

Association of Cannabis Use With Risk of Subsequent Falls Among Adults Aging With HIV

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Background. Potential harms of preventable/modifiable use of substances, such as cannabis, among aging people with HIV (PWH) are unclear. We characterized longitudinal associations between current cannabis use and subsequent fall risk among aging PWH.

Method. Participants in the Advancing Clinical Therapeutics Globally (ACTG) A5322 study self-reported current cannabis use and any fall(s) annually and semiannually, respectively. Generalized linear models and inverse probability weighting were used to assess associations between cannabis use and subsequent fall risk, adjusting for baseline covariates (age, sex assigned at birth, and race/ethnicity), time-varying confounders, and study attrition.

Results. Among 957 participants (median age, 51 years), 18.2% reported current cannabis use at baseline; 18.6% reported falling in the first year of the longitudinal study. Current cannabis use was associated with moderate risk of any falls in the following year in baseline covariate-adjusted analysis (risk ratio [RR], 1.27 95% CI, 1.02, 1.57; $P = .029$), but not in analyses additionally adjusted for fall history, nonprescribed psychoactive substance use, psychotropic and analgesic medication use, heavy alcohol use, peripheral neuropathy, and cigarette smoking status (adjusted RR, 1.11 [95% CI, .83, 1.49]; $P = .49$). Cigarette smoking status was the main variable that attenuated the association between falls and cannabis use.

Conclusions. Among aging PWH, the association between current cannabis use and fall risk was primarily confounded by cigarette smoking status. Future studies should incorporate more granular cannabis use data on falls risk, including cannabis composition or strain and dose.

Keywords. aging; cannabis; falls; HIV; physical function.

The consistent use of suppressive antiretroviral therapy (ART) has led to significant improvement in life expectancy among people with HIV-1 (PWH), who are increasingly surviving into older age. In 2022, the Centers for Disease Control and

Prevention estimated that 54% of diagnosed PWH in the United States (US) were aged 50 and above [1]. The increasing age of PWH has been linked to an elevated risk for comorbidities, such as cardiovascular disease, impaired renal function, and cognitive decline [2–6]. Importantly, PWH may also experience accelerated or accentuated aging, wherein age-related comorbidities, including frailty and physical function impairments, occur earlier or more frequently than in people without HIV [7, 8]. Notably, the earlier and increased occurrence of age-associated comorbidities among PWH results in a greater risk of falls [6, 7, 9].

Falls are a key cause of mortality and morbidity. Indeed, weighted national estimates indicated that the 27.6% of US adults aged ≥ 65 years experienced at least 1 fall annually [10]. Among older adults in the general population, fall risk factors include age, numerous prescribed medications, orthostatic hypotension, and functional and cognitive impairments [11, 12]. However, PWH have additional specific fall risk factors,

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including current use of efavirenz, neuropathy from exposure to older ART regimens, detectable HIV-1 RNA level, and psychoactive substance use [13, 14]. Given the accelerated and/or accentuated aging that PWH may experience, identification of modifiable risk factors for falls is essential for the development of strategies to prevent falls and fall-related injuries.

Cannabis (*Cannabis sativa*) is a commonly used substance, and estimated rates of cannabis use have increased among older individuals. Indeed, weighted data from the 2021 to 2023 US National Survey on Drug Use and Health (NSDUH) indicated that the estimated prevalence of past-month cannabis use among adults aged 65 years and older increased from 4.8% in 2021 to 7.0% in 2023 [15]. Cannabis use by PWH is particularly high, with a study using weighted data from the 2005 to 2014 US NSDUH estimating the prevalence of lifetime cannabis use among PWH to be 76.7% as compared with 44.5% among people without HIV [16]. Similarly, the estimated proportion of PWH with past-year (34.2%) and past-month (24.9%) cannabis use was significantly elevated as compared with people without HIV (11.1% and 6.7%, respectively) [16]. Within the Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections (ACTG) study A5322, a prospective observational study of PWH aged 40 years old or older, 18% of participants reported current cannabis use.

