MMSE (standard deviation 1.90), with 66% having scores that declined by at least one point. Significant numbers of scores declined by three points or more (15% of participants in the 18–29 age group). There were no significant differences in cognitive decline between heavy users, light users, and nonusers of cannabis. There were also no male-female differences in cognitive decline in relation to cannabis use. The authors conclude that over long time periods, in persons under age 65 years, cognitive decline occurs in all age groups. This decline is closely associated with aging and educational level but does not appear to be associated with cannabis use. Am J Epidemiol 1999;149:794–800.
The major correlate of cognitive decline is increasing age (10–14). Higher educational level (14) and higher functioning (13) are associated with less cognitive decline. Being female or encountering stressful life events is not associated with cognitive decline (11, 13). Risk factors for dementia include age, prior cognitive impairment, stroke, high blood pressure, heart disease, diabetes mellitus, alcohol consumption, and depression (15–28). The use of nicotine via smoking has also been associated with a lower risk for dementia, although this finding is controversial (29). Being female has not been associated with the incidence of dementia (15, 17). Two recent studies (30, 31) have reported that lesser educational attainment is a risk factor for dementia. However, this finding has not been supported universally (17, 32, 33).

The relation between cognitive functioning or cognitive decline and use of cannabis (marijuana) has received limited attention in epidemiologic studies. Two cognitive effects of cannabis must be distinguished: acute effects, those associated with intoxication, and residual effects, which persist after the drug has left the central nervous system (34). The latter effects might be short term or long term. Cross-sectional studies, either experimentally administering cannabis or comparing users with nonusers, support the existence of short term residual effects of cannabis use on attention, ability to perform psychomotor tasks, and short term memory (34, 35). These effects are more severe in women (36) and in heavy users of cannabis as compared with light users (37).

To our knowledge, no study with published results has investigated the long term effects of cannabis use on cognition in an epidemiologic sample. According to Pope et al. (34), study designs best suited to addressing this issue are naturalistic comparisons, in large epidemiologic samples, of heavy users, light users, and nonusers of cannabis. These studies must also account for the concurrent use of alcohol and other drugs, both illicit and legal (e.g., nicotine). In addition, such studies must adjust for other factors known to influence cognition over time, such as age and education, and must investigate possible interactions between the cognitive effects of cannabis use and gender (being female).

We recently reported findings from a 13-year follow-up of 1,488 persons of all ages who had participated in the Baltimore, Maryland, portion of the Epidemiologic Catchment Area study (38). The Mini-Mental State Examination (MMSE) (39), a widely used quantitative measure of cognition, was administered to participants during wave I (1981) and during two follow-up waves in 1982 and 1993–1996. The design of the study allowed us to examine cognitive decline between waves 2 and 3 in a large epidemiologic sample. We found that cognitive decline occurred in all age groups. Age, education, and minority status were all significantly associated with greater cognitive decline.

In this follow-up paper, we focus our investigation on persons under age 65 years. To our knowledge, this is the first population study that has investigated cognitive decline in this age group, in which the prevalence of dementia is very low. This permits better study of cognitive decline as a phenomenon distinct from dementia, as well as its associated risk factors. We had two goals: 1) to further delineate the epidemiology of age-specific cognitive decline in persons under 65 and 2) to investigate any long term association between cognitive decline and use of cannabis using a design similar to the one proposed by Pope et al. (34).

**MATERIALS AND METHODS**

**Baltimore Epidemiologic Catchment Area follow-up**

The Epidemiologic Catchment Area program has been described in detail elsewhere (40, 41). The Baltimore arm of this five-site study first entered the field in 1981, when the first wave of in-person assessments was completed. A second wave of assessment (including wave 2 administration of the MMSE) was conducted 1 year later, in 1982. The Baltimore Epidemiologic Catchment Area target population consisted of the adult household residents of eastern Baltimore City, an area with 175,211 inhabitants. During wave 1, 4,238 individuals were designated for interview by probability sampling methods, and 3,481 (82 percent) completed interviews. Of these persons, 2,695 completed interviews during wave 2.

In 1993, all 3,481 initial participants were targeted for tracing and interviewing. A total of 848 participants were found to have died; the remaining 2,633 were presumed to be alive, but 415 of them could not be successfully traced. Of the 2,218 persons located, 298 refused to participate, and 1,920 completed interviews. Of these, 1,488 had completed the MMSE during all three waves, approximately 11.5 years after wave 2. All study participants signed informed consent statements approved by the Institutional Review Board of the Johns Hopkins University School of Hygiene and Public Health.

