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ORIGINAL RESEARCH ARTICLE

Patients' Health-Related Quality of Life and Use of Medicinal Cannabis: A Cross-Sectional Survey Study

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Abstract

Background Studies on medicinal cannabis (MC) have primarily investigated effects on diseases and symptoms, while there is only sparse knowledge on patients' health-related quality of life. Our aim was, firstly, to compare the health-related quality of life of patients (MC users and non-users) within four specified diagnostic indications (multiple sclerosis, paraplegia, neuropathy, and nausea and vomiting after chemotherapy) with that of patients with other diagnostic indications (MC users only) and the adult population (non-users only). Secondly, we estimate the associations between use of MC and health-related quality of life for patients in the four specified diagnostic indications.

Methods We collected data on quality-adjusted life years (QALYs), using EQ-5D-3L, and patients' self-reported use of MC in a Danish nationwide online survey distributed to 23,846 patients in October 2020. We compared QALY scores of all groups using a two-tailed *t*-test, listed QALY scores of MC users versus non-users, and investigated associations between QALY score and MC use using unadjusted and adjusted linear regression analyses. Significance level was set to p-value < 0.05.

Results A total of 9265 patients took part in the survey. All diagnostic indications had a statistically significant lower QALY score than the adult population (0.87). Paraplegia patients had the lowest QALY score, being 0.36 lower, followed by other diagnostic indication (− 0.34), multiple sclerosis (− 0.20), neuropathy (− 0.13), and nausea and vomiting after chemotherapy (− 0.06). MC users had a statistically significant lower QALY score than non-users (0.44 vs 0.74). Users redeeming 1–6 and ≥ 7 MC prescriptions (except for paraplegia patients) had a statistically significant lower QALY score than non-users, ranging between 0.11–0.24 and 0.26–0.32 lower than non-users, accordingly. Although, it should be noted that the number of users was small when stratifying by number of prescriptions.

Conclusion Patients with either multiple sclerosis, paraplegia, neuropathy, or nausea and vomiting after chemotherapy had a significantly lower health-related quality of life than individuals from the adult population. Users of medicinal cannabis also had a significantly lower health-related quality of life compared with non-users, in all diagnostic indications.

Key Points

Patients with either multiple sclerosis, paraplegia, neuropathy, or nausea and vomiting after chemotherapy had a significantly lower health-related quality of life than individuals from the adult population.

Health-related quality of life was significantly lower among users of medicinal cannabis compared with non-users in all diagnostic indications.

Patients redeeming the highest number of medicinal cannabis prescriptions had a lower health-related quality of life compared with patients redeeming fewer prescriptions and non-users, except for patients diagnosed with paraplegia.

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1 Background

Cannabis for medicinal purposes is legalized in many western countries [1–4]. The rationale is the assumption that it can add to current treatment by reducing chronic and neuropathic pain, spasms, nausea, and vomiting, and consequently improve quality of life [5–8]. Studies on medicinal cannabis (MC) have primarily investigated effects on diseases and symptoms, while there is only sparse knowledge on health-related quality of life (HRQoL). However, HRQoL is relevant to target, not least because it represents an amalgam of each person's disease, symptoms, and social life. A systematic review on the effects of cannabinoids on HRQoL was inconclusive [5]. An Australian cohort study found significant HRQoL improvements over time in functionality, mobility, pain, depression, and anxiety among patients prescribed MC, but they did not compare patients according to their diagnostic indications [9]. Earlier data exists on Danish patients' HRQoL across a diverse range of chronic conditions, although many biomedical developments have happened in the Danish Healthcare System since then [10, 11]. In this study, we first aim to compare the HRQoL of patients (MC users and non-users) within four specified diagnostic indications with that of patients with other diagnostic indications (MC users only) and the adult population (non-users only). Secondly, we estimate the associations between use of MC and HRQoL for the four diagnostic indications.

