

SYSTEMATIC REVIEW

Adverse events caused by cannabinoids in middle aged and older adults for all indications: a meta-analysis of incidence rate difference

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Abstract

Background: Cannabinoid-based medicines (CBMs) are being used widely in older people. However, information on the incidence of adverse events (AEs) is limited.

Objective: To quantify the incidence rate difference (IRD) of AEs in middle aged and older adults of age ≥ 50 years receiving CBMs and also examine associations with weekly doses.

Design: Systematic review and meta-analysis.

Data sources: MEDLINE, PubMed, EMBASE, CINAHL, PsychInfo, Cochrane Library and [ClinicalTrials.gov](https://clinicaltrials.gov) (1st Jan 1990–12th June 2023).

Methods: We included randomised clinical trials (RCTs) using CBMs with mean participant age ≥ 50 years for medicinal purposes for all clinical indications. Paired reviewers independently screened studies, extracted data and appraised risk of bias. We estimated pooled effect-sizes IRD under the random-effects model.

Results: Data from 58 RCTs (37 moderate-high quality studies, pooled $n = 6611$, mean age range 50–87 years, 50% male, $n = 3450$ receiving CBMs) showed that compared with controls, the incidence of all-cause and treatment-related AEs attributable to delta-9-tetrahydrocannabinol (THC)-containing CBMs were: THC alone [IRD:18.83(95% Confidence Interval [CI], 1.47–55.79) and 16.35(95% CI, 1.25–48.56)] respectively; THC:cannabidiol (CBD) combination [IRD:19.37(95% CI, 4.24–45.47) and 11.36(95% CI, 2.55–26.48)] respectively. IRDs of serious AEs, withdrawals and deaths were not significantly greater for CBMs containing THC with or without CBD. THC dose-dependently increased the incidence of dry mouth, dizziness/lightheadedness, mobility/balance/coordination difficulties, dissociative/thinking/perception problems and somnolence/drowsiness. The interaction of weekly THC:CBD doses played a role in mostly neurological, psychiatric and cardiac side-effects.

Conclusions: Although CBMs in general are safe and acceptable in middle aged and older adults, one needs to be mindful of certain common dose-dependent side-effects of THC-containing CBMs.

Keywords: cannabinoid-based medication; delta-9-tetrahydrocannabinol (THC); cannabidiol; adverse events; middle aged and older adults; systematic review; older people

Key Points

- There is a particular need to quantify risk of various adverse events (AEs) with use of cannabinoid-based medicines (CBMs) in older people.
- We examined incidence rate differences of AEs in middle aged and older adults receiving CBMs for all conditions.
- Delta-9-tetrahydrocannabinol (THC) containing CBMs were associated with gastrointestinal, neurological and psychiatric side-effects in a dose-related manner.

- Cumulative weekly doses of delta-9-THC and CBDs played a role in mostly neurological, psychiatric and cardiac side-effects.
 - We present age-specific safety/tolerability information about cannabinoids that is critical to prescribing in older people.
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Introduction

Cannabinoid-based medicines (CBMs) are increasingly being used in the older people, a fast-growing segment of the population [1, 2]. The term cannabinoid generally refers to chemicals that have a certain (terpenophenolic) structure, which are naturally present in the extract of the cannabis plant (when they are also known as phytocannabinoids) or may have a synthetic origin. Out of 150 cannabinoids in the cannabis plant, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are commonly used for medicinal purposes with a range of reported benefits [3–6].

For any novel treatment, safety and tolerability must be weighed up against clinical benefits to inform their use in different contexts. This is of particular importance in middle aged and older adults, who often have various comorbid health conditions requiring treatments that may interact with any additional treatment being prescribed. They are also more sensitive to side-effects of medications than many other demographic groups. With growing usage of CBMs, there is a particular need therefore to quantify the risk of various adverse events (AEs) associated with CBM use, so as to enable informed risk–benefit analysis during clinical use. However, to the best of our knowledge there is limited evidence in this regard. Although, a number of randomised clinical trials (RCTs) of CBMs have been carried out, the sample sizes of these RCTs on their own are underpowered to systematically and meaningfully estimate the risk of individual AEs. Against this background and in the absence of large-scale population level pharmaco-vigilance data which will only accrue over time, meta-analytic pooling of incidence rate data of individual AEs across placebo-controlled RCTs allows the best estimate of risk associated with CBM treatments based on available evidence. By estimating difference in the incidence rate between the CBM and control intervention arms, such evidence can help understand the additional risk of AEs associated with CBM use. A number of previous reviews [7–10] have examined whether CBMs are associated with greater risk (either as odds or risk ratios or incident rate ratios) of side-effects and reported them as ratios. However, estimates of relative effect such as these do not lend themselves as easily to use in a clinical context unless the risk in the control group is readily known. Incident rate difference (IRD), which in this context refers to the additional risk of AEs estimated as the number of events per person-years of exposure associated with CBM use over and above a control intervention may be more easily understood but has not been systematically examined before. Another gap in current evidence relates to understanding about how the risk of AEs relate to the range of doses or ratio of doses used in formulations containing single or multiple cannabinoids respectively being used in the clinical settings.

With limited number of studies being available, there is a paucity of data for any clinical indication-specific dose–response relationships with regard to AEs (that may exist) to become easily apparent. Meta-analytic pooling of data therefore will allow for an estimation of the likelihood of such risks at different doses across clinical indications to inform clinicians and researchers. Such a detailed assessment may help inform use of CBM in older people, in whom certain side-effects may be more directly related to morbidity and even mortality. For example, dizziness, which may contribute to risk for falls in older people, can in turn result in serious injuries such as fractures, head injuries or accidental deaths [11, 12]. Furthermore, certain AEs and dose–response relationships may be systematically different between THC and THC:CBD formulations [8]. Therefore, the overarching objective of the present endeavour was to address these gaps in knowledge by conducting a search of evidence from placebo-controlled RCTs and systematically report the incidence rate of all individual AEs attributable to the use of different types of CBMs. Specifically, we aimed to quantify the IRDs of AEs in people receiving THC only and THC-CBD combination treatment in middle aged and older adults with mean age of 50 years and older. We also aimed to examine the association of AEs with the weekly doses of THC and CBD.

Methods

Search strategy and selection criteria

The review was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [13] and registered with PROSPERO (CRD42019148869). A detailed description of the bibliographic search strategy, as previously published, is presented in Supplementary Methods [8]. We identified studies published from 1 January 1990 up to 12 June 2023, from several electronic databases. Studies were independently assessed by pair of researchers (LV, KM, SP, MD) and disagreements resolved through consensus or discussions with senior researcher.

As described in our previous meta-analysis [8], studies were included if [1] published from 1990 onwards; [2] included middle aged and older adults (defined as mean age ≥ 50 years) or reported a distinct subgroup of middle aged and older adults and provided separate results for this subgroup; and [3] provided data on the safety and tolerability of medical cannabinoids administered by any route, at any dose, for any duration and for any indication. Studies were excluded if they [1] included exclusively younger subjects (≤ 50 years); [2] studied effects of cannabinoids for

recreational purposes or failed to provide the dosage of cannabinoids and [3] were not reported in English language. Here we focus on results from RCTs.

