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METHODS AND TECHNIQUES

ADDICTION SSA

Enhanced cannabis timeline followback (EC-TLFB): Comprehensive assessment of cannabis use including standard THC units and validation through biological measures

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Abstract

Aims: The aims of this study were to present an enhanced cannabis timeline followback (EC-TLFB) enabling comprehensive assessment of cannabis use measures, including standard tetrahydrocannabinol (THC) units, and to validate these against objectively indexed urinary 11-nor-9-carboxy-tetrahydrocannabinol (THC-COOH) concentrations.

Design: We used cross-sectional baseline data from the 'CannTeen' observational longitudinal study.

Setting: The study was conducted in London, UK.

Participants: A total of 147 participants who used cannabis regularly took part in the study (n = 71 female, n = 76 male; mean age = 21.90, standard deviation = 5.32).

Measurements: The EC-TLFB was used to calculate frequency of cannabis use, method of administration, including co-administration with tobacco, amount of cannabis used (measured with unaided self-report and also using pictorial aided self-report) and type of cannabis product (flower, hash) which was used to estimate THC concentration (both from published data on THC concentration of products and analysis of cannabis samples donated by participants in this study). We calculated total weekly standard THC units (i.e. 5 mg THC for all cannabis products and methods of administration) using the EC-TLFB. The outcome variable for validation of past week EC-TLFB assessments was creatinine-normalized carboxy-tetrahydrocannabinol (THC-COOH) in urine.

Findings: All measures of cannabis exposure included in this analysis were positively correlated with levels of THC-COOH in urine (r = 0.41–0.52). Standard THC units, calculated with average concentrations of THC in cannabis in the UK and unaided self-report measures of amount of cannabis used in grams showed the strongest correlation with THC-COOH in urine (r = 0.52, 95% bias-corrected and accelerated = 0.26–0.70).

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Conclusions: The enhanced cannabis timeline followback (EC-TLFB) can provide a valid assessment of a comprehensive set of cannabis use measures including standard tetrahydrocannabinol units as well as and traditional TLFB assessments (e.g. frequency of use and grams of cannabis use).

KEYWORDS
Assessment, cannabis, dose, EC-TLFB, measurement, standardization

INTRODUCTION

Cannabis is the third most widely used drug world-wide after alcohol and tobacco, with 4% of the global population reporting use in 2020 [1]. While the research on the effects of cannabis is extensive, measuring cannabis use is inherently difficult. Cannabis can be used with a variety of methods of administration, such as inhaled using joints, bongs, pipes or vaporizers, or ingested in the form of gummies or other consumables. The composition of cannabis products as well as their legality varies across countries [2], leading to variation on the measures of exposure used across studies. Thus, standardized measures of cannabis use are needed to improve integration of evidence across studies and facilitate advancement of the field.

One measure to aid recall of substance use that has been recommended as a measurement of cannabis use [3] is the timeline followback (TLFB). The TLFB is a retrospective calendar, initially developed to measure alcohol consumption, and used to collect substance use data for every day over a defined period of time [4]. The TLFB has been adapted to assess cannabis use [5] and shows good validity and test–retest reliability [6, 7]. As a result, the TLFB has been recommended by expert consensus to quantify additional aspects of cannabis use across multiple settings, when more detailed information is required besides a single measure of frequency of cannabis use [3].

Previous studies using the TLFB to measure cannabis use have included measures of frequency of use and quantity of cannabis use as number of joints consumed [7–9] or grams of cannabis consumed [5, 10]. However, these studies do not account for variation in the amount of cannabis added to a joint and whether the joint is shared with others, as is commonly used by people who use cannabis [11]. In addition, they have not captured variation in the method of cannabis use (e.g. smoked, vaporized and oral administration) or cannabis and tobacco co-administration, which is common in Europe [12], and has been suggested to influence cognitive and health outcomes [13].

Previous versions of the TLFB are also not able to capture differences in cannabis products with a range of delta-9-tetrahydrocannabinol (THC) concentrations. Assessing these differences can be clinically relevant because use of higher potency products has been associated with worse health outcomes, in particular for cannabis use disorder and psychotic disorders [14]. With the emergence of new cannabis products and methods of administration, as well as increasing THC potency in cannabis products [15, 16], a comprehensive assessment of cannabis use may be particularly important in order to be able to accurately capture cannabis use, raise awareness of current trends and their changes over time, as well as to be able to study the effects of cannabis in health outcomes more effectively.

More recently, a study validated an on-line version of the TLFB using a previously validated measure, the marijuana dependence scale (MDS) [17]. Participants provided information on the type of cannabis use as flower, edibles, concentrated and others, such as topical creams. They also reported the overall amount used in that day and the THC and cannabidiol (CBD) concentration of the product if known. However, potency reported as the concentration of THC is not information readily available in illicit markets and consumer knowledge of THC concentration may be low, even in legal markets [18]. In this study, only approximately a third of participants who endorsed flower use reported the THC concentration of the product [17].