2 Methods

2.1 Setting

Since January 2018, MC has been legal in Denmark [12, 13]. All Danish physicians can prescribe MC. It is recommended for, but not limited to, (i) painful spasms caused by multiple sclerosis, (ii) painful spasms due to spinal cord injury (paraplegia), (iii) nausea and vomiting after chemotherapy, and (iv) neuropathic pain (i.e., pain due to disease of the brain, spinal cord, or nerves). The guideline from the Danish Medicines Agency states that treatment with MC should only be considered when all authorized conventional treatments have proved insufficient [12].

2.2 Study Design, Data Collection, and Populations

We conducted a nationwide online survey from mid-October to mid-November 2020 on patients' HRQoL, attitudes, and experiences with MC. Our target population was MC users and non-users from the four recommended diagnostic indications, MC users from other diagnostic indications, and a group of non-users from the adult population. Accordingly, we define our subpopulations as patients being diagnosed as having (1) multiple sclerosis, (2) painful spasms due to spinal cord injury (paraplegia), (3) nausea and vomiting after chemotherapy, or (4) neuropathic pain (i.e., pain due to disease of the brain, spinal cord, or nerves); and (5) patients with other diagnostic indications using MC; and (6) individuals from the adult population not using MC and not having any of the four diagnostic indications. The latter two groups serve as comparison groups in the first research question. Statistics Denmark Survey collected all data. The patients from the target population were identified in The Danish National Patient Register and in The Danish Register of Pharmaceutical Sales (Online Resource 1 shows the diagnosis, procedure, and ATC codes used to identify the patients, see electronic supplementary material [ESM]) [14, 15]. Individuals from the adult population were randomly chosen via the Danish Civil Registration System [16]. Statistics Denmark selected about 20,000 eligible patients based on the prevalence rates of each diagnostic indication group in Denmark, and about 3000 individuals not using MC from the adult population, via simple random sampling. All sampled individuals received an invitation with a link to access the questionnaire in e-Boks, a digital mailbox linked to the individual's Danish personal registration number. They received up to three reminders via their e-Boks if they had not answered. The first reminder came after 10 days, the next after another 10 days, and the last a few days before the end of data collection in mid-November 2020. Respondents were excluded if they (i) were < 18 years old, (ii) had missing background variables of either age, gender, education, income, region of residence, civil status, or Charlson Comorbidity index (CCI) in the registers, or (iii) had incomplete responses to the questionnaire.

2.3 Questionnaire Development

The questionnaire comprised items about HRQoL measured via EQ5D-3L, attitudes and knowledge about MC, and use of and experiences with MC and cannabis-based medicinal products (CBMP) prescribed by a physician (Online Resource 2 and 3 show the items included in the questionnaire, see ESM). The questionnaire was tested in both a qualitative and a quantitative pilot study. We invited five patients in the first qualitative phase, three males and two females. The patients had at least one indication recommended for MC prescription by the Danish Medicines Agency. The patients filled in the questionnaire either at the University of Southern Denmark or in their home, while being observed. The patients were subsequently interviewed about their

experiences and the questionnaire was consequently adjusted where needed. In the second quantitative phase, four females and three males having indications recommended for MC prescription filled in the survey and commented in free-text fields, and the questionnaire was further revised. We checked the questionnaire according to the COSMIN Study Design checklist for patient-reported outcome measurement instruments (Online Resource 4 shows the COSMIN Study Design checklist filled in where applicable, see ESM) [17].