Both PWH and people without HIV use cannabis to mitigate specific symptoms, including anxious mood level, depressed mood level, nausea, and pain, as well as to increase appetite [17, 18]. However, conflicting data exist on the impact of cannabis use on the health of PWH. Some reports indicate that cannabis use by middle-aged and older adult PWH is associated with greater sleep time [19] and “SuperAging,” or superior neurocognitive functioning [20]. Additionally, occasional cannabis use was associated with better global cognition over time in aging PWH [21], lower central nervous system inflammation [22], and is increasingly recognized as a possible treatment for agitation among people experiencing agitation due to dementia, including Alzheimer’s disease [23]. Conversely, cannabis use among aging PWH has been linked with frailty [24], premature aging [25], and decreased ART adherence [26].

The association of cannabis use with risk for falls specifically among middle-aged and older PWH is less well described. A previous cross-sectional analysis of middle-aged women with and without HIV in the Women’s Interagency HIV Study showed that current (past 6 months) and past cannabis use (ever use) were associated with any falls and multiple (≥ 2) falls [27]. In a subsequent longitudinal analysis, current cannabis use was associated with any falls in women with HIV but not women without HIV [28]. Notably, these previous studies included only women and had predominantly nonwhite participants [27, 28]. More data on how cannabis use by PWH of additional populations may impact falls is critically needed as it can inform the safety of cannabis use among PWH. This is

especially important among aging PWH, who may have an increased fall risk and a greater burden of physical impairments as compared with younger PWH [5, 29]. In the current study, we leveraged longitudinal data from ACTG A5322 to examine associations of current cannabis use by aging PWH on subsequent risk of falls.

METHODS

Study Population

This study utilized data collected through ACTG A5322 (the HIV Infection, Aging, and Immune Function Long-term Observational study, HAILO). A5322 was a longitudinal, multicenter prospective observational study that enrolled 1035 PWH aged ≥ 40 years at 32 clinical research sites in the continental United States and Puerto Rico between November 2013 and July 2014. Participants were followed through December 2021. Biannual study visits included assessment of current medications and adherence and fall assessments. Annual assessments included substance use questionnaires. The current analysis included all A5322 participants with data on both cannabis use and falls.

Participant Consent Statement

All A5322 participants provided written informed consent before enrollment. A5322 was approved by the local institutional review board at each site.

Falls

Falls were reported retrospectively for the prior 6 months at study visits conducted every 24 weeks, starting at week 24, using interview-administered questionnaires. A fall was defined as an unexpected event in which the study participant lost their balance and landed on the floor, ground, or a lower level or hit an object, as previously described [6, 11, 30]. Participants were asked about the occurrence of falls in the past 6 months. In this analysis, the outcome was categorized as no falls versus any falls (≥ 1) in reports from 2 consecutive visits on the 24-week schedule, which were combined to create a variable documenting any falls over each 48-week period.

Cannabis Exposures

Cannabis use data were collected every 48 weeks throughout A5322 follow-up. As previously described [26], self-reported cannabis use was assessed by asking participants “When was the last time you used marijuana (pot, hashish)?” with the following possible answers: (0) never used; (1) > 1 year ago; (2) within the past year up until 1 month ago; or (3) within the past month. For the main analysis, we classified individuals reporting category 0, 1, or 2 as not using cannabis versus category 3 as currently using cannabis (in the past month). Sensitivity analyses were also conducted comparing categories 0 or 1 (no use in the past year) to categories 2 and 3 (any use within the past year).

Covariates

Covariates were identified for consideration on the basis of epidemiological evidence from the previous literature. Each covariate was evaluated by adding it to a univariable log-binomial regression model predicting falls associated with cannabis use. Any variable that changed the effect of cannabis use on the log risk of falls by $\geq 10\%$ was considered a confounder. Potential confounders assessed included sex assigned at birth, age at baseline (A5322 study entry), race/ethnicity, education level at baseline, taking ≥ 5 medications other than ART, use of prescribed psychotropic medications (including antidepressants, antianxiety medications, and opioid pain medications), HIV-1 RNA, nadir CD4 count, years on ART at baseline, ART regimen, cigarette smoking status, high level of alcohol use (including binge drinking: men: >14 drinks/week or ≥ 5 drinks in 2 hours; women: >7 drinks/week or ≥ 4 drinks in 2 hours), other psychoactive substance use (including opioids, cocaine, amphetamines, hallucinogens, inhalants, or other nonprescribed substances), and diagnosis of comorbidities (including cancer within 5 years, cardiovascular disease, hypertension, diabetes, renal, liver, or hepatitis C diagnosis, or neuropathology). Each comorbidity was considered separately except for renal, liver, or hepatitis C diagnoses, which were grouped due to low frequency. Comorbidity diagnoses were self-reported and, in most cases, confirmed via medical records, medication use, or labs. Neuropathy diagnosis was based on study assessments. All variables were time-updated unless otherwise noted.