In this study we present the enhanced cannabis TLFB (EC-TLFB). The EC-TLFB was developed to collect detailed information on cannabis use, as well as alcohol and other drug use. For cannabis use, the EC-TLFB collects information on the frequency of use, amount of cannabis used, types of cannabis products, methods of administration and co-administration with tobacco using measures that are relevant in both regulated and illicit markets. The EC-TLFB can be used to estimate cannabis potency in markets where information on the concentration of THC in cannabis is not readily available. This is conducted using pictorial aids to identify use of cannabis products which can be utilized as a proxy of cannabis potency. In the United Kingdom (UK), self-reported identification of cannabis type has been found to be associated with objectively quantified THC concentration in cannabis [19]. In addition, the EC-TLFB includes measures of tobacco use, because cannabis and tobacco are commonly used by the same individuals [20], and tobacco use may influence the association between cannabis use and health outcomes [21–23]. The EC-TLFB can measure the use of cannabis with tobacco simultaneously, for example in a joint, as well as concurrent use of cannabis and tobacco, such as smoking cannabis and smoking cigarettes separately. Full instructions of the EC-TLFB are presented in the Supporting information, Data S1.

The EC-TLFB is also able to assess the total dosage of THC as expressed by the standard THC unit [2] in both regulated and illicit markets. The standard THC unit (a low dose of 5 mg THC, applied to all products and methods of administration) provides a standardized measure of dose based on the primary psychoactive constituent in cannabis, similar to alcohol units which are also based on the quantity

of active pharmacological constituent [2]. This is important, as cannabis products are increasingly diverse [24], and a standard unit of dose is thus necessary to ensure that drug use assessments (e.g. the TLFB) can fully capture and combine data from all cannabis use occasions. Furthermore, by including data on frequency, amount used and product potency, standard THC units can provide the most comprehensive measure of THC exposure in research and clinical settings. In addition, investigators are now required to report cannabis use in standard THC units both in funding applications and research reporting by the US National Institutes of Health [25], thus necessitating the development of tools that measure standard THC units in observational studies.

In this paper, we aimed to validate cannabis use measures from the EC-TLFB method using objectively indexed urinary 11-nor-9-carboxy-tetrahydrocannabinol (THC-COOH) concentrations. THC-COOH in urine has been recommended by expert consensus [3] as an objective gold standard measure, as it is able to confirm regular cannabis use status as well as to corroborate quantity of THC exposure [3], in addition to being associated with outcomes relevant to problematic cannabis use [26]. This urinary measure was used to validate measures of past week cannabis use recorded in the EC-TLFB, including traditional TLFB assessments (frequency of use, grams of cannabis use) and more novel and detailed measures (standard THC units). THC accumulates in various tissues of people who use cannabis chronically due to its high lipophilicity [27]. THC undergoes hydroxylation to form the psychoactive metabolite 11-hydroxy-THC, which is then further oxidized into the inactive metabolite THC-COOH [27]. In this study, we focused upon evaluating a 1-week window of association between EC-TLFB measures and THC-COOH in urine, as this period of THC-COOH in urine is suitable for capturing recent cannabis use at mild, moderate and heavy levels of use [28], and weekly assessments of THC-COOH in urine are widely employed in clinical trials of cannabis use disorder [29–31]. While THC-COOH in urine can be detected for longer than 7 days, differentiating recent cannabis use from residual drug excretion from previous cannabis exposure can become problematic in heavy chronic users [28]. Here, we aim to use THC-COOH in urine as an objective measure of quantity of THC exposure by investigating how it correlates with self-report measures of cannabis use over the past week.

We aim to present the EC-TLFB as a comprehensive measure of cannabis use for a range of measures, including frequency of use, grams of cannabis use and standard THC units, and to validate these measures against THC-COOH in urine as an objective biological measure of cannabis use. While the EC-TLFB can be used to measure different cannabis products, such as flower, concentrates and edibles, this analysis focuses upon the use of herbal cannabis and hash as these are the most common types of cannabis products used in the UK, where this study was conducted. The validation and implementation of the EC-TLFB has the potential to inform future research and as a first step to help reducing heterogeneity of measures across studies, thus improving standardization, integration of evidence and aiding advancement of the field.

METHODS

Design

This study used cross-sectional baseline data from the 'CannTeen' observational longitudinal study. The overall study aims, participants, data collection procedures and power analysis are described in the full study protocol [32]. Ethical approval was obtained from University College London (UCL) ethics committee, project ID 5929/003. The study was conducted in line with the Declaration of Helsinki, and all participants provided written informed consent to participating.