2.4 Key Variables

Our outcome of interest is HRQoL measured in quality-adjusted life years (QALYs). The QALYs are derived from responses to the EQ5D-3L items and calculated using the official Danish time-trade-off weights for the European Quality of Life (EuroQol) survey [18]. QALY scores range from −0.55 to 1.00 with a higher score indicating better HRQoL [18]. Our independent variables of interest were use of MC, binarily measured by self-reported use of MC (Yes or No) in the questionnaire, and if Yes, self-reported number of MC prescriptions issued since the beginning of the pilot program (1 January 2018), divided into categories (1–6 and ≥ 7 prescriptions). The questionnaire had the following prescription categories: (i) 1–3 prescriptions, (ii) 4–6 prescriptions, (iii) 7–10 prescriptions, and (iv) 11 or more prescriptions, but we ended up with the two binary categories in the analysis out of necessity, as we needed to make sure that there were at least five patients in each category. This was a requirement from Statistics Denmark to be able to use data for research. The adjustment variables are all derived from Danish national registries [14–16, 19–22]. Biological sex is binarily defined as male or female. Age is divided into categories 18–39, 40–59, and 60+ years. Education is divided into categories < 13, ≥ 13–14.5, and > 14.5 years. Income is stratified by age and divided into the lower, middle, and upper tertile for each age category. Region of residence contains the five Danish regions, the North Denmark Region, Central Denmark Region, Region of Southern Denmark, Capital Region of Denmark, and Region Zealand. Civil status is binary and registered as either married/registered partnership or unmarried. CCI measuring the patients' degree of comorbidity is categorized as 0–1 and ≥ 2 [23].

2.5 Statistical Analyses

We reported descriptive statistics of all included variables for the whole sample and for all six subpopulations separately. We then listed and compared the QALY scores of all groups using two-tailed *t*-tests, to test for significant differences in mean QALY scores between diagnostic indications and the adult comparison population. We displayed the distribution of QALY scores by using a violin plot that is a modification of box plots that add plots of the estimated kernel density [24]. Next, we listed the mean QALY scores of MC users versus non-users within the four diagnostic groups and investigated the associations between QALY score and use of MC, using linear regression models with the QALY score as our outcome variable and use/non-use of MC as the independent variables. The distribution between users and non-users for each group was displayed in a violin plot. We performed two regression analyses stratified by diagnostic indication, a crude unadjusted regression, and a regression adjusting for potential confounding variables of age, gender, education, income, employment status, civil status, region of residence, and CCI. Patients that had more than one indication were included in the separate analyses for all relevant indications. In those analyses, we adjusted for patients who belong to more than one indication group. Finally, we investigated the same associations between QALY score and use of MC by including frequency of MC use, with 1–6 and ≥ 7 prescriptions as independent variables. We used the same approach as above. We defined the significance level as $p < 0.05$. All analyses were done using Stata version 18 [25, 26].

3 Results

Table 1 displays the respondent selection process. It shows the total number of individuals in the target population, invited individuals from the target population, respondents, and the final included study population. More than one third of the invited population chose to respond to our survey. After excluding respondents < 18 years of age, missing data in registers, and partial responses, the study population included 9265 (39%) individuals. The final response rate varied between groups. Patients receiving MC for other indications had the highest rate (47%), followed by multiple sclerosis patients (46%), patients with nausea and vomiting after chemotherapy (41%), patients with neuropathy (38%), individuals from the comparison population (34%), and paraplegia patients (29%).

Table 2 describes the characteristics of the study population. The typical respondents were females between 40 and 59 years having an education of at least 14.5 years, employed, married or in registered partnership, with a CCI of 0–1, and living in the Capital Region of Denmark. The characteristics varied to a certain extent between the different patient groups and the adult population group.

The QALY scores ranged between − 0.55 and 1.00 and they varied in their distribution across the groups. The adult population had the highest mean QALY score of 0.87 followed by the patients with nausea and vomiting after chemotherapy (0.81), neuropathy (0.74), multiple sclerosis (0.67),

Table 1 Populations and selection of respondents among diagnostic indications and the adult population group

Group	Target population *N*	Invited *N* (% target population)	Respondents *N* (% invited)	Study population[a] *N* (% invited)
Multiple sclerosis	5752	1595 (27.7)	850 (53.3)	730 (45.8)
Paraplegia	2246	655 (29.2)	239 (36.5)	192 (29.3)
Neuropathy	47249	15,604 (33.0)	7049 (45.2)	5999 (38.4)
Nausea and vomiting	9795	1248 (12.7)	580 (46.5)	509 (40.8)
Other diagnostic indications (MC-users)[b]	2120	1784 (84.2)	1003 (56.2)	830 (46.5)
Adult population (non-users)[c]	4,683,525	3105 (0.07)	1291 (41.6)	1061 (34.2)
Total	4,750,687	23,846 (0.5)	10,947 (45.9)	9265 (38.9)

The sum of groups equals more than the total number of patients, as some patients belong to more than one of the first four groups

[a]Sample included in final analysis after excluding respondents < 18 years old, missing data in registers, and partial responses

[b]Patients receiving prescribed MC for any indication other than the four above

[c]Adult Danish population as of 01 October 2020

other diagnostic indications (0.53), and paraplegia patients (0.51) (see Fig. 1 and Online Resource 5 in the ESM).