**Participants**

In these analyses, we included only those participants who were under age 65 at wave 1 and who completed the MMSE during all three study waves (n = 1,318).
Measurement of cognitive decline. For each participant, an MMSE score difference was calculated by subtracting the wave 3 (1993–1996) MMSE score from the wave 2 (1982) MMSE score. The mean time interval between the points at which these MMSEs were administered was 11.6 years (standard error 0.01 years). The median interval was 11.5 years, the 25th percentile was 11.3 years, and the 75th percentile was 11.9 years. Change in MMSE score between waves 2 and 3 was the primary dependent variable in the analyses.

Classification of participants according to use of cannabis. Participants were separated into five groups based on their self-reported drug use during all three waves of the study. Group 1 (nonusers) were those who reported in all three waves that they had never used cannabis in any form (n = 806 (61 percent)). Group 2 (light users) were participants who had used cannabis but had never used it daily or more often for over 2 weeks (n = 235 (18 percent)). Group 3 were light users who reported use of any other illicit substance in any study wave (n = 131 (10 percent)). Group 4 (heavy users) reported during at least one study wave that they had used cannabis daily or more often for over 2 weeks (n = 137 (10 percent)). Group 5 were heavy users of cannabis who reported use of other illicit drugs as well (n = 8 (1 percent)). Information on cannabis use was missing for one participant.

Classification of participants according to use of alcohol or tobacco. On the basis of the highest alcohol intake reported for the past month during any of the three study waves, participants were placed into three groups: never drinkers (n = 67 (5 percent)), light-to-moderate drinkers (n = 778 (59 percent)), and heavy drinkers, defined as those who had had more than four drinks on any one day during the past month (n = 473 (36 percent)). With respect to smoking, three groups were defined on the basis of self-report during any of the three waves: never smokers (n = 347 (26 percent)); occasional smokers (n = 573 (44 percent)); heavy smokers, defined as those who smoked 20–39 cigarettes per day (or the equivalent in cigars or pipefuls of tobacco) (n = 310 (24 percent)); and very heavy smokers, those who smoked two or more packs of cigarettes per day (or the equivalent) (n = 85 (6 percent)). Information on smoking was missing for three participants.

Other variables associated with cognitive decline used as covariates. Information on other variables associated with cognitive decline was recorded at wave 1. Gender was indicated as male or female. Age was grouped as follows: 18–30, 31–40, 41–50, 51–60, and 61–64 years. Minority status was indicated as African-American or Hispanic versus other ethnicity (non-Hispanic white). Five educational subgroups were developed: 0–8 years, 9–11 years, 12 years or General Equivalency Diploma, 13–15 years, and ≥16 years, in conformance with common educational landmarks (grade school, some high school, completed high school or the equivalent, some college, and completed college). It is possible that some study participants, especially those in younger age groups at wave 1, completed their education after wave 1 and were thus misclassified.

Analyses

Mean MMSE score changes between waves 2 and 3 (with 95 percent confidence intervals) are reported in the tables for the entire cohort and for subgroups by age. The proportions of individuals who evidenced any increase, no change, a one-point decline, a two-point decline, a three-point decline, or a four-point or greater decline are also reported by age group. Mean change in MMSE score (with its 95 percent confidence interval) by level of cannabis use was estimated for men and women separately. The relation between level of cannabis use and MMSE score change between waves 2 and 3 was examined in a series of linear regression models with MMSE score change as the dependent variable and cannabis use as the independent variable, with or without inclusion of the other covariates. For both univariate and multiple regression models, the association of cannabis use with change in MMSE score is reported in the form of regression coefficients (with 95 percent confidence intervals). Subgroups were entered into regression models individually as "dummy" variables to allow direct comparisons of regression coefficients using one of the subgroups as the reference category.

To validate the findings from the linear regression models, we also constructed a series of proportional odds logit models (42) relating diseases or substance use to MMSE score change. These were bivariate or multivariate "analogs" to the linear models. The dependent variable was "change in MMSE score," grouped as follows: any increase, no change, a one-point decline, a two-point decline, a three-point decline, or a four-point or greater decline. Findings from these models were similar to those obtained from the linear models. For simplicity, we report only findings from the linear models.