Participants

A total of 274 participants completed the baseline testing session, 147 of whom used cannabis and 127 were control participants who did not use cannabis. Only the 147 participants who used cannabis (n = 71 female, n = 76 male) were included in this analysis. The sample of 147 people who used cannabis comprised 76 adolescents (aged 16–17 years) and 71 adults (aged 26–29 years). These groups were selected in relation to the overall study design, which investigated the long-term effects of cannabis use in teenagers' and adults' cognition, mental health and brains. Full details of this study have been previously published [33]. No age-group analysis was conducted as part of the main analysis. A total of 132 participants were included in the final analysis. Seven participants were excluded because they did not use cannabis in the time frame defined for this analysis. One participant was excluded due to missing creatinine in urine data and two participants were excluded due to incomplete EC-TLFBs. Five participants were excluded from the primary analysis due to the use of weak cannabis, as specified in the pre-registered analysis plan. Sensitivity analyses including weak cannabis were conducted including these five participants and results are presented in the Supporting information, Data S1.

Participant recruitment involved on-line advertisement on Facebook, Instagram, Gumtree and Reddit, school assemblies, flyers and word-of-mouth. Potential participants were screened for inclusion and exclusion criteria. Eligible participants were compensated for completing each of the testing sessions (five sessions during a 12-month period).

The main inclusion criteria were 16–17-year-old adolescents and 26–29-year-old adults who used cannabis 1–7 days per week. Exclusion criteria were currently daily use of psychotrophic medication, current treatment for a mental health disorder including cannabis use disorder, a personal history of psychotic disorder or use of any illicit drug more than twice per month with the exception of cannabis. For full eligibility criteria see the Supporting information, Data S1.

Procedure

Participants completed a telephone screening to assess the inclusion criteria. Potential participants were invited to a baseline session and their eligibility was checked further. Prior to the day of the testing,

they were asked to abstain from using cannabis or alcohol within 12 hours and any other drug use within 48 hours. Abstinence was checked using self-report, a clear saliva drug test and an alcohol breathalyzer with a reading of zero. All participants completed the testing session, including the EC-TLFB, urine sample collection, cannabis sample donation and further measures reported elsewhere [34].

The EC-TLFB had two steps. The first step involved collecting data on the types, methods, amount of cannabis and of tobacco (if co-administration is applicable) used over the past 3 months. The second step involved conducting a TLFB calendar, as reported in previous research [4], using the information collected during step 1.

Pictorial aids were used to help participants identify the types of cannabis they had used during the past 3 months. These pictorial tools were developed for use in the UK and should be adapted where necessary according to country- or region-specific variation in cannabis products and methods of use. These were labelled as 'strong cannabis', such as sinsemilla or skunk, 'weak cannabis', such as imported Thai/low-grade cannabis, 'hash or hashish' and 'other' (Figure 1). The categories of cannabis products included in the EC-TLFB (Figure 1) were based on previous work, including a naturalistic study that analysed cannabis samples of participants in the UK [19], as well as studies analysing illicit cannabis samples seized by the police in England [35, 36]. The amount of cannabis portrayed in photographs measuring grams of cannabis use (Figure 2) were based on the range of amounts of cannabis use reported in previous research studies [19, 37]. The length of the spread of cannabis in these photographs was selected to mimic the same length as a typical rolling paper used for joints in the UK.

Pictorial aids were incorporated because in markets where cannabis is illegally sold and purchased, information on THC concentration in cannabis is not readily available. Thus, data on cannabis products can be used as proxy to estimate their potency together with the country's average THC concentration in cannabis. This is analogous to the use of different types of alcohol product (e.g. beer, wine and spirits) as proxies for their typical alcohol by volume (e.g. 5, 12 and 40%, respectively). In the UK, self-reported identification of cannabis type has been found to be associated with objectively quantified THC concentration [19]. For example, participants' endorsement of use of a particular cannabis type, such as 'strong cannabis', can be used as an estimate of exposure to a concentration of 14% THC based on average concentrations in cannabis products in the UK [36]. In markets where cannabis is sold legally, pictorial aids may also be used in the same way. In addition to this, information may also be available on product labelling regarding the type of cannabis product and its potency or THC content. The EC-TLFB can be used to estimate standard THC units (5 mg of THC, applied to all products and method of administration [2]) by combining data on the cannabis product used, estimates of its potency or THC content and the amount of product used.