There were 255 users of MC and 7175 non-users among patients with the four diagnostic indications (multiple sclerosis, paraplegia, neuropathy, and nausea and vomiting) who answered the EQ-5D-3L questionnaire in the study population. The percentage of users varied between the groups, ranging from 10.9% in the paraplegia group to 2.5% in the neuropathy group. The highest difference in mean score between users and non-users was 0.33, seen among the patients with neuropathy. This was followed by multiple sclerosis (0.28), paraplegia (0.19), and nausea and vomiting patients (0.15) (see Fig. 2 and Table 3). Users of MC had a statistically significant lower QALY score than non-users in total (0.44 vs 0.74) and among all patient groups in the stratified adjusted regression models. When analyzing the association by frequency of MC use, adjusted estimates indicated that patients among all diagnostic indications using 1–6 prescriptions, and multiple sclerosis, neuropathy, and nausea and vomiting patients using ≥ 7 prescriptions, had a lower QALY score than non-users (see Table 4).

4 Discussion

4.1 Summary of Findings

The users of MC had a significantly lower QALY score than non-users (0.44 vs 0.74) in all patient groups. The highest significant score difference between users and non-users was seen in the neuropathy group (0.33) and the smallest was seen in the nausea and vomiting group (0.15).

The distribution of QALY scores varied considerably between the groups in our study. The adult population group had the highest mean score of 0.87, corresponding to earlier data from the Danish National Health Survey [10, 11]. The paraplegia patients had the lowest mean score of 0.51, which was considerably lower than other spine-related disorders included in earlier studies, ranging between 0.62 and 0.73 [11].

4.2 Explanations and Interpretations

The finding that users had a lower QALY score than non-users was backed up in the literature by a systematic review including qualitative evidence about MC use in palliative care. The review noted that patients often resort to MC after having experienced little to no effect, or unacceptable adverse effects, from conventional prescription medication [27]. Other research investigating QALYs and use of opioids had indicated that long-term opioid use may lead to lower QALY scores due to reduced quality of life from side effects and dependency. However, opioids can improve QALY scores in the short term by providing effective pain relief [28]. It was surprising that all patient groups had patients with the highest possible QALY score of 1, as every patient was expected to have some kind of debilitation due to their diagnostic indication. However, earlier literature has shown that patients tend to rate themselves higher than healthy individuals would rate them [29].

Patients in the group with other diagnostic indications had one of the lowest QALY scores of 0.53 next after the paraplegia patients. This group consisted of MC users only and could not be characterized by specific diagnostic indications. However, most of these patients received MC prescriptions for 'no specific indication', according to numbers from the study period from the Danish Health Data Authority [30]. This could mean that many of these patients were suffering from rare or multiple conditions that do not fit properly into conventional treatment regimens, with their general practitioners (GPs) turning to MC. These potentially failed attempts to achieve the desired effects could also be a

Table 2 Descriptive table of population characteristics across diagnostic indications and the adult population group