Statistical Methods

Generalized linear models fitted using generalized estimating equations (GEEs) were used to assess the association between cannabis use and falls. The models employed the log link and the binomial distribution to estimate risk ratios (RRs). Time was modeled as visit number, with baseline (visit 1) defined as the first visit with cannabis and subsequent falls data. An independence covariance structure was used to mitigate GEE bias from time-dependent confounding [31].

Generalized estimating equation independence does not address time-dependent confounding. Therefore, to assess cannabis use and falls at multiple time points while controlling for time-varying confounders and loss to follow-up, inverse probability weighting (IPW) was employed. The methods used to create IPWs have been described previously [31, 32]. Here, stabilized inverse probability (IP) of treatment (cannabis use group) weights (IPTWs) were calculated as the probability of treatment given baseline covariates divided by the probability of treatment given baseline and time-varying covariates. Probabilities were modeled via multinomial logistic regression models, using cannabis use at the previous visit and falls during the prior 48 weeks (considered “history of falls”) as predictors. For the baseline visits, cannabis use at the previous visit and

falls history were omitted from the models. Stabilized IP of censoring weights (IPCWs) were estimated using cannabis use, falls, and the covariates selected for the IPTW models from the most recent visit. The final overall IPWs were the product of the IPTWs and IPCWs.

Due to their cumulative nature, IPW requires full model data at each scheduled visit. To account for this, missing variables were imputed with last observation carried forward. For data missing at baseline, the first available observation was carried backward (omitted from Sensitivity model 4, see [Supplementary Table 2](#)). The IPW were evaluated by checking their distributions by visit and by comparing the distributions of time-updated variables before and after weighting ([Supplementary Methods](#) and [Supplementary Tables 1 and 2](#)). All data analysis was completed using SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Study Population Characteristics

A total of 957 participants had data on both falls and cannabis use at 1 visit or more and contributed 4663 person-years of follow-up to the present analysis. At baseline, the overall median (quartiles: Q1, Q3) age was 51 (47, 57) years ([Table 1](#)). Most participants were assigned male sex at birth (80.8%) (gender identity was not collected); 48.5% of participants identified as White non-Hispanic, 30.2% as Black non-Hispanic, 18.4% as Hispanic of any race, and 2.9% as another race/ethnicity. At baseline, 37.2% of participants reported use of prescribed psychotropic medications; 7.2% reported use of nonprescribed psychoactive substances, including heroin, cocaine, amphetamines, or other nonprescribed psychoactive substances; 25.5% reported being current cigarette smokers and 33.1% reported being prior cigarette smokers; 17.9% reported heavy alcohol use; and 41.2% reported symptoms of peripheral neuropathy at baseline. Finally, at baseline, 18.6% of participants reported any fall during the first time period (prior 12 months).

Baseline Characteristics by Cannabis Use

At baseline, there were 174 (18.2%) participants with current cannabis use and 783 (81.8%) participants without cannabis use ([Table 1](#)). More participants with current cannabis use reported antidepressant, antianxiety, or opioid pain medication use at baseline as compared with participants without cannabis use (47.1% vs 35.0%; $P = .003$). More participants with current cannabis use reported current use of nonprescribed psychoactive substance use as compared with participants without cannabis use (18.4% vs 4.7%, $P < .001$). About twice as many participants with current cannabis use were also current cigarette smokers (42.5% vs 21.7%, $P < .001$) and reported heavy alcohol use (31.6% vs 14.8%, $P < .001$) as compared with participants without cannabis use.