Data analysis

All relevant available data for examination of the safety and tolerability of different CBMs (THC:CBD combination or THC alone) was collected from eligible studies, complemented with information from www.ClinicalTrials.gov and we also contacted study authors to supplement information. Data were extracted for study design, participant characteristics, indication, dosage and duration of intervention, all cause and treatment-related AEs and serious AEs (SAEs), AE-related withdrawals and deaths. AEs and SAEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) 'system organ classes' (SOC). Data were extracted for the top five (as reported by each study) AEs for each SOC, where available. Withdrawals and deaths outcomes were extracted as reported in the studies from the text and tables for each treatment arm. Data extraction and coding was verified by a medically qualified researcher and discrepancies resolved following discussions with senior researcher. The disease conditions investigated were classified into broader subgroups for analysis purpose [8]. Overall quality of evidence was assessed using recommended criteria [14] and summarised to reflect confidence in estimates [15].

Pooled effect-sizes were estimated (as square root transformed incident rate difference; IRSD) if there were two or more RCTs within each group or sub-group under the random-effects model using the restricted maximum-likelihood estimator because of anticipated heterogeneity. For reporting purposes, IRSDs have been converted to IRDs for ease of understanding, unless otherwise specified. However, for dose-response relationships (as in Tables 2 and 4), we have reported the IRSD values to allow an interested reader to estimate the expected IRD for a particular dose of CBM and shown an example calculation in table footnotes. Doses of both THC and CBD were included separately, as well as their interaction as predictors, in the same regression model for studies using THC:CBD combinations (Table 4). For each category of intervention, analyses combined both parallel-arm and crossover RCTs, with the latter treated as parallel-arm design [16] for pooled analyses. We also report results by RCT design. In studies with more than one active treatment arm, each active arm was considered as a different study. Throughout the manuscript, results are reported for analyses treating all studies as independent. We investigated heterogeneity using forest-plots and the *QE* statistic (and its significance; *QEp*) and publication bias using Egger's regression test [17] and the 'Trim and fill' method [18]. Data for all clinical conditions were combined. We also examined the effect of treatment, design, clinical condition and weekly dose of THC and CBD and their interaction in THC:CBD combination studies using meta-regression except for the route of administration which was oral for all the included

studies. Statistical analyses were performed using the metafor package in R (version 3.6.3) [19].

Results

A total of 58 RCTs ($n = 6611$ participants; 1655.84 person-years of cannabinoid exposure) from 47 published articles were included (see Fig. 1, PRISMA flow chart for summary of study selection procedure and Supplementary Table 1a-b in the Supplementary Material for main study characteristics).

Supplementary Figures 1-7 (THC studies) and Figs 8-14 (THC: CBD combination studies) show the forest-plots and results stratified according to study design, for all cause and treatment-related AEs and SAEs, withdrawals, deaths, respectively.

Overall study quality (Grading of Recommendations Assessment, Development and Evaluation, GRADE) [15] is reported in Supplementary Table 1a and 1b. Risk of bias estimates are reported in Supplementary Figs 15(a,b) and 16(a,b). Sub-group meta-analysis at SOC level was done for systems with three or more AEs for THC (Supplementary Table 2a) and THC-CBD combination treatment (Supplementary Table 2b).

THC studies

In total, 31 RCTs (15 crossover and 16 parallel-arm) from 29 articles [20-48] (see Supplementary Table 1a in the Supplementary Material), reported on 1473 patients (analysed 1429; 1255.82 person-years; mean \pm SD: 40.51 \pm 181.32 person-years) on active and 1265 (analysed 1224) on control intervention, with mean reported ages across studies ranging from 50-87 years (males: 0-100%). All except four studies used placebo as control [20, 23, 32, 43].

Pooled IRDs for all cause ($k = 21$) and treatment-related AEs ($k = 9$) from all RCTs were 18.83 (95% Confidence Interval [CI], 1.47-55.79) and 16.35 (95% CI, 1.25-48.56) AEs per 1000 person-years, respectively. Pooled IRDs of the most commonly reported AEs (Table 1) suggested significantly higher incidence rate of dizziness/lightheadedness, somnolence/drowsiness, impaired mobility/balance/coordination, sedation, headache, dissociative/thinking/perception disorders, euphoria and dry mouth, amounting on average to an additional incidence of 0.819 (95% CI 0.489-1.232), 0.684 (95% CI 0.055-2.014), 0.078 (95% CI 0.006-0.234), 11.103 (95% CI 0.596-34.721), 5.287 (95% CI 0.191-17.324), 0.510 (95% CI 0.260-0.844), 9.117 (95% CI 0.765-26.669) and 1.059 (95% CI 0.346-2.161) per 1000 person-years respectively in active compared to control arms.

Meta-regression analyses suggested a significant association between cumulative THC dose per week across THC studies and incidence rate (expressed as IRSD) of some of the AEs (Table 2) such as dry mouth, dizziness/light-headedness, mobility/balance/coordination difficulties, dissociative/thinking perception and somnolence/drowsiness.

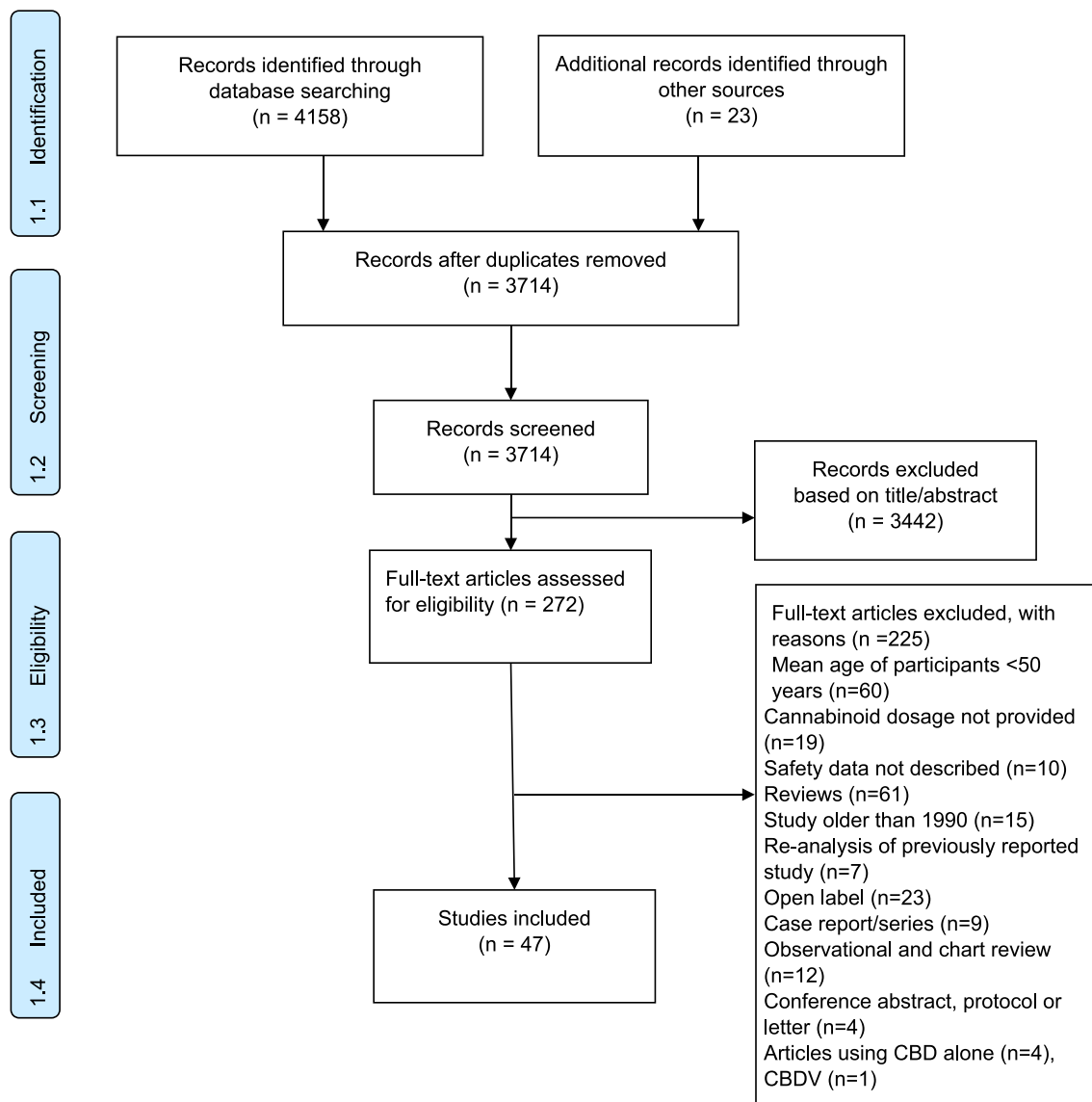


Figure 1. PRISMA flow diagram. In total, 58 studies were obtained from 47 papers, as in studies with more than one active treatment arm, each active arm was considered as a different study.

