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Changes in delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: systematic review and meta-analysis

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ABSTRACT

Background and aims Cannabis products with high delta-9-tetrahydrocannabinol (THC) concentrations carry an increased risk of addiction and mental health disorders, while it has been suggested that cannabidiol (CBD) may moderate the effects of THC. This study aimed to systematically review and meta-analyse changes in THC and CBD concentrations in cannabis over time (PROSPERO registration: CRD42019130055). **Design** Embase, MEDLINE® and Epub Ahead of Print, In-Process and Other Non-Indexed Citations and Daily, Global Health, PsycINFO and Scopus were searched from inception to 27/03/2019 for observational studies reporting changes in mean THC and/or CBD concentration in cannabis over at least three annual time points. Searches and extraction were conducted by two independent reviewers. Random effects meta-regression models estimated annual changes in THC and CBD for each product within each study; these estimates were pooled across studies in random effects models. **Results** We identified 12 eligible studies from the USA, UK, Netherlands, France, Denmark, Italy and New Zealand. For all herbal cannabis, THC concentrations increased by 0.29% each year (95% CI: 0.11, 0.47), $P < 0.001$ based on 66747 cannabis samples from eight studies, 1970–2017. For cannabis resin, THC concentrations increased by 0.57% each year (95% CI: 0.10, 1.03), $P = 0.017$ based on 17 371 samples from eight studies, 1975–2017. There was no evidence for changes in CBD in herbal cannabis [−0.01% (95% CI: −0.02, 0.01), $P = 0.280$; 49434 samples from five studies, 1995–2017] or cannabis resin [0.03% (95% CI: −0.11, 0.18), $P = 0.651$; 11382 samples from six studies, 1992–2017]. Risk of bias was low apart from non-random sampling in most studies. There was evidence of moderate to substantial heterogeneity. **Conclusions** Concentrations of delta-9-tetrahydrocannabinol (THC) in international cannabis markets increased from 1970 to 2017 while cannabidiol (CBD) remained stable. Increases in THC were greater in cannabis resin than herbal cannabis. Rising THC in herbal cannabis was attributable to an increased market share of high-THC sinsemilla relative to low-THC traditional herbal cannabis.

Keywords Cannabis, Cannabis resin, CBD, potency, Sinsemilla, THC.

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INTRODUCTION

Concentrations of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) vary considerably across different cannabis products, which may have important health consequences for the consumer. THC acts as a partial agonist at cannabinoid type 1 receptors, which are densely located in reward, cognition, and habit-related brain circuits [1] and brain regions such as the hippocampus, amygdala, cerebellum, thalamus and basal ganglia [2]. CBD shows minimal direct activity at cannabinoid type 1 receptors but has a broad pharmacology including negative allosteric modulation of the cannabinoid type 1 receptor [3], inhibition of the reuptake and inhibition of anandamide [4], and

several other targets within and beyond the endocannabinoid system [5].

Human laboratory studies show that THC administration causes dose-dependent increases in intoxication, cognitive impairment, anxiety and psychotic-like symptoms [6,7]. As THC concentration varies in cannabis, people partially titrate their THC consumption by adapting their smoking behaviour (e.g. by adjusting their inhalation volume or the amount they roll in 'joints') [8,9]. However, this does not fully compensate for differences in THC concentrations and as a result, increasing concentrations of THC in cannabis deliver higher doses of THC to the consumer. In terms of long-term effects, use of high THC products is associated with an increased severity of cannabis use disorder symptomology [10–13] and elevated risk of psychotic disorders [14,15]. Following a first-episode of psychosis, frequent use of high THC products is associated with an increased risk of relapse, shorter latency to relapse, a greater number of relapses, and more intensive psychiatric care [16]. Increases in THC concentrations at the population level have been associated with a faster latency to develop symptoms of problematic cannabis use [17] and increases in the treated incidence of both cannabis use disorders [18] and first-episode psychosis [15].

THC and CBD production is determined by plant genetics, with three main chemotypes: high THC/low CBD, low THC/high CBD, or moderate THC/moderate CBD [19]. While the majority of cannabis products are obtained from high THC/low CBD chemotype plants to increase THC yields, some contain a balance of THC and CBD, such as cannabis resin produced from mixed chemotypes in traditional landrace crops [20,21]. When cannabis contains a combination of THC and CBD, CBD may moderate the effects of THC [22,23]. Findings from experimental studies have been mixed, but some studies have found that CBD reduced the acute effects of THC on psychotic-like symptoms, anxiety, reward, and emotional processing [24].