Table 1. Baseline Characteristics by Cannabis Use

Characteristics		Cannabis Use In Past Month			P Value ^a
		Nonuser (N = 783), n (%)	Current User (N = 174), n (%)	Total (N = 957), n (%)	
Age (years)	Median (Q1, Q3)	52 (47, 57)	50 (45, 55)	51 (47, 57)	...
	40–49	328 (41.9)	89 (51.1)	417 (43.6)	.038
	50–59	327 (41.8)	67 (38.5)	394 (41.2)	...
	≥60	128 (16.3)	18 (10.3)	146 (15.3)	...
Sex (assigned at birth)	Male	623 (79.6)	150 (86.2)	773 (80.8)	.044
	Female	160 (20.4)	24 (13.8)	184 (19.2)	...
Race/ethnicity	White non-Hispanic	374 (47.8)	90 (51.7)	464 (48.5)	.060
	Black non-Hispanic	230 (29.4)	59 (33.9)	289 (30.2)	...
	Hispanic	156 (19.9)	20 (11.5)	176 (18.4)	...
	Another race/ethnicity ^b	23 (2.9)	5 (2.9)	28 (2.9)	...
Medication use ^c	...	274 (35.0)	82 (47.1)	356 (37.2)	.003
Nonprescribed psychoactive substance use ^d	...	37 (4.7)	32 (18.4)	69 (7.2)	<.001
Cigarette smoking status ^e	Never	365 (46.6)	31 (17.8)	396 (41.4)	<.001
	Prior	248 (31.7)	69 (39.7)	317 (33.1)	...
	Current	170 (21.7)	74 (42.5)	244 (25.5)	...
Heavy alcohol use	...	116 (14.8)	55 (31.6)	171 (17.9)	<.001
Neuropathy diagnosis	...	325 (41.5)	69 (39.7)	394 (41.2)	.671
Falls in past 12 mo	...	139 (17.8)	39 (22.4)	178 (18.6)	.162

^aFisher's exact test.^bCombined with Hispanics for analysis.^cMedications include antidepressants, antianxiety medications, and opioid pain medications.^dNonprescribed psychoactive substances include heroin, cocaine, amphetamines, or other nonprescribed drugs.^eSmoking status: never, no use; prior, if the participant has a history of smoking cigarettes; current, if the participant smokes cigarettes currently.

Association Between Cannabis Use and Fall Risk

More participants with current cannabis use reported falling in the first year of this longitudinal study as compared with participants without cannabis use (22.4% vs 17.8%, $P = .162$; Table 1). Including data on falls collected across the entire longitudinal study period and adjusted for baseline covariates, including age, race/ethnicity, and sex assigned at birth, and IP weighted for study dropout, current cannabis use was found to be associated with greater risk of having any falls in the following year as compared with no cannabis use (RR, 1.27 [95% CI, 1.02, 1.57]; $P = .029$; Figure 1). In multivariable analyses further adjusted for history of falls, time-varying illicit substance use, medication use, heavy alcohol use, peripheral neuropathy, and cigarette smoking status, the effect was attenuated and no longer significant (adjusted RR [aRR], 1.11 [95% CI, .83, 1.49]; $P = .49$). In sensitivity models assessing the association of risk of falls with cannabis use in the past year (rather than the past month), results were almost identical (aRR 1.09 [95% CI, .84, 1.41]; $P = .39$). A sensitivity model controlling for cigarette smoking status as a covariate instead of via IPW found that adjustment for cigarette smoking status (in addition to age, sex, race/ethnicity) gave an aRR for cannabis use of 1.15 (95% CI, .93, 1.42; $P = .20$), indicating that the attenuation of the association of cannabis use during the past month with risk of falls was consistent with confounding by cigarette smoking status. Compared with participants who reported never

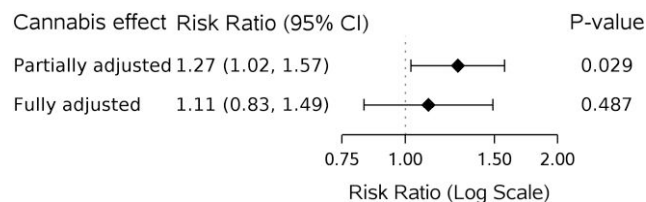


Figure 1. Associations between cannabis use and fall risk among aging people with HIV. Generalized linear models fitted using GEE were used to assess the association between cannabis use and falls. Data are depicted as a forest plot of the fall risk ratio (RR with 95% CI). All models were adjusted for baseline covariates (age group, sex at birth, race/ethnicity) and inverse probability (IP)-weighted for dropout. Fully adjusted models were also IP-weighted for falls at prior visit and time-varying confounders, including nonprescribed psychoactive substance use (heroin, cocaine, amphetamines, or other nonprescribed drugs), prescribed medication use (antidepressants, antianxiety, or opioid pain medications), heavy alcohol use, peripheral neuropathy, and smoking status.