However, these estimates need to be interpreted with caution due to heterogeneity across the studies reporting the AEs.

Pooled IRDs for all cause ($k = 28$) and treatment-related ($k = 24$) SAEs from all RCTs were 0.002 (95% CI, 0.117–0.188) and 0.908 (95% CI, 0.05–4.54) SAEs per 1000 person years respectively. Pooled IRDs for all cause ($k = 14$) and treatment-related withdrawals ($k = 28$) from all RCTs were 0.052 (95% CI, 0.43–0.04) and 0.517 (95% CI, 0.01–2.34) withdrawals per 1000 person years respectively. IRDs for all cause deaths ($k = 31$) from all RCTs were 0.023 (95% CI, 0.002–0.012) deaths per 1000 person-years.

Neither Egger's test nor 'Trim and fill' method indicated publication or other selection bias for any of the other outcomes except for all cause AEs (Supplementary Figs 17a-f, 18a-f, 19a-e, 20a-c). For all cause AEs for all RCTs as outcome, Egger's test was $p = 0.0265$, and Trim and fill method

indicated one missing study. Meta-regression analyses indicated effects of clinical condition on estimated effect of THC treatment on all cause AEs, which seemed to be mainly related to a significantly lower estimated effect in crossover studies investigating neurodegenerative disorder ($p = 0.005$) patients compared to other conditions.

THC: CBD combination

A total of 27 studies (five crossover and 22 were parallel-arm; see Supplementary Table 1b in the Supplementary Material for additional details) from 22 articles [24, 26, 27, 31, 42, 49–64] reported on 1977 patients (analysed 1952; 400.02 person-years; mean \pm SD: 14.82 ± 27.71 person-years) on active and 1896 (analysed 1872) on placebo, with mean reported ages across studies ranging from 51

Table 1. Effect of cumulative THC treatment across studies expressed as incidence rate difference (IRD, indicated by the summary estimate) followed by 95% confidence intervals and associated *P* value for each type of adverse event.

MedDRA high-level grouping	Individual AE	Summary estimate	95% CI (lower, upper)	<i>P</i> value	N	Q	Qp
Blood/Lymphatic System	Anaemia	0.002	0.162, 0.230	0.863	16	2.105	1.000
Cardiac	Dyspnoea	0.002	0.159, 0.233	0.852	16	1.329	1.000
	Palpitation	0.000	0.000, 0.000	0.992	15	1.436	1.000
	Chest pain	0.000	0.219, 0.187	0.938	16	3.720	0.999
Ear & Labyrinth	Vertigo	0.000	0.185, 0.222	0.929	15	3.992	0.996
Eye Disorders	Visual impairment/disturbances	0.141	0.006, 0.681	0.103	15	1.201	1.000
Gastrointestinal	Nausea	0.021	0.082, 0.330	0.511	22	29.595	0.100
	Vomiting	0.040	0.047, 0.378	0.348	18	10.998	0.857
	Dry Mouth	1.059	0.346, 2.161	<0.001	20	43.062	0.001
General	Pain: non-specific	0.000	0.178, 0.209	0.937	17	3.552	0.999
	Fatigue/tiredness	0.003	0.024, 0.067	0.615	21	4.958	1.000
	Weakness/reduced mobility	0.009	0.125, 0.299	0.674	16	2.911	1.000
Infections	Unspecified	0.001	0.030, 0.058	0.754	16	2.738	1.000
	UTI	0.009	0.013, 0.091	0.378	16	0.210	1.000
	RTI	0.001	0.178, 0.226	0.908	16	14.231	0.508
Injury/Poisoning	Falls & injuries	0.001	0.029, 0.060	0.723	15	2.330	1.000
Investigations	Raised Gamma GT	0.001	0.171, 0.232	0.881	16	3.370	0.999
Metabolism/Nutritional	Fluid retention	0.001	0.157, 0.196	0.913	16	2.129	1.000
	Decreased appetite	0.001	0.169, 0.232	0.877	16	5.407	0.988
	Increased appetite	0.001	0.182, 0.223	0.920	16	1.990	1.000
Musculoskeletal	Spasm stiffness	0.000	0.035, 0.052	0.852	17	1.998	1.000
	Joint disorders	0.005	0.019, 0.077	0.513	16	0.116	1.000
	Musculoskeletal pain	0.039	0.000, 0.163,	0.062	18	13.544	0.699
Nervous System	Sedation	11.103	0.596, 34.721	0.011	2	1.855	0.173
	Dizziness/Lightheaded	0.819	0.489, 1.232	<0.001	25	61.099	<0.001
	Mobility/Balance/Coordination	0.078	0.006, 0.234	0.007	17	21.216	0.170
	Muscle weakness	0.006	0.016, 0.082	0.453	18	5.052	0.998
	Headache/migraine	5.287	0.191, 17.324	0.016	8	10.475	0.163
Psychiatric	Sleep problems/Insomnia	0.110	0.158, 1.125	0.373	17	9.656	0.884
	Dissociative/Thinking/Perception	0.510	0.260, 0.844	<0.001	17	17.454	0.357
	Somnolence/Drowsiness	0.684	0.055, 2.014	0.006	20	53.934	<0.001
	Anxiety/Depression	0.008	0.014, 0.089	0.399	13	2.708	0.997
	Concentration/attention problem	6.361	0.051, 27.778	0.072	5	2.146	0.709
Euphoria	9.117	0.765, 26.669	0.006	6	3.171	0.674	
Renal and Urinary	Bladder symptoms	0.009	0.128, 0.295	0.686	15	0.020	1.000
Reproductive system	Male impotence	0.058	0.438, 0.032	0.260	15	8.150	0.881
Respiratory/Thoracic	Nose tenderness	0.001	0.178, 0.229	0.902	15	1.985	1.000
Skin/Subcutaneous	Other skin problem	0.072	0.515, 0.033	0.244	15	3.397	0.998
	Rash	0.002	0.161, 0.249	0.831	15	1.968	1.000
	Pressure sore	0.108	0.606, 0.015	0.153	15	1.225	1.000
Vascular	Hypotension	0.000	0.195, 0.205	0.980	16	3.999	0.998

I^2 = percent of total variability (heterogeneity plus sampling variability) attributed to heterogeneity amongst the true effects. N = number of studies included in analysis. QE = test statistic for the test of heterogeneity. QEp = *P* value for the test of heterogeneity. UTI, Urinary tract infection. RTI, Respiratory tract infection. NA = not applicable. Statistically significant results are presented in bold.

to 67 years (males: 0–80%). All studies used placebo as control.