A relatively new development is the emergence of low THC/high CBD products which may circumvent drug control laws due to their low THC concentrations [25]. When administered alone, CBD is not intoxicating at typical doses [26] and is not associated with a risk of dependency [27]. CBD has generated considerable interest for its potential medicinal uses [28] including the treatment of psychosis [29,30] and addiction [31,32]. However, these effects are dose-dependent [31] and the doses tested in clinical trials are considerably higher than those in commercial CBD products [28].

Because of their dose-related effects, information on THC and CBD concentrations can provide important information about the possible health effects of cannabis. Current evidence-based Lower Risk Cannabis Use Guidelines [33] recommend that consumers should choose products with low concentrations of THC or a balanced level of THC and CBD. As information on THC and CBD concentrations is not available to consumers in most jurisdictions, monitoring studies provide an essential tool for assessing the possible health effects of different products and how they change over time.

Studies investigating changes in THC and CBD in cannabis have typically been country-specific [34–45]. We are aware of only one systematic review and meta-analysis of international studies [46]. That study found evidence for increases in THC concentrations (% by weight) in herbal cannabis of 0.21% each year (95% CI 0.16, 0.27). As that study used data from 1970 to 2009, more recent estimates are warranted. Furthermore, this previous systematic review and meta-analysis [46] only included data for herbal cannabis, with no estimates for cannabis resin. Cannabis resin forms an important component of the cannabis market and has changed significantly in recent years [47]. Furthermore, no previous systematic reviews or meta-analyses have quantified changes in CBD in cannabis. The aims of this study were to systematically review and meta-analyse changes in concentrations of THC (primary aim) and CBD (secondary aim) in cannabis over time.

METHODS

Protocol and registration

This systematic review and meta-analysis was registered on PROSPERO: CRD42019130055. It was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Supplementary Table S1).

Eligibility criteria

Studies were included if they met the following inclusion criteria (a) Observational study (b) Providing data on mean concentrations of THC and/or CBD in cannabis (c) Mean THC and/or CBD concentrations reported over at least three annual time points. In contrast to a previous meta-analysis [46] which permitted inclusion of individual data points collected from a single time and region, we required a minimum of three annual time points from the same study. This criterion was chosen because estimates of change can be more reliable when estimated within the same study, as data are typically collected from the same region, using the same sampling methodology and analytical protocol. A minimum of two time points was initially planned, but this was adjusted to three time points in order to permit within-study meta-regression analysis. Studies were excluded if they did not report original data.

Information sources and search

A systematic search was performed by two independent reviewers using the following electronic databases: Embase, MEDLINE® and Epub Ahead of Print, In-Process and Other Non-Indexed Citations and Daily, Global Health, PsycINFO and Scopus, from inception to 27/03/2019. We did not include a specific date restriction, and as result our search returned some early abstracts (i.e. published before 1980) for which full texts were not available on any online database and therefore could not be accessed (see Fig. 1). We used the following key words, with truncations (*) and Boolean operators (in parentheses) for the search: cannabis (or) marijuana (or) hash* (or) resin (or) sinsemilla (and) potenc* (or) concentration* (or) content* (or) percent* (and) *thc (or) *tetrahydrocannabinol (or) cannabinoid (or) cbd (or) cannabidiol. Searches were limited to peer-reviewed papers and no language or publication date restrictions were imposed.

Study selection

Studies were screened by two independent reviewers, using a title-only first method [48]. Each study was rated for eligibility as 'Yes', 'No', or 'Ambiguous' across three stages. In the title-only search, studies that received two 'Yes' ratings were included for full text search, studies receiving two 'No' ratings were excluded, and any other combination of 'Yes', 'No', or 'Ambiguous' ratings resulted in title and abstract search by both reviewers. All studies that did not receive two 'No' ratings in the title and abstract search were selected for full-text search by both reviewers, where final eligibility was determined and specific reasons for exclusion were reported. Any discrepancies were discussed and resolved by mutual consent.

Data collection process

Data were extracted independently and uniformly by two researchers using a standardised and pre-piloted extraction template. The following data were extracted: First author, publication year, region, sampling method, mean (standard deviation; SD) and sample size for THC concentration separately for each type of cannabis at each time point and mean (SD) and sample size for CBD concentration separately for each type of cannabis at each time point. If articles did not provide all of these data – or other data which we could use to determine these data (e.g. we