After identifying all types of cannabis used over the past 3 months, participants specified the methods of administrations used for each of the types of cannabis used; for example, joint, pipe or bong. Furthermore, for each of these methods used to consume each of the types of cannabis, participants specified, in the following order:

1. What proportion of each method was personally consumed by the participant versus shared with others, as follows: 'Please rate on this scale how much of a <method> you have typically personally consumed over the past 3 months. The scale ranges from 0 which would mean you have typically consumed "None of it" to 10, which would mean you have typically used "All of it"'.
2. Unaided self-report estimates of the amount of cannabis added, as follows: 'Over the past 3 months, how many grams of <cannabis type> have you tended to add to any single <method>?'.
3. Unaided self-report estimates of the amount of tobacco added (if applicable), as follows: 'Over the past 3 months, how many grams of tobacco have you tended to add to any single <method>?'.

FIGURE 1 Cannabis products, pictorial aid enhanced cannabis timeline followback (EC-TLFB).

FIGURE 2 Example of pictorial aid used to measure amount of cannabis used.

4. The amount of cannabis added based on pictorial representations of different amounts of cannabis (see Figure 2 for example), as follows: 'Over the past 3 months, which photo best represents how much <cannabis type> you have tended to add to any single <method>?'.
5. The amount of tobacco added based on pictorial representations of different amounts of tobacco (see Figure 2 for example), as follows: 'Over the past 3 months, which photo best represents how much tobacco you have tended to add to any single <method>?'.

Therefore, completing step 1 of the EC-TLFB resulted in the following past 3-month cannabis use data collected:

- Types of cannabis used (strong, weak, hash, other; Figure 1).
- Methods of cannabis used per cannabis type (joint, pipe, bong, vape, ingested, other).
- Unaided self-report amounts of cannabis and tobacco (if applicable) added to each method-type of cannabis used.
- Amount of cannabis and tobacco (if applicable) added to each method-type of cannabis used measured with pictorial aids.
- Proportion used by the participant for each of these method-types of cannabis used (i.e. sharing versus used on their own from 0 to 10). This question was included as the shared experience of cannabis use is important: cannabis-sharing through social networks is an integral part of cannabis culture [11]. Therefore, the amount of cannabis added to a method of administration does not necessarily equal the amount of cannabis used by the participant, as they might have shared this method with other people. This question was used to calculate the amount of cannabis personally consumed by the participant to increase precision of measurement.

These data were then used to enhance the TLFB in step 2 (Figure 3). After identifying the amount of cannabis typically used for each method of administration for each different type of cannabis over the past 3 months, participants were guided by a researcher to complete the TLFB calendar, as reported in previous research [4]. Participants were first asked to recall specific events that happened each day over the past 3 months. For example, this could be going to the cinema, a birthday party or paydays. This information was then used to aid recall of the drugs used by participants on each day. Participants were then asked to specify use of cannabis, alcohol, cigarette and any other illicit drug use.

On the days that participants reported having used cannabis, the researcher asked the participant which of the method-type of cannabis specified in step 1 was used in this instance. For example, this could be 'joint of hash with tobacco' or 'pipe of strong cannabis without tobacco'. As the typical amount of cannabis added to these methods was already specified in step 1, participants could specify the number of times a method-type of cannabis preparation was used (for example, two joints of hash with tobacco). While we used a constant amount for typical use over the past 3 months, if on any occasion participants reported using an amount that was not typical of their regular cannabis use (different amount added to a method of administration, or different proportion used), this was adjusted when collecting the calendar data. This information was communicated to participants as follows: 'For each day on which you used cannabis, please indicate the method used, the type of cannabis, and how many you had that day (e.g. "3 joints with tobacco, strong cannabis" or "1 cookie, hash, no tobacco"). If you used a dose that was smaller or larger than usual, we can record this: e.g. "(1 joint with tobacco, strong cannabis) × 1.5"' (Supporting information, Data S1). All methods and types of cannabis mentioned during step 1 were included in step 2, the TLFB part, of the EC-TLFB.

On average, step 1 of the EC-TLFB took a mean of 8 minutes to complete, with time varying from 2 to 32 minutes depending upon the number of different cannabis types and methods of administration used by the participant. Part 2 of the EC-TLFB took, on average, a mean of 32 minutes to complete for a period of