RESULTS

Table 1 provides a description of the study cohort at wave 1 with regard to sociodemographic variables. It also shows mean MMSE scores at each study wave.
Cognitive decline between waves 2 and 3

Table 2 shows the mean change in MMSE score between waves 2 and 3 for every age group. It also shows the proportions of participants in each age group with specific changes in MMSE score, as described above. Persons in all age groups had mean declines greater than zero, with two thirds declining in score by at least one point. The mean decline and the proportion of persons with declining scores increased steadily with age, as expected. It is noteworthy that in every age group there was a notable proportion of participants whose score declined three points or more—a change of magnitude that merits clinical attention (43, 44). These estimated declines must be considered in the context of MMSE measurement error, the MMSE ceiling effect, and normal variation in MMSE scores over time (see Discussion).

Association between cannabis use and score decline

Table 3 displays estimated mean changes in MMSE score according to level of cannabis use for men and women separately. Women who were nonusers of cannabis had scores that declined more than those of men who were nonusers. However, within male-female groups, there were no evident differences in score decline by cannabis use for either men or women.

Table 4 displays results from the linear regression models with MMSE change between waves 2 and 3 used as the dependent variable. The numbers shown in the table are regression coefficients estimating the relative change in MMSE score for a given group of cannabis users relative to nonusers. Model 1 included only cannabis use as the covariate. Model 2 included cannabis use and use of alcohol and tobacco. Model 3 included cannabis use plus age, gender, education, minority status, alcohol use, and tobacco use. Model 4 included cannabis use plus all of the variables from models 2 and 3. Both light and heavy users of cannabis exhibited less cognitive decline than nonusers, although this finding was not statistically significant at...
TABLE 3. Mean change in Mini-Mental State Examination (MMSE) score between wave 2 (1982) and wave 3 (1993–1996) in men and women, by level of cannabis use, Baltimore Epidemiologic Catchment Area study follow-up

<table>
<thead>
<tr>
<th>Gender and level of cannabis use</th>
<th>No.</th>
<th>Mean score change in MMSE</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonusers</td>
<td>251</td>
<td>-1.00</td>
<td>-0.73 to -1.27</td>
</tr>
<tr>
<td>Light users</td>
<td>104</td>
<td>-1.03</td>
<td>-0.67 to -1.39</td>
</tr>
<tr>
<td>Light users plus use of drugs</td>
<td>48</td>
<td>-1.06</td>
<td>-0.57 to -1.55</td>
</tr>
<tr>
<td>Heavy users</td>
<td>82</td>
<td>-0.84</td>
<td>-0.46 to -1.22</td>
</tr>
<tr>
<td>Heavy users plus use of drugs</td>
<td>3</td>
<td>-0.33</td>
<td>+5.93 to -6.59</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonusers</td>
<td>555</td>
<td>-1.46</td>
<td>-1.29 to -1.63</td>
</tr>
<tr>
<td>Light users</td>
<td>131</td>
<td>-1.04</td>
<td>-0.71 to -1.37</td>
</tr>
<tr>
<td>Light users plus use of drugs</td>
<td>83</td>
<td>-1.07</td>
<td>-0.77 to -1.37</td>
</tr>
<tr>
<td>Heavy users</td>
<td>55</td>
<td>-1.15</td>
<td>-0.47 to -1.83</td>
</tr>
<tr>
<td>Heavy users plus use of drugs</td>
<td>5</td>
<td>-0.60</td>
<td>+3.09 to -4.29</td>
</tr>
</tbody>
</table>

* CI, confidence interval.

The conventional level of $p < 0.05$ (model 1). After adjustment for the other variables in models 2–4, there was no association between cannabis use and cognitive decline.

DISCUSSION

Cognitive decline is an age-related phenomenon that affects persons of all ages, including those under age 30 years. It becomes more pronounced with increasing age and is most evident in persons over age 59. A significant proportion (>15 percent) of persons in all population age groups evidence declines that approach clinical significance. We offer two interpretations of this finding. One is that cognitive decline might be an inevitable phenomenon of aging, perhaps modified by genetic makeup, education, nutrition, disease, and environmental exposure. Another is that the declines are the result of slowly progressive neurodegenerative diseases (such as Alzheimer's disease) which might be lifelong in evolution but do not lead to clinical symptoms until much later in life (8). While these two lines of reasoning are not mutually exclusive, the relation between age and cognitive decline across all age groups reported here lends greater support to the former.