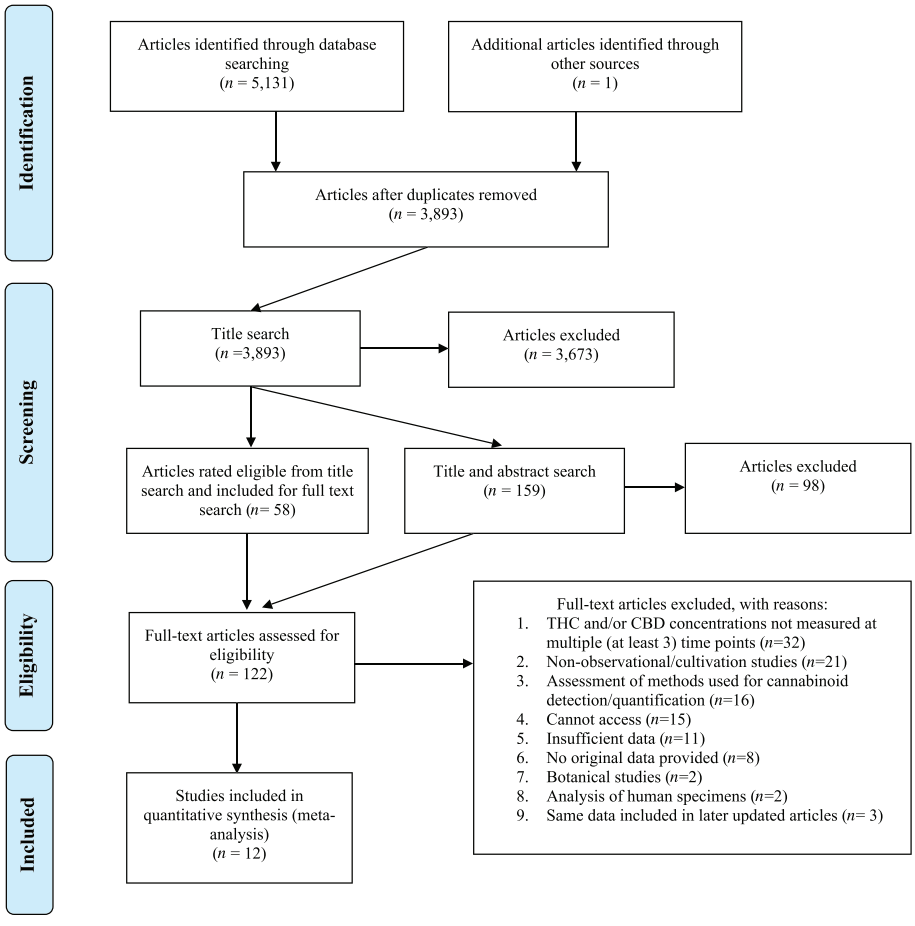


Figure 1 PRISMA flowchart outlining the study selection process. [Colour figure can be viewed at wileyonlinelibrary.com]

calculated SDs if articles only reported means with standard errors (SEs) and sample sizes) – but otherwise met the inclusion criteria, we contacted the corresponding author and requested the required data. Only articles for which all of the required data could be obtained were included.

Risk of bias

We searched for suitable risk of bias assessments using information in the Cochrane handbook [49], the National Institute of Health, systematic reviews and journal articles [50]. Several tools were identified but none were deemed suitable for this systematic review which focused on observational non-human studies. We designed a review-specific risk of bias assessment. For each study risk of bias was assessed across four different criteria, with ratings stratified according to cannabinoid (THC or CBD) and cannabis product: sampling method (low risk = randomised, high risk = non-random); minimum sample size per measurement (low risk = ≥19, high risk = <19; based on a power calculation for detecting annual changes in THC concentrations [40]), location of sampling (low risk = consistent across measurement points, high risk = not consistent across measurement points) and analytical protocol (low risk = consistent across measurement points, high risk = not consistent across measurement points). The assessment was conducted by a single researcher and any criterion that could not be determined was rated as 'unclear risk of bias'. We summarised risk of bias in individual studies to assess the risk of bias across studies.

Data analysis

Analyses were conducted using Stata (version 15.1 [51]). Firstly, to calculate a standardised effect estimate for each year of data collection within each study, we calculated the inverse-variance weighted mean difference (WMD) (and standard error; SE) in THC and CBD concentrations between the study's first and each subsequent year of data collection. Then to estimate the overall effect size for each study, these were then individually entered as dependent variables in within-study random effects meta-regression models (Stata command 'metareg'; [52]) with year of data collection fitted as a linear trend, to estimate annual changes in THC or CBD (+/− 95% Confidence Interval; CI). This approach is closely related to the between-effects estimator in a random effects regression model for panel data, but is more appropriate when data for each unit are summarized using an effect estimate (and its SE). Importantly, this approach allowed us to account for differences in sample sizes between years of data collection and incorporate residual heterogeneity by fitting each year as a random effect. Analyses were stratified by cannabis type where data were available as follows: 1) all herbal cannabis (unspecified herbal cannabis, or combining sinsemilla, traditional herbal cannabis and/or other herbal products such as 'ditchweed'), 2) sinsemilla, 3) traditional herbal cannabis and 4) cannabis resin or 'hashish'). Next, these study-specific estimates were pooled across all available studies in random effects models using inverse variance weighting (Stata command 'metan'; [53]). The proportion of variation attributable to heterogeneity was estimated using the I^2 statistic, with interpretation guided by the Cochrane handbook [49].