Pooled IRDs for all cause ($k = 16$) and treatment-related ($k = 10$) AEs from all RCTs was 19.37 (95% CI, 4.24–45.47) and 11.36 (95% CI, 2.55–26.48) respectively. Pooled IRDs of AEs (Table 3) from cumulative THC: CBD combination treatment across all studies per 1000 person-years for each single AE suggested significantly higher incidence rate of nausea, vomiting, dry mouth, fatigue/tiredness, dizziness/lightheadedness, somnolence/drowsiness and disorientation, amounting on average to an additional incidence of 0.674 (95% CI 0.100–1.7 54), 0.214 (95% CI 0.000–0.837), 1.227 (95% CI 0.093–3.650), 0.439 (95% CI 0.025–1.361), 2.467 (95% CI 0.519–5.862), 1.650 (95% CI

0.361–3.875) and 2.536 (95% CI 0.458–6.290)per 1000 person-years respectively in active compared to control arms.

Meta-regression analyses suggested a significant association between individual AEs and weekly doses of THC and CBD and their interaction expressed as IRSD (Table 4) for some of the AEs such as palpitations (CBD and THC* CBD interaction), altered taste (CBD), dizziness and lightheadedness (THC), concentration and attention problems (THC, CBD, THC* CBD interaction) and disorientation (THC).

Pooled IRDs for all cause ($k = 26$) and treatment-related ($k = 22$) SAEs from all RCTs was 0.056 (95% CI, 0.02–0.39) and 0.058 (95% CI, 0.08–0.59) respectively. Pooled IRDs for all cause ($k = 22$) and treatment related ($k = 27$) withdrawals from all RCTs was 0.036 (95% CI, 0.44–0.08)

Table 2. Effect of cumulative THC dose per week across THC studies expressed as square root transformed incidence rate difference (IRSD, i.e. summary estimate) for each single adverse event. Summary estimates are reported here for intercept and THC dose per week (i.e. regression coefficient), followed by 95% confidence intervals and associated *P* value.

MedDRA high-level grouping	Individual AE	MODEL	Summary estimate	95% CI (lower, upper)	<i>P</i> value	N	QE	QEp
Gastrointestinal	Nausea	Intercept	0.013	−0.010, 0.036	0.268	22	28.800	0.092
		THC	0.000	−0.000, 0.000	0.373	22		
	Vomiting	Intercept	0.016	−0.005, 0.037	0.139	18	9.686	0.883
		THC	0.000	0.000, 0.000	0.252	18		
	Dry mouth	Intercept	0.075	0.050, 0.100	<0.001	20	27.136	0.076
		THC	−0.00005	−0.00001, 0.00003	<0.001	20		
Nervous System	Dizziness/Lightheaded	Intercept	0.055	0.038, 0.071	<0.001	25	49.357	0.001
		THC	−0.00001	−0.00003, −0.00001	0.001	25		
	Mobility/Balance/Coordination	Intercept	0.025	0.009, 0.041	0.002	17	16.338	0.360
		THC	−0.000005	−0.00001, −0.000001	0.027	17		
	Muscle weakness	Intercept	0.003	−0.015, 0.020	0.744	18	5.049	0.996
		THC	0.000	0.000, 0.000	0.961	18		
Headache/migraine	Intercept	0.004	−0.095, 0.104	0.936	8	7.667	0.264	
	THC	0.002	0.000, 0.004	0.094	8			
Sedation	Intercept	0.260	0.023, 0.498	0.032	2	0.000	1.000	
	THC	−0.013	−0.032, 0.006	0.173	2			
Psychiatric	Sleep problems/Insomnia	Intercept	0.039	−0.024, 0.102	0.222	16	8.723	0.848
		THC	0.000	−0.001, 0.000	0.338	16		
	Dissociative/Thinking/Perception	Intercept	0.002	−0.013, 0.018	0.761	17	9.988	0.820
		THC	0.00001	0.000002, 0.000001	0.006	17		
	Somnolence/Drowsiness	Intercept	0.064	0.030, 0.097	<0.001	20	47.142	<0.001
		THC	−0.0003	−0.00001, −0.001	0.009	20		
Anxiety/Depression	Intercept	−0.002	−0.020, 0.016	0.824	13	2.377	0.997	
	THC	0.000	0.000, 0.000	0.565	13			
Concentration/attention problem	Intercept	0.119	0.006, 0.232	0.039	5	1.004	0.800	
	THC	−0.001	−0.004, 0.001	0.285	5			
Euphoria	Intercept	0.098	−0.030, 0.226	0.135	6	3.169	0.530	
	THC	0.000	−0.003, 0.002	0.967	6			
Cardiac	Dyspnoea	Intercept	0.004	−0.021, 0.029	0.744	16	1.256	1.000
		THC	0.000	0.000, 0.000	0.788	16		
Palpitation	Intercept	0.000	−0.001, 0.001	0.973	15	1.434	1.000	
	THC	0.000	0.000, 0.000	0.968	15			
Chest pain	Intercept	−0.002	−0.029, 0.025	0.886	16	3.706	0.997	
	THC	0.000	0.000, 0.000	0.904	16			
Vascular	Hypotension	Intercept	0.001	−0.026, 0.027	0.963	16	3.998	0.995
		THC	0.000	0.000, 0.000	0.969	16		
Infections	Unspecified	Intercept	−0.006	−0.024, 0.011	0.470	16	2.312	1.000
		THC	0.000	0.000, 0.000	0.514	16		
UTI	Intercept	0.001	−0.017, 0.018	0.929	16	0.006	1.000	
	THC	0.000	0.000, 0.000	0.651	16			
RTI	Intercept	0.008	−0.018, 0.035	0.534	15	7.858	0.853	
	THC	0.000	0.000, 0.000	0.601	15			
General	Pain: non-specific	Intercept	−0.009	−0.034, 0.016	0.490	16	2.554	1.000
		THC	0.000	0.000, 0.000	0.416	16		
Fatigue/tiredness	Intercept	0.005	−0.012, 0.022	0.584	21	4.812	1.000	
	THC	0.000	0.000, 0.000	0.702	21		1.000	
Weakness/reduced mobility	Intercept	0.015	−0.012, 0.042	0.271	16	0.451	1.000	
	THC	0.000	0.000, 0.000	0.117	16			
Blood/Lymphatic System	Anaemia	Intercept	0.004	−0.021, 0.029	0.761	16	2.042	1.000
		THC	0.000	0.000, 0.000	0.802	16		

(Continued)