To our knowledge, this was the first long term prospective study in the United States that had a community sample large enough to investigate the relation between cannabis use and cognitive decline in persons under age 65 years. Other studies have found short term residual effects of cannabis use on memory and cognition (34, 35) that are more severe among women (36) and heavy users (37). However, our data suggest that over the long term cannabis use is not associated with greater declines in cognition among men, women, or heavy users. The study design we used included several of the features proposed by Pope et al. (34) as critical to addressing the long term effects of cannabis on cognition: naturalistic follow-up, a large sample size, a population basis, comparison of light cannabis use with heavy use, and the construction of models accounting for the effects of gender and use of illicit drugs, alcohol, and tobacco. Therefore, these results would seem to provide strong evidence of the absence of a long term residual effect of cannabis use on cognition.

TABLE 4. Regression coefficients ($\beta$) indicating relative differences in Mini-Mental State Examination (MMSE) score change between wave 2 (1982) and wave 3 (1993–1996), by level of cannabis use, in four regression models, Baltimore Epidemiologic Catchment Area study follow-up†

<table>
<thead>
<tr>
<th>Level of cannabis use</th>
<th>Model 1 (cannabis use)</th>
<th>Model 2 (cannabis use plus use of alcohol and tobacco)</th>
<th>Model 3 (cannabis use plus age, gender, minority status, and education)</th>
<th>Model 4 (cannabis use plus age, gender, minority status, education, and use of alcohol and tobacco)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonusers§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light users</td>
<td>0.28*</td>
<td>0.22</td>
<td>-0.001</td>
<td>-0.02</td>
</tr>
<tr>
<td>Light users plus use of drugs</td>
<td>0.25</td>
<td>0.17</td>
<td>-0.07</td>
<td>-0.10</td>
</tr>
<tr>
<td>Heavy users</td>
<td>0.35*</td>
<td>0.27</td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Heavy users plus use of drugs</td>
<td>0.81</td>
<td>0.66</td>
<td>0.79</td>
<td>0.69</td>
</tr>
</tbody>
</table>

* $p < 0.10$.
† Positive numbers indicate MMSE score increases relative to the reference group; negative numbers indicate relative decreases in MMSE score.
‡ SE, standard error.
§ Reference group.
Notable limitations of this study include loss to follow-up and mortality. Cognitive functioning at baseline was a predictor of both mortality and loss to follow-up in the Epidemiologic Catchment Area study (40). Additionally, it is possible that some cannabis users in the study may have used cannabis on the day the MMSE was administered. Given the acute effects on cannabis on cognition (34), this would have tended to reduce their MMSE score on that day. This may have adversely affected accurate measurement of MMSE score changes over time.

Given that a lower level of cognitive functioning was associated with greater cognitive decline, these estimates of decline may be underestimates. The assessment of cannabis use was based on self-reports and was not confirmed with biologic measures or controlled in an experimental setting. This may have led to underestimation of cannabis use in persons with poor memory.

Another important limitation of the study is that the MMSE is not a very sensitive measure of cognitive decline, even though it specifically tests memory and attention. Thus, small or subtle effects of cannabis use on cognition or psychomotor speed may have been missed. The MMSE is not intended for the purpose for which it was used in this study, and it contains some items that assess neurologic function as well as cognition. Additionally, MMSE item analysis was not performed in this study. Given the MMSE’s ease of use and widespread application, it was the most practical instrument available for brief assessment of cognitive functioning at the time the multisite Epidemiologic Catchment Area study was planned in the late 1970s. Also, given its limited sensitivity, declines noted on the MMSE are probably underestimates of true declines.

Other limitations of the MMSE include the fact that small errors, such as forgetting the present day’s date, may be due to measurement error and not to true decline. Measurement error on the MMSE might be caused by a variety of factors, including the ambient environment in which the test is taken, the respondent’s mood or emotional state, the respondent’s adequacy of sleep the night before, the time of day at which the test is given, and other factors. However, such errors ought to be random and not systematic (equally distributed between study waves), so the effect on mean estimates should “average out” across the population and across waves of assessment.

MMSE scores in this study exhibited a ceiling effect, given that most participants scored in the 27–30 range during wave 1. However, the ceiling effect was limited to a minority of participants, those who scored 30 points at baseline, since most declines were small. Finally, the small but tangible beneficial “practice effect” of repeated testing on MMSE scores would tend to lead to higher, not lower, MMSE scores at follow-up.

We conclude that cognitive decline occurs across all age groups, with a significant proportion of persons of all ages showing declines near clinically significant levels after 12 years. Such decline is not associated with cannabis use in either men or women. A better understanding of predictors of cognitive decline in persons under age 65 years might lead to interventions designed to slow or arrest such decline. This in turn might reduce the incidence of dementia at older ages.

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