RESULTS

Study selection

Study selection is shown in the PRISMA flowchart (Fig. 1). After deduplication, a total of 3893 articles were identified, screened and assessed for eligibility, with 122 selected for full text search. A total of 12 [34–45] articles met the inclusion criteria, with data collected in the USA [34, 35, 37, 38, 43], UK [41], Netherlands [39,40], France [36], Denmark [45], Italy [44] and New Zealand [42], spanning 1970–2017.

Study characteristics

The majority of articles reported data on samples of seized illicit material, though two studies from the Netherlands [39,40] obtained cannabis samples by direct purchase from retail outlets using a randomised sampling method. All 12 studies reported eligible data on THC whilst five studies [34–37,45] reported eligible data on CBD. Several studies [35,37,38,43] reported data on samples received from the same source (federal seizures from the Drug Enforcement Agency in the USA). Although these studies used different sampling procedures, the time period covered by them overlapped in some cases. In order to ensure there was no duplication of data during overlapping years, we only presented and analysed data from the most recently published study, and omitted data from any other studies during these overlapping time points. Notably, 3 studies [35,37,40] provided THC data for sinsemilla, traditional herbal cannabis and all herbal cannabis. Therefore, some data overlapped across (but not within) these stratified analyses. Due to limited data on CBD in different herbal cannabis products and the absence of overlapping data, CBD data for herbal cannabis (all herbal cannabis, sinsemilla and traditional herbal cannabis) were combined into a single random effects meta-regression model. Further study characteristics are provided in Supplementary Table S2 for studies providing data on changes in THC, and in Supplementary Table S3 for studies providing data on changes in CBD.

Changes in THC concentrations over time

All herbal cannabis

Data from 66747 cannabis samples from seven studies were included in analysis of all herbal cannabis from 1970 to 2017. Mean (SE) concentrations of THC in individual studies are shown in Fig. 2 and the results of within-study random effects meta-regressions are shown in Fig. 3. The pooled estimate including data from the USA [34,35,37,43], UK [41], Italy [44] and New Zealand [42] indicated that THC concentrations increased by 0.29% each year (95% CI: 0.11, 0.47), $P < 0.001$, Fig. 3. There was a considerable level of estimated heterogeneity across studies ($I^2 = 94.2\%$).

Sinsemilla

Data from 15882 samples of sinsemilla from five studies were analysed from 1986 to 2017. Mean (SE) concentrations of THC in individual studies over time are shown in Supplementary Fig. S1 and the results of within-study random effects meta-regressions are shown in Supplementary Fig. S2. One study [40] reported a very large increase in THC of 3.11% per year (95% CI: 2.06, 4.17) in the Netherlands from 2000–2004 [40]. However, the pooled estimate across all data from studies in the USA [35,37], Netherlands [39,40] and New Zealand [42] did not provide evidence for a change in THC concentrations over time, with an estimate of 0.26% each year (95% CI: −0.09, 0.61), $P = 0.141$, Supplementary Fig. S2. There was a substantial level of estimated heterogeneity across studies ($I^2 = 89.4\%$).

Traditional herbal cannabis

A total of 28418 traditional herbal cannabis samples from five studies were analysed from 1986 to 2017. Mean (SE) concentrations of THC in individual studies over time are shown in Supplementary Fig. S3 and the results of within-study random effects meta-regressions are shown in Supplementary Fig. S4. The pooled estimate across all studies including data from the USA [35,37], Netherlands [39, 40] and New Zealand [42] did not provide evidence for changes in THC concentrations over time, with an estimate of 0.17% each year (95% CI: −0.02, 0.36), $P = 0.079$, Supplementary Fig. S4. There was a moderate level of estimated heterogeneity across studies ($I^2 = 48.1\%$).

Cannabis resin

THC data were available for a total of 17371 cannabis resin samples from eight studies from 1975 to 2017. Mean (SE) concentrations of THC in individual studies over time are shown in Fig. 4 and the results of within-study random effects meta-regressions are shown in Fig. 5. The pooled estimate including studies from the USA [35, 38], UK [41], Netherlands [39,40], France [36], Denmark [45] and Italy [44] indicated that THC concentrations in cannabis resin increased by 0.57% each year (95% CI: 0.10, 1.03), $P = 0.017$, Fig. 5. There was a substantial level of estimated heterogeneity across studies ($I^2 = 79.1\%$).