smoking cigarettes, participants who reported current cigarette use had an aRR for falls of 1.62 (95% CI, 1.28, 2.04) and participants with previous cigarette use had an aRR of 1.32 (95% CI, 1.05, 1.66).

DISCUSSION

Prior work has demonstrated that PWH have a greater risk of having an injurious fall as compared with people without HIV [9, 33]. Cannabis use in PWH is more frequent than in people

without HIV, raising concerns about adverse events such as falls. Here, we explored associations between current cannabis use and fall risk in a large cohort of middle-aged and older PWH. We observed that current cannabis use was moderately associated with fall risk, although this association was not maintained when adjusted for additional fall risk factors including cigarette smoking status, previous falls, other psychoactive substance use, prescribed psychotropic medication use, heavy alcohol use, and peripheral neuropathy, suggesting that these other factors may have a greater influence than cannabis use on fall risk. Among these other factors, cigarette smoking status was an important risk factor that appeared to be the strongest predictive variable leading to the attenuation of the association of fall risk with cannabis use. Given that cannabis use is highly prevalent among PWH [16], that falls are a significant cause of mortality and morbidity [11], and that people who use cannabis are also more likely to use cigarettes, identifying the co-occurrence of cigarette and cannabis use may assist in the risk stratification of PWH who are aging, as these individuals may be at higher risk of experiencing falls. Our findings, therefore, highlight the importance of screening for substance use. Our results suggest that cigarette smoking contributes to fall risk in this cohort; future interventional studies are needed to determine whether reduction or cessation of cigarette smoking and/or cannabis use can effectively decrease fall incidence, an outcome that would complement the well-known benefits of smoking cessation, among PWH. Future studies should also examine whether specific parameters of cannabis use (eg, composition, dose, and frequency) influence fall risk and whether lower-risk patterns of use can be defined for aging PWH.

Our partially adjusted findings agree with previous reports of an association between current cannabis use and falls in middle-aged women with HIV [27, 28], extending these findings to PWH primarily assigned male sex at birth. The attenuation of this association in our fully adjusted models aligns with prior work showing no association between long-term cannabis use and balance disturbances after adjustment among PWH [34], supporting the interpretation that associations observed in less fully adjusted analyses may reflect confounding by co-occurring exposures. Finally, our findings align with previous work indicating that tobacco-using PWH were more likely to fall recurrently [9], although the mechanism for this association is likely multifactorial. People who use cigarettes are more likely to have additional comorbidities (eg, diabetes, hypertension, and cardiovascular disease) that require additional medications, with both multimorbidity and polypharmacy increasing the fall risk. Cigarette smoking associates with elevated inflammation among ART-treated PWH [35, 36], and elevated inflammation associates with frailty and function impairments in PWH [37, 38], an additional risk factor for falls among PWH. In contrast, cannabis use associates with lower inflammation among PWH [26, 39]. Thus, our findings could indicate that the modest anti-inflammatory

effects of cannabis are not sufficient to overcome the influence of cigarette smoking and associated increased risk for falls. Additional research is needed to determine how cannabis use, cigarette smoking, inflammation, and physical function intersect, particularly among older PWH.