	Total *N* (%)	Multiple sclerosis *N* (%)	Paraplegia *N* (%)	Neuropathy *N* (%)	Nausea and vomiting *N* (%)	Other diagnostic indication *N* (%)	Adult population *N* (%)
Total	9265 (100.0)	730 (100.0)	192 (100.0)	5999 (100.0)	509 (100.0)	830 (100.0)	1061 (100.0)
Sex							
Male	4207 (45.4)	206 (28.2)	119 (62.0)	2916 (48.6)	261 (51.3)	284 (34.2)	449 (42.3)
Female	5058 (54.6)	524 (71.8)	73 (38.0)	3083 (51.4)	248 (48.7)	546 (65.8)	612 (57.7)
Age group							
18–39	1368 (14.8)	130 (17.8)	23 (12.0)	761 (12.7)	41 (8.1)	112 (13.5)	304 (28.7)
40–59	4492 (48.5)	428 (58.6)	82 (42.7)	3052 (50.9)	165 (32.4)	357 (43.0)	434 (40.9)
60+	3405 (36.8)	172 (23.6)	87 (45.3)	2186 (36.4)	303 (59.5)	361 (43.5)	323 (30.4)
Education							
< 13 years	2729 (29.5)	206 (28.2)	58 (30.2)	1734 (28.9)	137 (26.9)	287 (34.6)	320 (30.2)
≥ 13–14.5 years	3221 (34.8)	268 (36.7)	59 (30.7)	2184 (36.4)	170 (33.4)	276 (33.3)	280 (26.4)
> 14.5 years	3315 (35.8)	256 (35.1)	75 (39.1)	2081 (34.7)	202 (39.7)	267 (32.2)	461 (43.4)
Income							
Lower tertile	3064 (33.1)	271 (37.1)	60 (31.3)	1925 (32.1)	177 (34.8)	320 (38.6)	327 (30.8)
Middle tertile	3089 (33.3)	247 (33.8)	72 (37.5)	2018 (33.6)	174 (34.2)	252 (30.4)	345 (32.5)
Upper tertile	3112 (33.6)	212 (29.0)	60 (31.3)	2056 (34.3)	158 (31.0)	258 (31.1)	389 (36.7)
Labor market affiliation							
Working	5176 (55.9)	297 (40.7)	65 (33.9)	3610 (60.2)	227 (44.6)	255 (30.7)	745 (70.2)
Pension	2152 (23.2)	88 (12.1)	57 (29.7)	1349 (22.5)	227 (44.6)	226 (27.2)	220 (20.7)
Out of workforce/ disability pension	1937 (20.9)	345 (47.3)	70 (36.5)	1040 (17.3)	55 (10.8)	349 (42.0)	96 (9.0)
Region of residence							
North Denmark Region	720 (7.8)	77 (10.5)	14 (7.3)	478 (8.0)	14 (2.8)	30 (3.6)	109 (10.3)
Central Denmark Region	2044 (22.1)	161 (22.1)	44 (22.9)	1491 (24.9)	63 (12.4)	88 (10.6)	212 (20.0)
Region of Southern Denmark	2289 (24.7)	198 (27.1)	42 (21.9)	1602 (26.7)	114 (22.4)	117 (14.1)	226 (21.3)
Capital Region of Denmark	2919 (31.5)	190 (26.0)	65 (33.9)	1652 (27.5)	261 (51.3)	417 (50.2)	356 (33.6)
Region Zealand	1293 (14.0)	104 (14.2)	27 (14.1)	776 (12.9)	57 (11.2)	178 (21.4)	158 (14.9)
Civil status							
Unmarried	3687 (39.8)	287 (39.3)	97 (50.5)	2292 (38.2)	190 (37.3)	379 (45.7)	464 (43.7)
Married/registered partnership	5578 (60.2)	443 (60.7)	95 (49.5)	3707 (61.8)	319 (62.7)	451 (54.3)	597 (56.3)
Charlson comorbidity index							
0–1	7849 (84.7)	689 (94.4)	N/A[a]	5427 (90.5)	57 (11.2)	686 (82.7)	1003 (94.5)
2+	1416 (15.3)	41 (5.6)	N/A[a]	572 (9.5)	452 (88.8)	144 (17.3)	58 (5.5)
More than one diagnostic indication[b]							
No	9209 (99.4)	708 (97.0)	164 (85.4)	5947 (99.1)	499 (98.0)	830 (100.0)	1061 (100.0)
Yes	56 (0.6)	22 (3.0)	28 (14.6)	52 (0.9)	10 (2.0)		

N/A not available

[a]Not possible to show Charlson comorbidity values for paraplegia due to an insufficient number of observations in one of the cells ($n < 5$)

[b]Having more than one diagnostic indication among the first four groups (multiple sclerosis, paraplegia, neuropathy, nausea, and vomiting)

possible explanation as to why this broad patient group had one of the lowest QALY scores [27].