Changes in CBD concentrations over time

Herbal cannabis (all herbal cannabis, sinsemilla and traditional herbal cannabis)

CBD data from all herbal cannabis, sinsemilla and traditional herbal cannabis were combined into a single analysis. Data were available from a total of 49434 herbal cannabis samples (47622 all herbal cannabis samples, 1510 sinsemilla samples, 302 traditional herbal cannabis

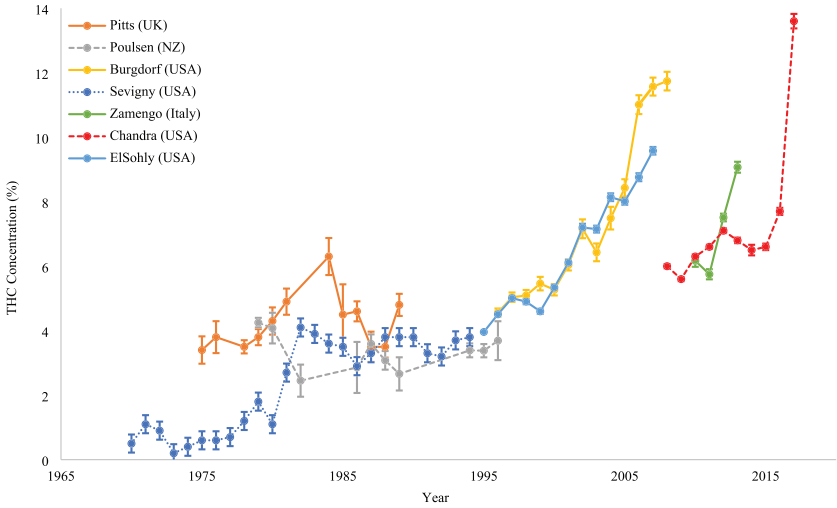
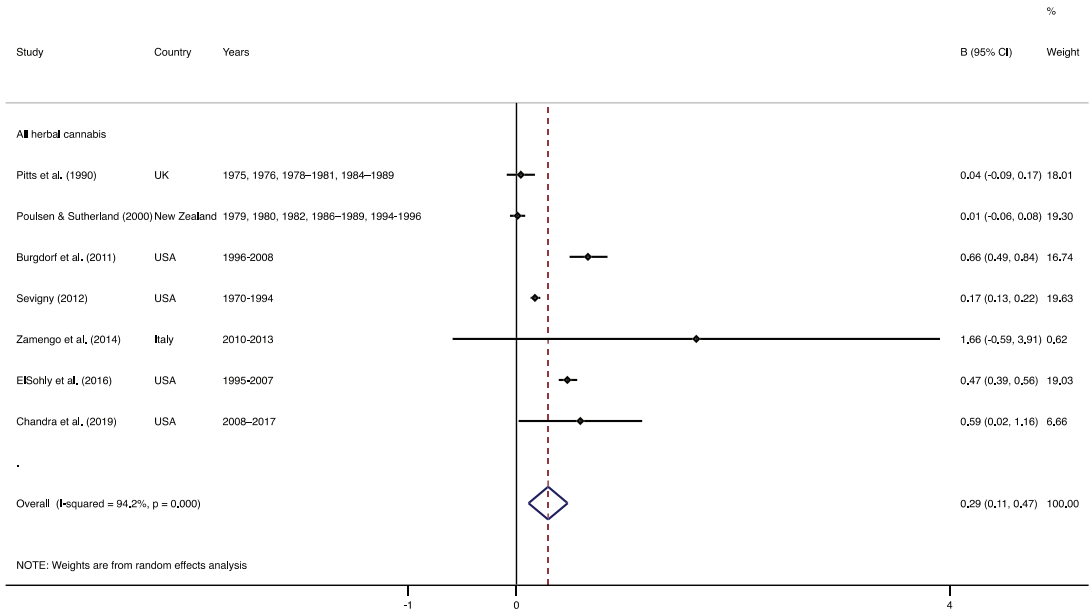


Figure 2 Mean (standard error) concentrations of delta-9-tetrahydrocannabinol (THC) in all herbal cannabis over time. [Colour figure can be viewed at wileyonlinelibrary.com]



B, Unstandardized meta-regression coefficients; 95% CI, 95% Confidence Intervals

Figure 3 Unstandardized meta-regression coefficients (95% Confidence Intervals) reflecting annual changes in delta-9-tetrahydrocannabinol (THC) concentrations for all herbal cannabis. Data show random effects meta-regression of individual studies, and overall random effects analysis pooled across all studies. [Colour figure can be viewed at wileyonlinelibrary.com]