Table 2. Continued

MedDRA high-level grouping	Individual AE	MODEL	Summary estimate	95% CI (lower, upper)	P value	N	QE	QEp
Ear & Labyrinth	Vertigo	Intercept	0.002	-0.024, 0.029	0.871	15	3.974	0.991
		THC	0.000	0.000, 0.000	0.892	15		
Eye Disorders	Visual impairment/disturbances	Intercept	0.010	-0.016, 0.037	0.451	15	1.182	1.000
		THC	0.000	0.000, 0.000	0.891	15		
Injury/Poisoning	Falls & injuries	Intercept	0.007	-0.011, 0.025	0.436	14	1.845	1.000
		THC	0.000	0.000, 0.000	0.486	14		
Investigations	Raised gamma GT	Intercept	0.004	-0.023, 0.030	0.792	16	3.322	0.998
		THC	0.000	0.000, 0.000	0.828	16		
Metabolism/Nutritional	Fluid retention	Intercept	-0.002	-0.024, 0.020	0.864	16	2.112	1.000
		THC	0.000	0.000, 0.000	0.895	16		
	Decreased appetite	Intercept	0.003	-0.023, 0.029	0.801	16	5.367	0.980
		THC	0.000	0.000, 0.000	0.841	16		
	Increased appetite	Intercept	0.002	-0.024, 0.029	0.863	16	1.970	1.000
		THC	0.000	0.000, 0.000	0.888	16		
Musculoskeletal	Spasm stiffness	Intercept	0.001	-0.016, 0.019	0.894	17	1.993	1.000
		THC	0.000	0.000, 0.000	0.945	17		
	Joint disorders	Intercept	0.001	-0.017, 0.018	0.947	16	0.003	1.000
		THC	0.000	0.000, 0.000	0.737	16		
	Musculoskeletal pain	Intercept	0.007	-0.010, 0.025	0.396	18	10.692	0.828
		THC	0.000	0.000, 0.000	0.091	18		
Reproductive system	Male impotence	Intercept	-0.020	-0.042, 0.002	0.072	15	6.188	0.939
		THC	0.000	0.000, 0.000	0.161	15		
Respiratory/Thoracic	Nose tenderness	Intercept	0.003	-0.024, 0.030	0.822	15	1.949	1.000
		THC	0.000	0.000, 0.000	0.850	15		
Skin/Subcutaneous	Other skin problem	Intercept	0.005	-0.021, 0.032	0.694	15	1.961	1.000
		THC	0.000	0.000, 0.000	0.231	15		
	Rash	Intercept	0.005	-0.021, 0.032	0.692	15	1.856	1.000
		THC	0.000	0.000, 0.000	0.738	15		
	Pressure sore	Intercept	0.002	-0.024, 0.029	0.864	15	0.007	1.000
		THC	0.000	0.000, 0.000	0.270	15		
Renal and Urinary	Bladder symptoms	Intercept	0.001	-0.025, 0.028	0.915	15	0.004	1.000
		THC	0.000	0.000, 0.000	0.898	15		

N = number of studies included in analysis. QE = test statistic for the test of heterogeneity. QEp = P value for the test of heterogeneity. NA = not applicable. Statistically significant results are presented in bold. A summary estimate of the intercept model represents the square root transformed incidence rate difference (IRSD) of a given AE when the dose of THC treatment (per week) is 0. The summary estimate for THC refers to the additional increase in incidence rate per milligramme of increase in weekly THC dose per person-year, over and above the corresponding summary estimate of the intercept. Reported here need to be converted into incidence rate difference to be meaningfully interpreted as shown in the example below. For example, the square root transformed incidence rate difference of developing dizziness/lightheadedness for a person taking 100 mg of THC per week over 1 year may be estimated using the formula [IRSD = intercept + summary estimate * (THC dose per week)] as $IRSD = 0.055 + (-0.00001) * 100 = 0.056$. To convert IRSD per person-year into incidence rate difference (IRD) per 1000 person-years (i.e. incidence rate difference associated with cumulative exposure at the specified dose over 1 year for 1000 individuals) one would need to use the formula $(IRSD^2 * 1000)$. Using this formula, the additional incidence (IRD) of dizziness/lightheadedness attributable to THC exposure of 100 mg/week in 1000 people over 1 year amounts to 3.136 per 1000 person-years. Therefore, in a sample of 1000 individuals taking 100 mg of THC per week over a 1-year period, 3.136 additional individuals will experience dizziness/lightheadedness attributable to their THC treatment.

and 0.489 (95% CI, 0.05–1.37) respectively. IRDs for all cause deaths ($k = 27$) from all RCTs were 0.010 (95% CI, 0.04–0.17).

Neither Egger’s test nor ‘Trim and fill’ method indicated significant effect of publication or other selection bias for any of the outcomes except for all cause AEs (Supplementary Figs 21a-d, 22a-f, 23a-e, 24a-c). For all cause AEs for all RCTs as outcome, Egger’s test was $p = 0.0332$, and ‘Trim and fill’ method indicated two missing studies. Meta-regression analysis indicated that there was a significant effect of neurodegenerative disorder on effect-size for all cause withdrawals ($p = 0.044$) compared to other conditions. Except these, moderators such as study design or type of intervention did not significantly influence estimated

effects of THC:CBD combination treatment on any of the outcomes assessed.

Discussion

In this systematic review and meta-analysis, we estimated the additional risk of organ-specific and total AEs attributable to exposure with medicinal cannabinoids in middle aged and older adults by assessing incidence rate differences of AEs. For medications containing THC-alone, on average this amounted to an additional incidence of ~19 all-cause and ~16 treatment-related AEs, whilst for THC:CBD combination treatments, there was an additional incidence

Table 3. Effect of cumulative THC:CBD combination treatment across THC:CBD studies expressed as incidence rate difference (IRD, indicated by the summary estimate, followed by 95% confidence intervals and associated *P* value).

MedDRA high-level grouping	Individual AE	Summary estimate	95% CI (lower, upper)	<i>P</i> value	N	Q	Qp
Blood/Lymphatic System	Anaemia	0.003	0.115, 0.204	0.780	14	2.248	1.000
Cardiac	Dyspnoea	0.004	0.112, 0.212	0.757	11	1.349	0.999
	Palpitation	0.002	0.153, 0.227	0.847	10	8.871	0.449
Ear & Labyrinth	Vertigo	1.602	0.001, 6.579	0.056	11	24.747	0.006
Eye Disorders	Visual impairment/disturbances	0.354	0.107, 2.305	0.206	9	7.400	0.494
Gastrointestinal	Nausea	0.674	0.100, 1.754	0.001	21	24.371	0.227
	Vomiting	0.214	0.000, 0.837	0.045	19	23.852	0.160
	Dry mouth	1.227	0.093, 3.650	0.007	17	52.664	<0.001
General	Pain: non-specific	0.005	0.276, 0.444	0.818	14	20.025	0.095
	Fatigue/tiredness	0.439	0.025, 1.361	0.010	19	29.920	0.038
	Weakness/reduced mobility	0.008	0.107, 0.258	0.670	14	5.839	0.952
Infections	Unspecified	0.002	0.159, 0.230	0.858	8	0.015	1.000
	UTI	0.005	0.111, 0.219	0.740	11	0.580	1.000
	RTI	0.000	0.142, 0.176	0.916	11	2.693	0.988
Injury/Poisoning	Falls & injuries	0.136	0.004, 0.644	0.096	10	4.121	0.903
Investigations	Raised Gamma GT	0.000	0.177, 0.201	0.951	10	0.323	1.000
Metabolism/Nutritional	Decreased appetite	0.011	0.076, 0.237	0.585	16	8.888	0.883
	Increased appetite	0.067	0.065, 0.600	0.323	10	6.947	0.643
	Anorexia	0.010	0.078, 0.228	0.606	14	13.756	0.391
Musculoskeletal	Back pain	0.000	0.187, 0.194	0.984	10	0.169	1.000
	Spasm stiffness	0.002	0.153, 0.232	0.839	10	5.902	0.750
	Musculoskeletal pain	0.000	0.178, 0.205	0.946	9	0.682	1.000
Neoplasms	Neoplasms progression	0.009	0.074, 0.217	0.606	16	9.477	0.851
Nervous System	Altered taste	0.237	0.039, 1.367	0.163	13	16.906	0.153
	Dizziness/Lightheaded	2.467	0.519, 5.862	<0.001	24	75.465	<0.001
	Headache/migraine	0.024	0.037, 0.250	0.385	18	19.517	0.300
	Numbness/paraesthesia	0.009	0.284, 0.117	0.668	9	0.111	1.000
Psychiatric	Sleep problems	0.001	0.148, 0.190	0.904	12	13.621	0.255
	Dissociative/Thinking/Perception	0.010	0.098, 0.258	0.640	12	12.317	0.340
	Somnolence/Drowsiness	1.650	0.361, 3.875	<0.001	19	32.569	0.019
	Anxiety/Depression	0.716	0.085, 3.933	0.145	11	30.209	0.001
	Concentration/attention problem	0.277	0.060, 1.685	0.181	11	15.614	0.111
	Disorientation	2.536	0.458, 6.290	0.001	15	40.301	<0.001
Renal and Urinary	Renal & urinary symptoms	0.001	0.161, 0.214	0.890	10	5.094	0.826
Respiratory/Thoracic	Nose Tenderness	0.001	0.136, 0.192	0.867	10	0.165	1.000
Skin/Subcutaneous	Other skin problem	0.029	0.072, 0.367	0.448	9	5.806	0.669
	Rash	0.000	0.150, 0.177	0.935	10	0.038	1.000
	Pressure Sore	0.059	0.037, 0.463	0.274	9	0.605	1.000
Vascular	Hypotension	0.003	0.141, 0.243	0.792	10	5.880	0.752

N = number of studies included in analysis. QE = test statistic for the test of heterogeneity. QEp = p value for the test of heterogeneity. NA = not applicable. Statistically significant results are presented in bold.

of ~19 all-cause and ~11 treatment-related AEs per 1000 person-years of exposure.