We noticed an uneven distribution in region of residence among responders, with most of them living in the Capital Region of Denmark and fewest in the North Denmark

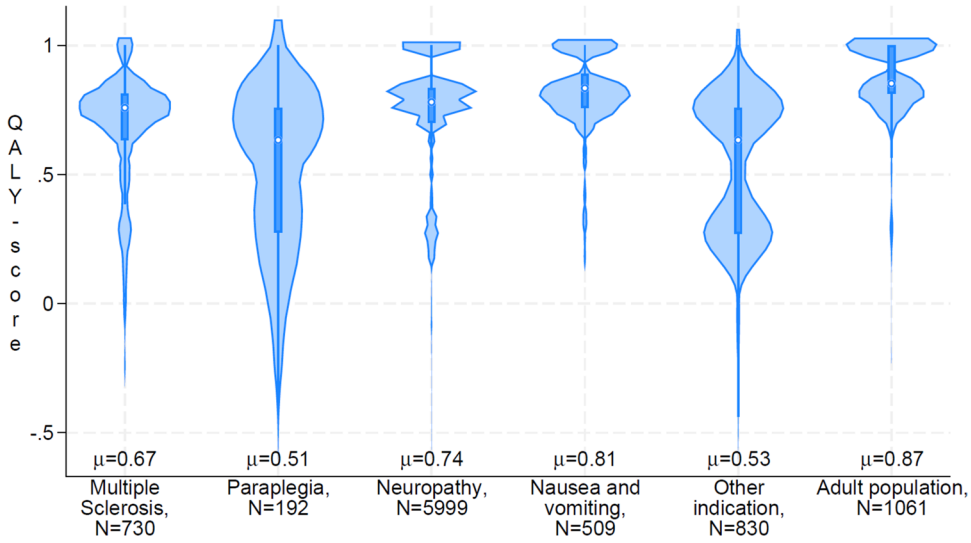

Fig. 1 Distribution of QALY scores among multiple sclerosis, paraplegia, neuropathy, nausea and vomiting, other diagnostic indication, and the comparison group. The violin plots are a modification of box plots that add plots of the estimated kernel density. The white dots indicate the medians, the dark blue boxes indicate the interquartile ranges, and the dark blue lines stretched from the bars indicate the lower/upper adjacent values. None of the observations are above 1 by definition [24]. The 'μ' indicates mean value for each group. *QALY* quality-adjusted life year