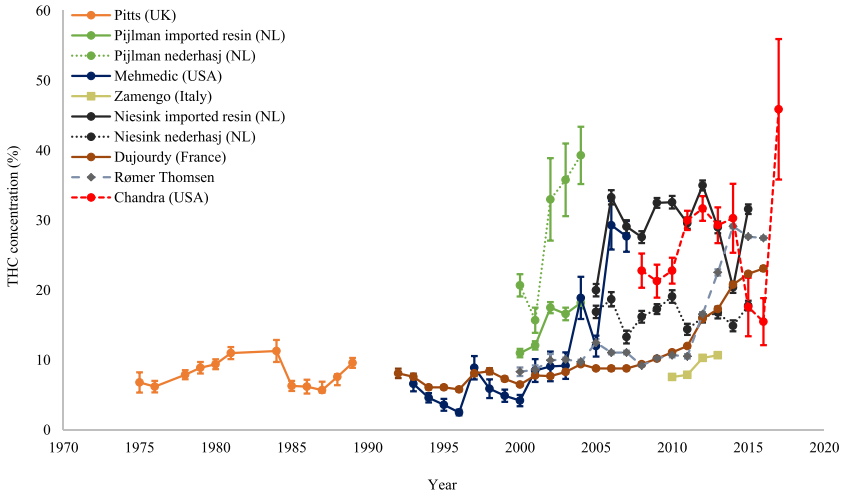


Figure 4 Mean (standard error) concentrations of delta-9-tetrahydrocannabinol (THC) in cannabis resin over time. [Colour figure can be viewed at wileyonlinelibrary.com]

samples) from five studies collected from 1995 to 2017. Mean (SE) concentrations of CBD in individual studies over time are shown in Supplementary Fig. S5 and the results of within-study random effects meta-regressions are shown in Supplementary Fig. S6. The pooled estimate across all studies [34,35,37,39,40] indicated that CBD concentrations did not change over time, with an estimate of −0.01% each year (95% CI: −0.02, 0.01), $P = 0.280$, Supplementary Fig. S6. There was a substantial level of estimated heterogeneity across studies ($I^2 = 66.0\%$).

Cannabis resin

Data on CBD concentrations were available from 11 382 cannabis resin samples from six studies collected from 1992 to 2017. Mean (SE) concentrations of CBD in individual studies over time are shown in Supplementary Fig. S7 and the results of within-study random effects meta-regressions are shown in Supplementary Fig. S8. The pooled estimate across all studies from the USA [35, 38] France [36] Denmark [45] and the Netherlands

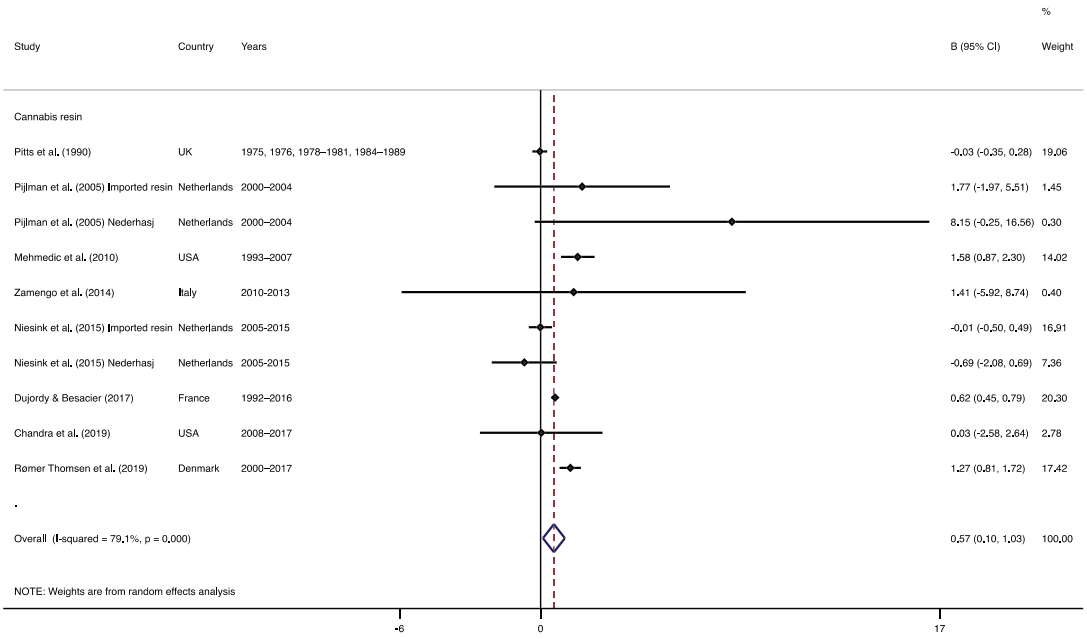


Figure 5 Unstandardized meta-regression coefficients (95% Confidence Intervals) reflecting annual changes in delta-9-tetrahydrocannabinol (THC) concentrations for cannabis resin. Data show random effects meta-regression of individual studies, and overall random effects analysis pooled across all studies. [Colour figure can be viewed at wileyonlinelibrary.com]