Importantly, in this meta-analysis, we identified specific AEs associated with THC in THC alone or THC: CBD combination treatments. We found that THC significantly increased the incidence of dizziness/lightheadedness, somnolence/drowsiness, impaired mobility/balance/coordination, sedation, headache, dissociative/thinking/perception disorders, euphoria and dry mouth amounting on average to an additional incidence from <1 to ~11 per 1000 person-years, respectively. Further, there was a dose-dependent increase in the additional incidence of the aforementioned AEs as well as dry mouth and dissociative/thinking/perception problems,

such that the higher the weekly dose of THC the higher was the additional attributable incidence of these specific AEs. These individual AEs are worth noting, as they not only impair quality of life but may also contribute to risk of falls in this age group [11, 65, 66], a leading cause of fatal and nonfatal injuries amongst older people [66, 67]. Incidence of psychotic-like experiences such as dissociative/thinking/perception abnormalities was significantly increased in THC alone studies and associated with higher THC doses as noted in our previous observation [9] and can be distressing to patients and their carers.

In addition, further analysis showed that THC and CBD in combination significantly increased the incidence of

Table 4. Effect of cumulative THC and CBD doses per week and THC* CBD dose interaction across THC:CBD combination studies expressed as square root transformed incidence rate difference (IRSD, i.e. summary estimate) for each single adverse event. Summary estimates (i.e. regression coefficient) are reported here for intercept and THC and CBD doses as well as their interaction, followed by 95% confidence intervals and associated *P* value.

MedDRA high-level grouping	Individual AE	Model	Summary estimate	95% CI (lower, upper)	<i>P</i> value	N	QE	QEp
Blood/Lymphatic System	Anaemia	Intercept	-0.007	-0.089, 0.075	0.871	14	0.773	1.000
		THC	0.000	-0.001, 0.000	0.890	14		
		CBD	0.000	-0.001, 0.001	0.889	14		
		THC* CBD interaction	0.000	0.000, 0.000	0.815	14		
Cardiac	Dyspnoea	Intercept	0.067	-0.073, 0.208	0.346	11	0.047	1.000
		THC	0.000	-0.002, 0.001	0.422	11		
		CBD	-0.001	-0.007, 0.005	0.730	11		
		THC* CBD interaction	0.000	0.000, 0.000	0.724	11		
	Palpitation	Intercept	0.437	-0.132, 1.005	0.132	10	1.919	0.927
		THC	-0.004	-0.008, 0.000	0.053	10		
		CBD	-0.008118	-0.016085, -0.000151	0.046	10		
	THC* CBD interaction	0.000066	0.000008, 0.000124	0.026	10			
Ear & Labyrinth	Vertigo	Intercept	0.024	-0.295, 0.344	0.881	11	5.204	0.635
		THC	-0.001	-0.002, 0.001	0.535	11		
		CBD	0.001	-0.001, 0.002	0.352	11		
		THC* CBD interaction	0.000	0.000, 0.000	0.920	11		
Eye Disorders	Visual impairment/disturbances	Intercept	0.018	-1.309, 1.345	0.979	9	6.621	0.250
		THC	0.000	-0.012, 0.011	0.941	9		
		CBD	0.000	-0.028, 0.028	0.999	9		
		THC* CBD interaction	0.000	0.000, 0.000	0.966	9		
Gastrointestinal	Nausea	Intercept	0.023	-0.054, 0.100	0.555	21	14.301	0.646
		THC	0.000	-0.001, 0.000	0.112	21		
		CBD	0.000	0.000, 0.001	0.202	21		
		THC* CBD interaction	0.000	0.000, 0.000	0.925	21		
	Vomiting	Intercept	-0.027	-0.159, 0.105	0.687	19	13.342	0.576
		THC	0.000	-0.001, 0.001	0.848	19		
		CBD	0.000	-0.001, 0.001	0.410	19		
	Dry Mouth	Intercept	0.020	-0.121, 0.162	0.777	17	49.346	<0.001
		THC	0.000	-0.001, 0.001	0.561	17		
		CBD	0.001	0.000, 0.002	0.323	17		
General	Pain: non-specific	Intercept	0.029	-0.053, 0.111	0.493	14	18.617	0.045
		THC	0.000	-0.001, 0.000	0.698	14		
		CBD	0.000	-0.002, 0.001	0.475	14		
		THC* CBD interaction	0.000	0.000, 0.000	0.316	14		
	Fatigue/tiredness	Intercept	0.024	-0.054, 0.102	0.544	19	24.526	0.057
		THC	0.000	-0.001, 0.000	0.266	19		
		CBD	0.000	0.000, 0.001	0.543	19		
	Weakness/reduced mobility	Intercept	-0.041	-0.202, 0.121	0.623	14	5.009	0.891
		THC	0.000	-0.001, 0.001	0.801	14		
		CBD	0.001	-0.001, 0.002	0.399	14		
Infections	Unspecified	Intercept	-0.007	-1.334, 1.321	0.992	8	0.014	1.000
		THC	0.000	-0.011, 0.011	0.994	8		
		CBD	0.000	-0.028, 0.028	0.991	8		
		THC* CBD interaction	0.000	0.000, 0.000	0.991	8		
	UTI	Intercept	-0.063	-0.867, 0.742	0.879	11	0.534	0.999
		THC	0.001	-0.006, 0.007	0.876	11		
		CBD	0.001	-0.014, 0.016	0.859	11		
	RTI	Intercept	0.078	-0.279, 0.435	0.668	11	0.476	1.000

(Continued)