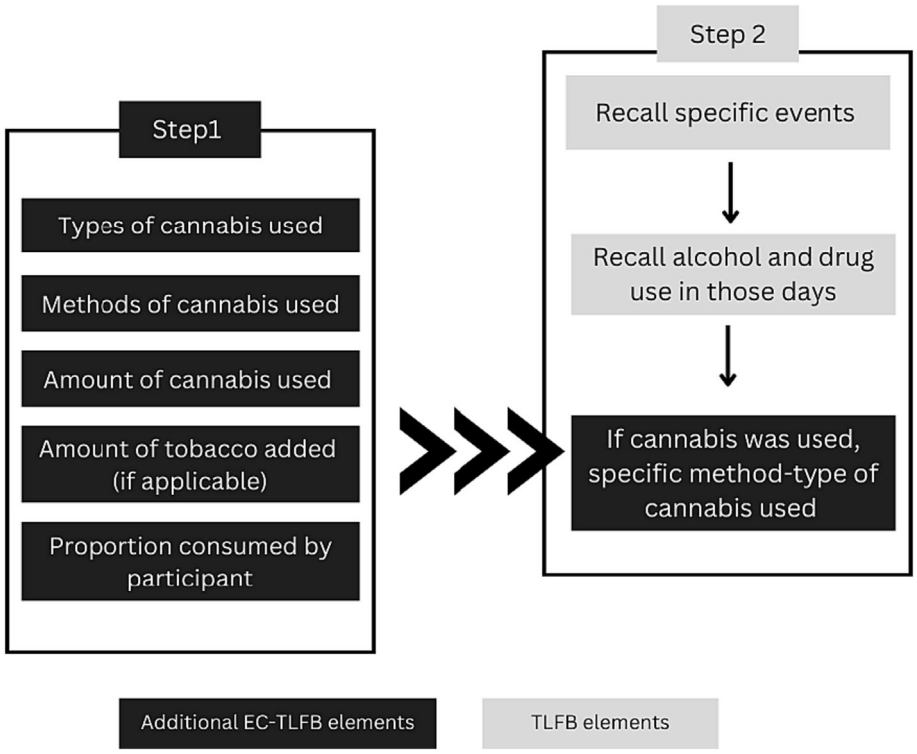

FIGURE 3 Visual representation of key elements of the timeline followback (TLFB) and additional elements added by the enhanced cannabis-TLFB (EC-TLFB).

90 days (2–32 minutes), or approximately 2.66 minutes for a single week.

Outcome variable

The outcome variable used for validation was creatine-normalized THC-COOH concentration in urine. Participants provided a urine sample during the baseline testing session. THC-COOH was quantified by isotope-dilution gas chromatography–mass spectrometry (GC/MS) following solvent extraction from urine. Urine creatine was calculated using Cayman's kit.

We used creatinine-normalized THC-COOH concentrations because they reduce variability in the concentration of THC-COOH due to hydration effects [38]. Creatinine-normalized THC-COOH were calculated by dividing the concentration of the participant's THC-COOH in nanograms per millilitre by the creatinine concentration in milligrams per decilitre and then multiplied by 100. Results are reported in nanograms of THC-COOH per milligram of creatinine [39].

Predictor variables

The following exposure variables were calculated using the EC-TLFB for participant's previous week of cannabis use: past days per week of cannabis use, past week total amount of cannabis used (unaided self-report assessment) and past week total amount of cannabis used (aided pictorial assessment). Both the unaided self-report and aided pictorial amounts of cannabis used were calculated taking into account the proportion personally consumed, specified by participants for each of the method-types of cannabis use. Additional variables not specified at the time of pre-registration of the analysis plan include a single measure of self-reported average frequency of cannabis use per week during the past 3 months as well as the self-reported average amount of cannabis grams consumed in a typical day during the past 3 months. Analysis using these variables is included in the Supporting information, Data S1.

Past week standard THC units were calculated with data collected from the EC-TLFB (past week amount and type of cannabis used) and the average THC concentration in products used by participants (hash and strong cannabis). To calculate THC units, we first calculated the grams of THC consumed using the amount of cannabis consumed and the concentration of THC in cannabis. For example, if the potency of cannabis was 10% THC and the total weight of cannabis consumed was 1 g, then the grams of THC consumed would have been 0.1 g. After this we calculate THC units (1 THC unit = 5 mg [2]) by dividing the grams of THC consumed by a THC unit. Following the example above, 0.1 g of THC consumed would be divided by 0.005 g (THC unit) to equal 20 THC units.

The average THC concentration was derived from two methods. First, this was conducted using existing average THC concentration data published for cannabis products in the UK (Table 1) in relation to the cannabis products used by participants as specified using pictorial aids [36]. Secondly, the average concentration of THC was estimated from cannabis samples donated by participants in this study (Table 2). To obtain an average concentration of THC in cannabis samples donated by participants, those who were carrying cannabis with them during one of the testing sessions were asked to donate a 0.3 g sample of their cannabis in order to objectively analyse THC concentration in this sample, and were reimbursed £10 for this. Participants were asked to donate the cannabis they were using at the time. We did not confirm whether the type of cannabis product donated matched the cannabis product reported by participants during the EC-TLFB. This sample was analysed by R.d.S. for concentration (%w/w) of THC by ultra-performance liquid chromatography (UPLC) using a photodiode array detector (PDA/UV). If the participant did not have cannabis with them at a testing session, they were not asked to donate a sample due to the illegality of the drug, which could have compromised their safety in carrying an illegal substance. As a result, we only collected 33 cannabis samples (n = 27 strong cannabis, n = six hash). As we did not collect any cannabis samples categorized as 'weak' or 'other', participants who used these types of cannabis during the last week were excluded from the primary analysis to ensure comparability between use assessment methods. Sensitivity analysis including participants who used weak cannabis are presented in the Supporting information, Data S1.