[39, 40] provided no evidence for a change in CBD, with an estimate of 0.03% each year (95% CI: −0.11, 0.18), $P = 0.651$, Supplementary Fig. S8. There was a substantial level of estimated heterogeneity across studies ($I^2 = 82.6\%$).

Risk of bias

Risk of bias ratings are shown in Supplementary Fig. S9. Only 2 studies [39, 40] which used randomised sampling from retail outlets, showed low risk of bias across all criteria for any product category. All other studies used a non-random sampling method (e.g. law enforcement seizures). The majority of studies had a mean of at least 19 samples per year across all categories, though some studies [39–42] (and [45] for CBD only) did not meet this criterion for at least one product category. All studies were rated as having low risk of bias for using consistent analytical procedures (with the exception of one study [34] for which this information was not reported, and thus risk of bias was unclear). All studies were rated as having a low risk of bias for using a consistent location of sampling across measurement points.

DISCUSSION

This systematic review and meta-analysis included data on THC and CBD concentrations in cannabis from 12 studies in the USA, UK, Netherlands, France, Denmark, Italy and New Zealand, spanning 1970–2017. We conducted random effects meta-regression models to quantify annual changes in THC and CBD concentrations within each of these studies. We then pooled these estimates from all international studies in random effects models. Our findings indicate that for all herbal cannabis, THC concentrations increased by approximately 0.29% each year from 1970 to 2017. For cannabis resin, THC concentrations increased by approximately 0.57% each year from 1975 to 2017.

In the context of typical use, our findings suggest that the quantity of THC in a typical gram of cannabis rose by 2.9 milligrams each year for all herbal cannabis, and by 5.7 milligrams each year for cannabis resin. These annual increases in milligrams of THC per gram of cannabis are in the range of low single doses that can produce mild intoxication, similar to a 'Standard THC Unit' of 5 milligrams [54]. The effects of acute THC are dose-dependent [6,7] and exposure to increasing doses of THC over time could increase long-term health risks such as severity of cannabis use disorders [10–13] risk of developing psychosis [14,15] and risk of relapse in people with psychosis [16]. Changes in THC concentrations over time could also influence the efficacy and safety of cannabis used for medicinal purposes [28], in the absence of standardised dosing information for illicit cannabis products.

A strength of our systematic-review and meta-analysis was the stratification of analysis based on cannabis type. In addition to separate analyses for all herbal cannabis and cannabis resin, we also conducted separate analyses for

specific types of herbal cannabis. These stratified analyses did not provide evidence for changes in THC concentrations over time in either high THC cannabis (sinsemilla) or low THC cannabis (traditional herbal cannabis). Although these analyses contained a smaller number of studies and cannabis samples, they suggest that the increase we found for THC in all herbal cannabis was attributable to changes in the relative market share of different herbal products (i.e. more high-THC sinsemilla relative to low-THC traditional herbal) rather than substantial changes within these specific types.

Analyses of CBD concentrations did not show any changes in either herbal cannabis or cannabis resin. Overall, concentrations of CBD were very low in herbal cannabis but were generally higher in cannabis resin. Increases in THC alongside stable CBD in cannabis resin may be attributable to the inclusion of greater plant material from high THC/low CBD plants relative to traditional mixed chemotype crops [55,56]. However, the comparatively smaller number of studies providing eligible CBD data suggests that these findings should be interpreted more cautiously than those for THC. Although THC was the primary cannabinoid of interest in this systematic review and meta-analysis, monitoring CBD should be encouraged to provide a comprehensive assessment of the possible health effects of cannabis [56]. This is especially important now due to the emergence of high CBD/low THC products in some jurisdictions.

Strengths of this systematic review include its PROSPERO registration, use of PRISMA reporting guidelines, and two independent reviewers for searches and data extraction. To our knowledge, this is the second meta-analysis of changes in THC in cannabis, the first meta-analysis of changes in CBD in cannabis, and the first to stratify analyses according to different types of cannabis product. All papers were peer-reviewed and risk of bias was typically low. We only included studies with a minimum of three time points to reliably estimate changes in THC or CBD concentrations within each study. All studies used a consistent sampling region across measurement points, and all studies (apart from one with unclear risk of bias) used a consistent analytical protocol across time points. The majority of studies were rated as adequately powered to detect annual changes in THC or CBD.