Table 4. Continued

MedDRA high-level grouping	Individual AE	Model	Summary estimate	95% CI (lower, upper)	P value	N	QE	QEp	
Injury/Poisoning	Falls & injuries	THC	0.000	-0.002, 0.002	0.674	11	1.252	0.974	
		CBD	-0.002	-0.005, 0.001	0.242	11			
		THC*CBD interaction	0.000	0.000, 0.000	0.238	11			
		Intercept	-0.251	-0.820, 0.317	0.386	10			
		THC	0.002	-0.002, 0.007	0.286	10			
		CBD	0.005	-0.003, 0.013	0.183	10			
Investigations	Raised Gamma GT	THC*CBD interaction	0.000	0.000, 0.000	0.172	10	0.015	1.000	
		Intercept	0.077	-0.434, 0.587	0.768	10			
		THC	-0.001	-0.004, 0.003	0.699	10			
		CBD	-0.002	-0.010, 0.007	0.707	10			
		THC*CBD interaction	0.000	0.000,0.000	0.671	10			
Metabolism/Nutritional	Decreased Appetite	Intercept	0.053	-0.031, 0.137	0.216	16	4.443	0.974	
		THC	0.000	-0.001,0.000	0.296	16			
		CBD	0.000	0.000,0.000	0.080	16			
		THC*CBD interaction	0.000	0.000,0.000	0.263	16			
		Intercept	-0.071	-0.571, 0.428	0.779	10			
		THC	0.000	-0.003, 0.003	0.884	10			
	Increased Appetite	Anorexia	CBD	0.002	-0.006, 0.011	0.616	10	2.657	0.850
			THC*CBD interaction	0.000	0.000,0.000	0.697	10		
			Intercept	-0.103	-0.249, 0.043	0.167	14		
			THC	0.000	0.000, 0.001	0.272	14		
			CBD	0.001	0.000, 0.002	0.158	14		
			THC*CBD interaction	0.000	0.000,0.000	0.229	14		
Musculoskeletal	Back pain	Intercept	0.084	-1.168, 1.335	0.896	10	0.138	1.000	
		THC	-0.001	-0.011, 0.010	0.898	10			
		CBD	-0.002	-0.028, 0.024	0.887	10			
		THC*CBD interaction	0.000	0.000, 0.000	0.891	10			
		Intercept	0.300	-0.952, 1.551	0.639	10			
		THC	-0.003	-0.014,0.008	0.578	10			
	Spasm stiffness	Musculoskeletal pain	CBD	-0.006	-0.032,0.020	0.659	10	4.242	0.644
			THC*CBD interaction	0.000	0.000,0.000	0.617	10		
			Intercept	-0.173	-1.500, 1.154	0.799	9		
			THC	0.001	-0.010, 0.012	0.859	9		
			CBD	0.002	-0.026, 0.029	0.915	9		
			THC*CBD interaction	0.000	0.000,0.000	0.929	9		
Neoplasms	Neoplasms progression	Intercept	0.120	-0.040, 0.279	0.142	16	6.544	0.886	
		THC	-0.001	-0.001,0.000	0.123	16			
		CBD	-0.001	-0.002, 0.001	0.340	16			
Nervous system	Altered taste	THC*CBD interaction	0.000	0.000,0.000	0.283	16	8.557	0.479	
		Intercept	-0.077	-0.226, 0.072	0.311	13			
		THC	0.000	-0.001,0.001	0.759	13			
		CBD	0.001	0.000,0.002	0.024	13			
		THC*CBD interaction	0.000	0.000,0.000	0.141	13			
	Dizziness/Light-headed	Headache/migraine	Intercept	-0.018	-0.077,0.041	0.549	24	14.376	0.422
			THC	0.000498	0.000080,	0.020	24		
			0.000916						
			CBD	0.000	0.000,0.000	0.628	24		
			THC*CBD interaction	0.000	0.000,0.000	0.602	24		
Numbness/paraesthesia	Numbness/paraesthesia	Intercept	0.087	-0.055,0.228	0.229	18	0.106	1.000	
		THC	-0.001	-0.001,0.000	0.102	18			
		CBD	0.000	-0.001,0.001	0.816	18			
		THC*CBD interaction	0.000	0.000,0.000	0.651	18			
		Intercept	-0.016	-1.343, 1.311	0.981	9			
		THC	0.000	-0.011, 0.011	0.985	9			
CBD	0.000	-0.027, 0.028	0.977	9					
THC*CBD interaction	0.000	0.000,0.000	0.979	9					

(Continued)

Table 4. Continued

MedDRA high-level grouping	Individual AE	Model	Summary estimate	95% CI (lower, upper)	P value	N	QE	QEp
Psychiatric	Sleep problems	Intercept	0.045	-0.117,0.206	0.587	12	12.044	0.149
		THC	0.000	-0.001,0.001	0.973	12		
		CBD	-0.001	-0.002,0.001	0.311	12		
		THC*CBD interaction	0.000	0.000,0.000	0.459	12		
	Dissociative/Thinking/Perception	Intercept	0.026	-0.135, 0.188	0.751	12	9.068	0.337
		THC	0.000	-0.001, 0.001	0.718	12		
		CBD	-0.001	-0.003,0.000	0.162	12		
		THC*CBD interaction	0.000	0.000,0.000	0.294	12		
	Somnolence/Drowsiness	Intercept	0.066	-0.067, 0.199	0.332	19	11.992	0.680
		THC	-0.001	-0.001,0.000	0.063	19		
		CBD	0.000	-0.001,0.001	0.500	19		
		THC*CBD interaction	0.000	0.000,0.000	0.465	19		
	Anxiety/Depression	Intercept	-0.027	-0.515, 0.461	0.915	11	16.508	0.021
		THC	0.000	-0.003,0.003	0.887	11		
		CBD	0.002	-0.006,0.010	0.580	11		
		THC*CBD interaction	0.000	0.000,0.000	0.733	11		
	Concentration/attention problem	Intercept	0.502257	0.145686, 0.858829	0.006	11	1.154	0.992
		THC	-0.003128	-0.005162, -0.001094	0.003	11		
		CBD	-0.003718	-0.006809, -0.000628	0.018	11		
		THC*CBD interaction	0.000024	0.000007, 0.000041	0.006	11		
Disorientation	Intercept	0.103	-0.045, 0.251	0.173	15	8.917	0.630	
	THC	-0.001014	-0.001833, -0.000194	0.015	15			
	CBD	0.001	-0.001,0.002	0.315	15			
	THC*CBD interaction	0.000	0.000,0.000	0.386	15			
Renal and Urinary	Renal & urinary symptoms	Intercept	0.490	-0.314, 1.295	0.233	10	1.199	0.977
		THC	-0.004	-0.011,0.003	0.237	10		
		CBD	-0.011	-0.026,0.004	0.154	10		
		THC*CBD interaction	0.000	0.000,0.000	0.178	10		
Respiratory/Thoracic	Nose Tenderness	Intercept	0.024	-0.475, 0.523	0.925	10	0.001	1.000
		THC	0.000	-0.003,0.003	0.895	10		
		CBD	-0.001	-0.009,0.008	0.906	10		
		THC*CBD interaction	0.000	0.000,0.000	0.888	10		
Skin/Subcutaneous	Other skin problem	Intercept	0.049	-1.277, 1.376	0.942	9	2.369	0.796
		THC	0.000	-0.011, 0.012	0.972	9		
		CBD	-0.002	-0.030, 0.026	0.883	9		
		THC*CBD interaction	0.000	0.000,0.000	0.952	9		
	Rash	Intercept	0.012	-0.488, 0.511	0.964	10	0.000	1.000
		THC	0.000	-0.003,0.003	0.949	10		
		CBD	0.000	-0.009,0.008	0.955	10		
		THC*CBD interaction	0.000	0.000,0.000	0.946	10		
	Pressure Sore	Intercept	-0.041	-1.368, 1.286	0.952	9	0.568	0.989
		THC	0.000	-0.011, 0.012	0.961	9		
		CBD	0.001	-0.027, 0.029	0.941	9		

(Continued)

Table 4. Continued

MedDRA high-level grouping	Individual AE	Model	Summary estimate	95% CI (lower, upper)	P value	N	QE	QEp
		THC*CBD interaction	0.000	0.000,0.000	0.946	9		
Vascular	Hypotension	Intercept	0.328	-0.182, 0.839	0.207	10	0.276	1.000
		THC	-0.003	-0.006, 0.001	0.099	10		
		CBD	-0.007	-0.016, 0.002	0.109	10		
		THC*CBD interaction	0.000	0.000, 0.000	0.070	10		