TABLE 1 Median THC concentration in cannabis as reported in Potter *et al.* [36].

Cannabis type	Median	Min–max
Sinsemilla (strong cannabis)	14.2	1.9–22.5
Hash or resin	6.3	<1–29
Seeded herbal (weak cannabis)	3.5	1.8–5.7

Abbreviations: Min–max = minimum–maximum; THC = tetrahydrocannabinol.

TABLE 2 Median percentage THC concentration in cannabis samples donated by participants.

Cannabis type	Median	Min–max
Strong cannabis (sinsemilla)	21.25	11.76–29.30
Hash or resin	24.98	6.84–37.22

Abbreviations: Min–max = minimum–maximum; THC = tetrahydrocannabinol.

Statistical analyses

Statistical analyses were conducted in R version 4.1.2, using the R Stats Package version 4.1.2 and following our pre-registered analysis plan [40]. We used Pearson's product–moment correlations to test the association between each of the exposure variables and the outcome variable. We used bootstrapping of 95% confidence

intervals (CIs) with 10 000 bootstrap re-samplings. This was performed using the package 'boot' version 1.3-28. This approach is based on re-sampling with replacement from the data creating an empirically generated sampling distribution, which allows estimating the sampling distribution of an estimator [41]. We present bias-corrected and accelerated bootstrap 95% CIs (95% BCaCI) as they correct for bias and skewness in the distribution of bootstrap estimates.

TABLE 3 Summary of participants demographics.

	Mean (SD)
Age (*n* = 132)	21.90 (5.32)
	n (%)
Gender (*n* = 132)	
Female	63 (47.7%)
Male	69 (52.3%)
Ethnicity (*n* = 132)	
White	86 (65.1%)
Mixed	21 (15.9%)
Asian	12 (9.1%)
Black	8 (6.1%)
Other	4 (3.1%)
Prefer not to say	1 (0.8%)
SES (*n* = 126)	
Mother's education below undergraduate degree	59 (46.8%)
Mother's education undergraduate degree or above	67 (53.2%)

Abbreviations: SD = standard deviation; SES = socio-economic status.

RESULTS

Participant characteristics

Data were available for 132 participants. Participants' demographics are presented in Table 3. Descriptive statistics for the exposures and outcomes are presented in Table 4.

EC-TLFB measures and THC-COOH

THC-COOH in urine was positively associated with self-reported past week frequency of cannabis use (r = 0.45, 95% BCaCI = 0.36–0.52). We also found a positive association between THC-COOH and both unaided self-reported (r = 0.50, 95% BCaCI = 0.25–0.70) and aided pictorial measures (r = 0.44, 95% BCaCI = 0.20–0.68) of amount of cannabis used in grams (Table 5).

TABLE 5 Association between frequency of use and grams of cannabis used and creatinine-normalized THC-COOH in urine.

Exposure (*n* = 132)	*r*	95% BCaCI
Frequency of use	0.44*	0.36, 0.52
Grams of cannabis (unaided self-report)	0.50*	0.25, 0.70
Grams of cannabis (pictorial aid)	0.44*	0.20, 0.68

Note: All predictors are past week measures.
Abbreviations: 95% BCaCI = 95% bias-corrected and accelerated bootstrap confidence interval; r = Pearson's correlation coefficient.
*P < 0.001.

TABLE 4 Descriptive statistics for the exposures and outcome.

	Mean	SD	Min–max
Predictors (*n* = 132)			
Frequency of use (days/week)	3.81	1.76	1.00–7.00
Grams of cannabis (unaided self-report)	3.08	4.41	0.0008–23.30
Grams of cannabis (pictorial aid)	1.51	2.39	0.02–15.60
Standard THC units (UK average, unaided self-report)	79.19	115.43	0.01–661.72
Standard THC units (UK average, pictorial aid)	40.03	66.89	0.32–443.04
Standard THC units (study average, unaided self-report)	134.42	194.80	0.04–1119.10
Standard THC units (study average, pictorial aid)	65.74	103.01	0.85–663.00
Outcome (*n* = 132)	**Mean**	**SD**	**Min–max**
THC-COOH	249.38	538.71	0.00–3660.19

Note: All predictors are past week measures. THC-COOH = creatinine corrected 11-nor-9-carboxy-tetrahydrocannabinol presented as nanograms of THC-COOH per milligram of creatinine. Standard THC units (UK average, unaided self-report) = measured using UK average concentrations of THC in cannabis [36] and unaided self-report measures of amount of cannabis used. Standard THC units (UK average, pictorial aid) = measured using UK average concentrations of THC in cannabis [36] and pictorial measures of amount of cannabis used. Standard THC units (study average, unaided self-report) = measured using average concentration of THC in cannabis samples donated by participants in this study and unaided self-report measures of amount of cannabis used. Standard THC units (study average, pictorial aid) = measured using average concentration of THC in cannabis samples donated by participants in this study and pictorial measures of amount of cannabis used.
Abbreviations: Min–max = minimum–maximum; SD = standard deviation.