However, a common source of bias was the use of non-random sampling methods (e.g. due to law enforcement). Data were included from a range of countries (USA, UK, Netherlands, France, Denmark, Italy and New Zealand) providing internationally relevant estimates, but these should not be interpreted as globally representative. In particular, a greater number of samples were included from the USA compared to other countries. Additionally, we used the mean and standard error to estimate annual changes in CBD. This differs from original papers presenting the median [39, 40] and may have biased our estimates. We analysed our data using time fitted as a linear trend to estimate annual changes in THC and CBD; non-linear trends were not estimated (see Figs. 2, 4, S1, S3, S5, S7). Our results should be interpreted with consideration of evidence for moderate to substantial levels of heterogeneity. For example, there was substantial heterogeneity across studies for changes in THC in sinsemilla, with one study [40] showing a substantial increase contrasting with the other included studies. It should also be noted that due to the small number of studies and unbalanced sample sizes, heterogeneity statistics may be biased [57].

Although heterogeneity in individual studies can influence interpretation of pooled estimates, it can also indicate important country- and time- specific findings, which we quantified for the first time using random effects meta-regression models within each study and cannabis type. Additionally, data from recently established legal cannabis markets could not be included due the limited duration of data available at present. Initial studies have documented substantial rises in THC concentrations in legal cannabis markets [58,59] highlighting the need for continued monitoring in this area.

In conclusion, concentrations of THC have continued to increase in herbal cannabis and cannabis resin. Increases in THC were greatest in cannabis resin whilst increases in herbal cannabis are primarily attributable to a greater market share of high-THC varieties such as sinsemilla. Concentrations of CBD remained stable in both herbal cannabis and cannabis resin. Increases in THC concentrations have important implications for the health effects of cannabis.

Declaration of interests

No authors report any declarations of interest. This study was funded by a Senior Academic Fellowship from the Society for the Study of Addiction awarded to TF. The funder had no role in the study design, data analysis, interpretation, writing of the report or the decision to submit for publication.

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Author contributions

Tom Freeman: Conceptualization; funding acquisition; investigation; methodology; project administration; supervision. **Sam Craft:** Data curation; formal analysis; investigation; methodology. **Jack Wilson:** Data curation; invetigation; methodology. **Stephan Stylianou:** Investigation; methodology. **Mahamoud El Sohly :** Supervision. **Marta Di Forti:** Supervision. **Michael Lynskey:** Methodology; project administration; supervision.

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[Correction added on 6 December 2020, after first online publication: Production errors in a citation and contact details were corrected in this version]

Supporting Information

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

Table S1 PRISMA Checklist.
Table S2 Characteristics of studies providing data on changes in delta-9-tetrahydrocannabinol (THC) over time.
Table S3 Characteristics of studies providing data on changes in cannabidiol (CBD) over time.
Figure S1 Mean (standard error) concentrations of delta-9-tetrahydrocannabinol (THC) in sinsemilla.

Figure S2 Unstandardized meta-regression coefficients (95% Confidence Intervals) reflecting annual changes in delta-9-tetrahydrocannabinol (THC) concentrations for sinsemilla. Data show random effects meta-regression of individual studies, and overall random effects analysis pooled across all studies.

Figure S3 Mean (standard error) concentrations of delta-9-tetrahydrocannabinol (THC) in traditional herbal cannabis.

Figure S4 Unstandardized meta-regression coefficients (95% Confidence Intervals) reflecting annual changes in delta-9-tetrahydrocannabinol (THC) concentrations for traditional herbal cannabis. Data show random effects meta-regression of individual studies, and overall random effects analysis pooled across all studies.

Figure S5 Mean (standard error) concentrations of cannabidiol (CBD) in all herbal cannabis, sinsemilla and traditional herbal cannabis.

Figure S6 Unstandardized meta-regression coefficients (95% Confidence Intervals) reflecting annual changes in cannabidiol (CBD) concentrations in all herbal cannabis. Data show random effects meta-regression of individual studies, and overall random effects analysis pooled across all studies.

Figure S7 Mean (standard error) concentrations of cannabidiol (CBD) in cannabis resin.

Figure S8 Unstandardized meta-regression coefficients (95% Confidence Intervals) reflecting annual changes in cannabidiol (CBD) concentrations in cannabis resin. Data show random effects meta-regression of individual studies, and overall random effects analysis pooled across all studies.

Figure S9 Risk of bias assessment.