The main strength of our investigation was the use of data from a large, well-established, geographically diverse, longitudinal cohort of aging PWH in the continental United States and Puerto Rico. An inherent limitation is that because the cohort was made up of individuals enrolled in a study with greater access to clinical care, there may have been more awareness among participants of the unclear impacts of cannabis use, resulting in the lower percentage of participants with past-month cannabis use in this group as compared with what has been observed previously [16]. Additionally, because the study population consisted of individuals engaged in a clinical trial and subsequent long-term observational study, our results may not be generalizable to all adults aging with HIV, which is also true related to associated demographic characteristics of the sample. Specifically, high levels of engagement in care, elevated rates of viral suppression, and specific demographics may not fully represent PWH in different geographic or clinical settings. Our study was also limited by the self-reporting of falls, which is subject to recall bias. Although there was a relatively short recall period for fall reporting [40], the number of actual falls may nonetheless have been underestimated. Relatedly, given that the number of falls reported in our participant population was relatively low, links between current cannabis use and fall risk may be over-fitted. Likewise, although self-report is a commonly used means of assessing cannabis use, it remains possible that inaccurate self-reporting could have affected our study findings. Additionally, our assessment of cannabis use was limited to self-reported use in the month prior to the annual study visits. Furthermore, as we did not collect data on cannabis consumption in the immediate period preceding a fall, we cannot distinguish between the potential acute versus long-term effects of chronic cannabis use. A related limitation is that A5322 did not collect data on indication, amount, frequency, or method of cannabis use, or cannabis strain or composition (eg, cannabidiol vs tetrahydrocannabinol), thus we cannot evaluate whether medicinal or recreational cannabis use or cannabis quantity, potency, route of administration, or formulation influenced associations between cannabis use and falls risk. Additionally, our exposure was operationalized as a binary indicator of current cannabis use versus no current use, which combines never users, former users, and intermittent users in the reference group. A sensitivity model combining intermittent users with current users (Supplementary Methods and Supplementary Table 3) produced comparative results to the main model, suggesting that the heterogeneity in the reference group did not meaningfully bias our findings toward the null. Furthermore, our findings may be impacted by confounding

by indication, as cannabis use among aging PWH may be a proxy for treating symptoms, such as chronic pain or neuropathy, that independently increase fall risk [9]. Although we adjusted for covariates, including pain and neuropathy, we cannot entirely rule out residual confounding. Finally, our use of last observation carried forward and first observation carried backward (FOCB) imputation in IPW analysis may introduce bias if imputed values differed systematically from true unobserved values, although a sensitivity analysis excluding baseline FOCB-imputed data yielded essentially identical results (Supplementary Methods and Supplementary Table 3).

Thus, our study highlights the need for future prospective and interventional studies to clarify the impact of more specific cannabis use, including strains/composition of cannabis, dose of cannabis, and patterns of use (ie, daily vs weekly) on fall incidence, and allow providers to best counsel patients on the potential risks and benefits of cannabis use. In particular, future studies are needed that include quantification of cannabis metabolites [41, 42], and that collect data on the amount and types of cannabis products used and reason for cannabis use. Future studies should also include control for ART medications associated with osteopenia, such as tenofovir disoproxil fumarate, ritonavir-boosted protease inhibitors, and efavirenz.

In summary, our findings indicate that a moderate association between cannabis use and increased risk of falls over the following year is likely mainly due to the confounding effects of cigarette smoking. Cannabis use and cigarette smoking may therefore serve as indicators for risk stratification in the care of adults aging with HIV. While cannabis use and cigarette smoking are modifiable factors, future interventional research is necessary to determine if cessation strategies could mitigate fall risk in this population. Additional knowledge is needed on how the beneficial effects of cannabis use, particularly non-psychoactive forms of cannabis, on inflammation intersects with the potentially detrimental impacts of cannabis use and cigarette smoking on functional outcomes and physical decline, particularly among older PWH. Finally, our findings highlight the relevance of identifying predictors of falls among PWH [43], particularly older PWH, for intervention beyond reduction of cannabis use, cigarette smoking, and polypharmacy. These fall-prevention intervention strategies, which may include clinical patient education about physical (eg, body position changes), behavioral (eg, promoting physical exercise, adequate nutrition/hydration, sleep hygiene, and stress management), and environmental (eg, removing fall hazards, adding grab bars/hand rails, and optimizing lighting) modifications represent areas of focus in future prospective studies aimed at reducing fall risk in this vulnerable population.

Supplementary Data

Supplementary materials are available at [Open Forum Infectious Diseases](#) online. Consisting of data provided by the authors to benefit the reader, the

posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Data availability. The deidentified raw data supporting the conclusions of this article are available and can be downloaded from <https://dataverse.harvard.edu/>.

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