TABLE 6 Association between THC units and creatinine-normalized THC-COOH concentration in urine.

Standard THC units (n = 132)	r	95% BCaCI
UK average, unaided self-report	0.52*	0.26–0.70
UK average, pictorial aid	0.41*	0.18–0.65
Study average, unaided self-report	0.49*	0.23–0.70
Study average, pictorial aid	0.45*	0.21–0.68

Note: Standard tetrahydrocannabinol (THC) units (UK average, unaided self-report) = measured using UK average concentrations of THC in cannabis [36] and unaided self-report measures of amount of cannabis used. Standard THC units (UK average, pictorial aid) = measured using UK average concentrations of THC in cannabis [36] and pictorial measures of amount of cannabis used. Standard THC units (study average, unaided self-report) = measured using average concentration of THC in cannabis samples donated by participants in this study and unaided self-report measures of amount of cannabis used. Standard THC units (study average, pictorial aid) = measured using average concentration of THC in cannabis samples donated by participants in this study and pictorial measures of amount of cannabis used.
Abbreviations: 95% BCaCI = 95% bias-corrected and accelerated bootstrap confidence interval; r = Pearson's correlation coefficient.
*P < 0.001.

Standard THC units and THC-COOH concentration in urine

All measures of standard THC units were positively associated with THC-COOH concentration in urine (Table 6). The strongest association with THC-COOH was found for standard THC units estimated using unaided self-report grams of cannabis and average THC concentrations in the cannabis samples in the UK (r = 0.52, 95% BCaCI = 0.26–0.70). However, all measures of standard THC units show overlapping bootstrap confidence intervals.

DISCUSSION

In this study we present the EC-TLFB, which allows for a detailed assessment of cannabis use, including standard THC units. We validated these self-report assessments of cannabis use with an objective biological measure of THC exposure, levels of creatinine-normalized THC-COOH in urine. Overall, the strongest relationship, with a large effect size (r = 0.52), was for standard THC units measured using UK average concentrations of THC in cannabis [36] and unaided self-report measures of amount of cannabis used in grams. These methods (using average THC concentrations from previously published studies, and self-reported grams) were also less resource-intensive than other methods used (e.g. THC concentrations from self-donated cannabis and pictorial prompts to estimate grams). This suggests that, overall, they may be the most helpful methods to use when enhancing the TLFB due to a limited increase in resource intensity and similar (or better) validity assessed using urinary THC-COOH. However, the way in which the EC-TLFB is used should depend upon the resources available, the objectives of the study and the context in which the study is conducted. Overall, the EC-TLFB provides a valid tool for assessment of standard THC units, in line with US National Institutes of Health guidance for investigators assessing and reporting research using standard THC units [25].

Participants provided higher estimates for unaided self-reported grams of cannabis used (mean = 3.08) compared to when reported using pictorial prompts (mean = 1.51). Previous studies have reported overestimates in self-report amounts of cannabis added to methods of administration by cannabis users [42, 43]. In this study, bootstrap CIs for both unaided and aided measures are wide and overlapping. Further work is needed to understand more clearly the accuracy of unaided and aided self-report measures of measures of amounts of cannabis used.

We validated the EC-TLFB in the UK, using UK data on average concentrations of THC as well as data from cannabis samples donated from a subset of participants. We found that using data from average THC concentrations in published studies [36] can provide similar or better validity than average THC concentrations from cannabis samples donated by participants. This is encouraging, as it suggests that the EC-TLFB could be informed by estimates of THC concentrations from a range of countries in which such data are available [15]. However, only a small convenient sample of cannabis samples were collected from participants, and future studies with a larger sample size of participant-donated cannabis samples and/or data linkage between each participant's own cannabis sample and their EC-TLFB assessment may produce superior validation results to those produced here.

This study also had some limitations. The study included a sample size of 132 participants, which limits the power of the analysis we can conduct. The work would benefit from replication in larger samples. Another limitation is that we are not able to provide evidence for incremental validity in comparison to simpler measures of cannabis use. However, this study adds to the literature by presenting a version of the TLFB which can be used to calculate a novel and detailed measure of cannabis use, standard THC units and validating a range of cannabis exposures according to objective biological measures with medium to large effect sizes.