Statistically significant results are presented in bold. A summary estimate of the intercept model represents the square root transformed incidence rate difference (IRSD) of a given AE when the doses of THC and CBD dose per week are 0. The incidence rate at a particular dose combination of THC and CBD formulation may be estimated using the formula: $IRSD = \text{intercept} + \text{summary estimate} * (\text{THC dose per week}) + \text{summary estimate} * (\text{CBD dose per week}) + \text{summary estimate} * (\text{THC dose per week}) * (\text{CBD dose per week})$. For example, the square root transformed incident rate difference (IRSD) of developing disorientation if a patient is taking a THC:CBD combination formulation containing 10 mg of THC per week and 10 mg of CBD per week will be $IRSD = 0.103 + (-0.001014)*10 + (0.001)*10 + (0.000)*10*10 = 0.10286$. To convert IRSD per person-year into incidence rate difference (IRD) per 1000 person-years (i.e. incidence rate difference associated with cumulative exposure at the specified doses of THC and CBD in combination over 1 year for 1000 individuals) one would need to use the formula $(IRSD^2 * 1000)$. Using this formula, the additional incidence (IRD) of disorientation attributable to THC:CBD combination exposure of 10 mg/week of THC and 10 mg/week of CBD in 1000 people over 1 year amounts to 10.58 per 1000 person-years. Therefore, in a sample of 1000 individuals taking a THC: CBD combination treatment containing 10 mg of THC and 10 mg of CBD per week over a 1-year period, 10.58 additional individuals will experience dizziness/lightheadedness attributable to their THC:CBD combination treatment.

nausea, vomiting, dry mouth, fatigue/tiredness, dizziness/lightheadedness, somnolence/drowsiness and disorientation, amounting on average to an additional incidence of <1 to ~3 per 1000 person-years, respectively. This highlights the need to be mindful of higher weekly doses of THC and CBD in the older population, who are also on other medications for multiple co-morbidities. Furthermore, there was a dose-dependent relationship of weekly CBD doses with palpitation, altered taste and problems of inattention and concentration. Some of these effects are consistent with another meta-analysis, though they also reported abnormal liver function tests, decreased appetite, diarrhoea, pneumonia [10]. However, most of the studies were in those with childhood epilepsies and authors conjectured that this may have been due to interaction of CBD with other medications such as clobazam and/or sodium valproate and excluding these studies showed only diarrhoea as an adverse event for CBD [10]. It is interesting to note that these side-effects were not found in our analysis for middle aged and older adults, although interaction with other medications was not examined.

This report, which includes data from 58 RCTs is an update of our previous meta-analysis summarising 46 RCTs, and confirms that whilst middle aged and older adults are at greater risk of both treatment-related and all cause AEs from CBMs containing THC, they are not associated with SAEs, withdrawals or death [8]. Critically, we extend previous literature by providing the first pooled estimate of incidence of AEs attributable to CBMs. As described before, previous reviews of AEs with CBMs have either been qualitative, did not specifically focus on middle aged and older adults, or did not consider the effects of THC, CBD, or their combination separately [8] or focused on specific clinical indications [7, 68–71]. They have sometimes reported conflicting findings in terms of AEs, likely contributed partly by varying pooled sample sizes, as well as the quality of included studies (details in Supplementary Discussion). In

general, those with larger number of pooled participants tend to show a modest but significant increase in risk of AEs as we have reported here, though results vary in terms of specific individual AEs reported [68–71]. By pooling data across all indications, here, we extend previous evidence to provide a more comprehensive and robust CBM-specific summary of the plethora of AEs associated with CBM use in adults over the age of 50. We also provide dose–response relationship estimates that have not been reported before to the best of our knowledge, which may help clinicians and researchers in dosage decisions in different contexts [72]. Further, across different meta-analyses, AEs have commonly been reported in terms of risk ratios, odds ratios or incidence rate ratios. Whilst these metrics are useful to convey whether there are significant additional risks associated with CBMs, they do not lend themselves as easily to everyday use. One needs to be aware of the baseline risk in the control (or placebo) group, which often remains unclear, to estimate the additional incidence associated with exposure to the CBM over a period of time. By estimating the additional incidence rate of all AEs as well as specific AEs associated with CBM use, we hope that results reported here will allow easier use of this information in the clinical and research contexts, especially in terms of estimating and communicating additional risk.

Limitations

Our review has some limitations. Using GRADE Framework, we found evidence of moderate to high quality evidence in ~64% of studies and low to very low quality in 36% of studies. Some of the trials had inadequate information about randomisation, allocation concealment, selective outcome reporting and objective outcomes which restricts interpretation of results (see supplementary material for full details of bias). However, we included double-blind studies to increase the methodological rigour of the contributing evidence. Therefore, these results need to be considered in

light of potential selective reporting of side-effects, often relatively short duration of treatment in included RCTs and imprecision in the estimated IRD values. Notwithstanding this, we provide estimates from a larger pool of patients with indication that publication or other selection biases are unlikely to have influenced the pooled estimates reported here [8]. Further, our dose–response relationship tables may also aid dosage and formulation decisions in clinicians and researchers using CBMs by allowing them to compute ballpark estimates of incidence of AEs at different dose ranges (see footnotes for Tables 2 and 4 for guidance on calculations).

Unlike in other recent meta-analyses, which reported summary effects separately based on indications [7, 68–71], we pooled safety and tolerability data in middle aged and older adults across a broad range of indications. Whilst this may have added to the heterogeneity of the data synthesised, it allowed us to comprehensively estimate separately the tolerability of the two broad categories of cannabinoid-based interventions i.e. THC only and THC:CBD combination, something that has not been done before. This is a key strength of the present approach, given the reported opposite effects of different cannabinoids [3, 73]. Another important strength of the present report relates to the analysis of the effects of moderators to examine the extent to which they may have influenced results, in particular relationship with cannabinoid weekly doses used and interaction.

There is growing evidence that THC and CBD may have opposing acute effects on autonomic arousal, brain [73] and cardiovascular function [74] and CBD may mitigate some of the harmful effects of THC on cognition and behaviour [73, 75, 76], consistent with their opposing effects on some of their molecular targets [3]. The suggestion that THC and CBD may have distinct tolerability profiles, with certain side-effects noticeable in those taking THC-only formulations whilst adverse effects may even be mitigated in those taking THC and CBD in combination, underscored the importance of examining their safety and tolerability separately as well as dose–response relationships as we have done here. Our findings of AEs are consistent with other meta-analyses but in addition show the association of weekly doses with some of the adverse effects of THC and CBD. Few studies have examined the drug–drug interaction of CBMs given their effect on cytochrome p450 enzymes [77], an important likely determinant of tolerability and dose adjustment in older people, and therefore worthy of investigation in future studies.

Conclusions

Results of the present study suggest that THC-containing CBMs are associated with certain gastrointestinal, neurological and psychiatric side-effects in a dose-related manner, both for THC only and for THC: CBD combinations some of which can be mitigated by CBD. Efficacy should additionally consider dose–response relationships with regard to

tolerability whilst prescribing CBMs, particularly in older people.

Supplementary Data: Supplementary data mentioned in the text are available to *subscribers in Age and Ageing* online.

Declaration of Conflicts of Interest: SB has participated in advisory boards for or received honoraria as a speaker from Reckitt Benckiser, EmpowerPharm/SanteCannabis and Britannia Pharmaceuticals. All of these honoraria were received as contributions towards research support through King’s College London, and not personally. SB and LV have collaborated with Beckley Canopy Therapeutics/Canopy Growth (investigator-initiated research) wherein they supplied study drug for free for charity (Parkinson’s UK) and NIHR (BRC) funded research.

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