The EC-TLFB relies upon the typical consumption of cannabis over a certain period of time when considering the amount of cannabis added to a particular method of administration and amount consumed by the participant from that method of administration (versus shared with others). While this could reduce the situational accuracy of the EC-TLFB (as it does not ask for a daily input of amount and proportion of cannabis used), participants were able to adjust the amount added to a particular method and/or proportion consumed if it differed from what was already established as their typical amount in order to improve accuracy. Overall, this approach can be considered a pragmatic approach to maximizing precision of the EC-TLFB while reducing burden and participant fatigue.

We present further analysis, not included in our pre-registered analysis plan, investigating the association between single-item measures of frequency and amount of cannabis use and their correlation with EC-TLFB measures as well as THC-COOH in urine (Supporting information, Data S1, p. 24). As these measures do not cover the same

time frame we are not able to provide evidence for incremental validity, but the results suggest convergent validity. In addition, the results suggest some weak evidence that validity might be slightly improved with use of the EC-TLB measure in comparison to a single-item measure of frequency of use, and that the EC-TLFB may improve validity when measuring amount of cannabis used. Replicating these results with a larger sample size might result in the narrowing of CIs and stronger evidence.

In addition, the present work is not seeking to replace single-item measures; rather, it provides a method to obtain and calculate detailed, setting-specific measures. The use of a simpler measure or a more complex and time-consuming measure such as the EC-TLFB should be dependent upon, for example, study design and resources available. While in some cases it will be more appropriate to use a single-item measure of cannabis use, in other cases more detailed information is necessary. This is explained further by the framework of the iCannToolKit [3], achieved by expert consensus, which recommends a three-layered hierarchical pyramid. Each of these layers reflects different levels of measurements as well as ease and cost of implementation. At the base of the pyramid there are simple measures that quantify self-reported cannabis use, while at the mid-layer there are setting-specific measures which are able to quantify cannabis in more detail, such as the TLFB; at the top layer there are biological measures, such as THC-COOH in urine, used in this study to validate the EC-TLFB [3].

The analysis in this study focused upon validation of EC-TLFB measures that should be associated with THC-COOH. Due to the elimination time course of THC-COOH we validated the EC-TLFB estimates during the past 7 days [28]. However, the EC-TLFB tool was administered over a longer time period in this study (past 3 months of use), with good acceptability and feasibility in this population reported in previous studies [7]. Due to the context in which this study was conducted and the time frame of data collection of just 1 week, all participants used herbal cannabis. While herbal cannabis remains the most common type of cannabis products used in Canada and US states, where cannabis is legally sold [24], the use of processed products such as edibles and concentrates is more common in such markets than in illicit markets such as the UK. While the EC-TLFB already provides a method to measure these cannabis products and methods of administration, further refinement and validation of the EC-TLFB in different countries and regions would be valuable, particularly in legal markets where use of other products such as concentrates and edibles is more common. The EC-TLFB can also be used to collect data on other measures of interest that were not validated in this study (as they did not measure cannabis use); for example, concurrent and co-use of cannabis with tobacco [42].

CONCLUSIONS

In this study we presented and validated the EC-TLFB as a comprehensive tool for detailed and standardized assessment of cannabis use in the UK. The measures presented in this study show strong associations with creatinine THC-COOH in urine and offer a valid tool with which to assess standard THC units. Use of the EC-TLFB could improve the quality of cannabis use assessment across different settings.

AUTHOR CONTRIBUTIONS

Kat Petrilli: Conceptualization; data curation; formal analysis; investigation; methodology; writing—original draft; writing—review and editing. **Will Lawn**: Conceptualization; investigation; methodology; project administration; writing—review and editing. **Rachel Lees**: Conceptualization; investigation; methodology; data curation; writing—review and editing. **Claire Mokrysz**: Conceptualization; funding acquisition; methodology; project administration. **Anya Borissova**: Conceptualization; investigation. **Shelan Ofori**: Conceptualization; investigation; writing—review and editing. **Katie Trinci**: Conceptualization; investigation; writing—review and editing. **Renato dos Santos**: Investigation. **Harry Leitch**: Conceptualization; investigation. **Shilpa Soni**: Conceptualization; investigation. **Lindsey A. Hines**: conceptualization; methodology; supervision. **Valentina Lorenzetti**: Conceptualization; methodology; writing—review and editing. **H. Valerie Curran**: Conceptualization; funding acquisition; methodology; project administration; writing—review and editing. **Tom P. Freeman**: Conceptualization; funding acquisition; methodology; project administration; supervision; writing—review and editing.

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DECLARATION OF INTERESTS

None to declare.

DATA AVAILABILITY STATEMENT

Data sharing was not consented to by participants. These data are not open or publicly available. The data were collected by researchers at the Clinical Psychopharmacology Unit, University College London.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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