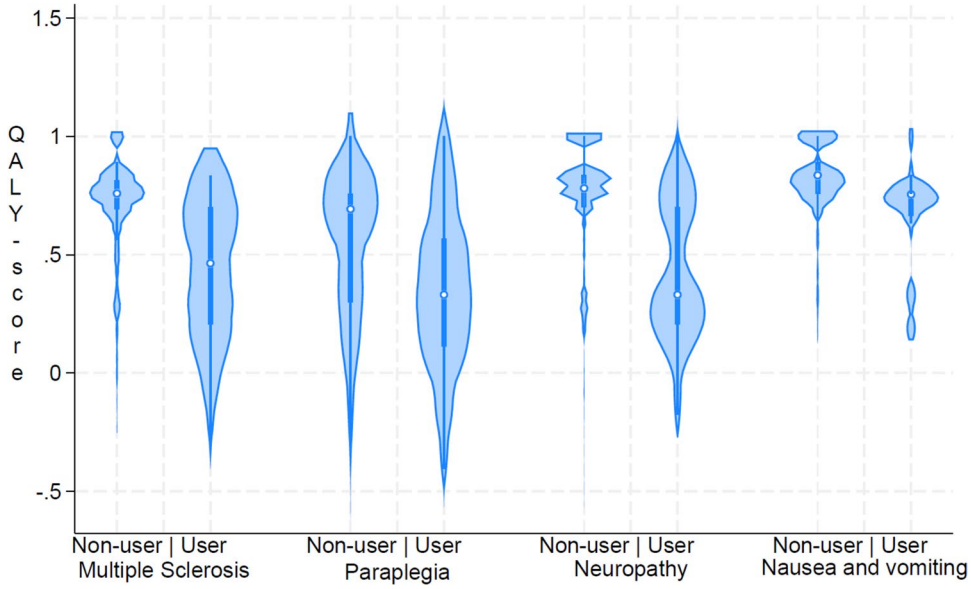

Fig. 2 Distribution of QALY scores among users and non-users of MC among multiple sclerosis, paraplegia, neuropathy, and nausea and vomiting patients. The violin plots are a modification of box plots that add plots of the estimated kernel density. The white dots indicate the medians, the dark blue boxes indicate the interquartile ranges, and the dark blue lines stretched from the bars indicate the lower/upper adjacent values. None of the observations are above 1 by definition [24]. *MC* medicinal cannabis, *QALY* quality-adjusted life year

Table 3 Comparison and distribution of QALY scores among users and non-users of MC, and the association between QALY score and use of MC compared with non-users for the four diagnostic indications, using separate linear regression models

	Non-users		Users		Crude model Coef. (95% CI)	Model 2[a] Coef. (95% CI)
	N (%)	Mean (SD)	*N* (%)	Mean (SD)		
Total	7175 (96.6)	0.74 (0.23)	255 (3.4)	0.44 (0.30)	n/a	n/a
Multiple sclerosis	665 (91.1)	0.70 (0.22)	65 (8.9)	0.42 (0.30)	− 0.28 (− 0.33 to − 0.22)	− 0.23 (− 0.31 to − 0.16)
Paraplegia	171 (89.1)	0.53 (0.31)	21 (10.9)	0.34 (0.35)	− 0.19 (− 0.34 to − 0.05)	− 0.18 (− 0.35 to − 0.01)
Neuropathy	5850 (97.5)	0.75 (0.23)	149 (2.5)	0.42 (0.29)	− 0.33 (− 0.36 to − 0.29)	− 0.27 (− 0.31 to − 0.22)
Nausea and vomiting	489 (96.1)	0.81 (0.16)	20 (3.9)	0.66 (0.22)	− 0.16 (− 0.23 to − 0.08)	− 0.16 (− 0.24 to − 0.07)

The adult population group and the other diagnostic indication group are omitted from this analysis, as all patients in these groups are non-users and users of MC, accordingly

[a]Adjusted for age, gender, region of residence, education, income, employment status, cohabitation, Charlson comorbidity index, and patients belonging to more than one indication

CI confidence interval, *MC* medicinal cannabis, *n/a* not applicable, *QALY* quality-adjusted life years

Table 4 Association between QALY score and frequency of MC use among the four diagnostic indications, using separate linear regression models

	Frequency of MC use		Crude model Coef. (95% CI)	Model 2[a] Coef. (95% CI)
	No. of prescriptions	*N* (%)		
Multiple sclerosis	0	665 (91.7)	Ref.	Ref.
	1–6	43 (5.9)	− 0.26 (− 0.33 to − 0.19)	− 0.21 (− 0.30 to − 0.12)
	≥ 7	17 (2.3)	− 0.29 (− 0.40 to − 0.18)	− 0.26 (− 0.41 to − 0.11)
Paraplegia	0	171 (89.1)	Ref.	Ref.
	1–6	16 (8.3)	− 0.22 (− 0.39 to − 0.06)	− 0.22 (− 0.43 to − 0.02)
	≥ 7	5 (2.6)	− 0.10 (− 0.38 to 0.19)	− 0.04 (− 0.32 to 0.24)
Neuropathy	0	5850 (97.6)	Ref.	Ref.
	1–6	97 (1.6)	− 0.30 (− 0.35 to − 0.26)	−0.24 (−0.30 to −0.19)
	≥ 7	49 (0.8)	− 0.38 (− 0.44 to − 0.32)	−0.32 (−0.39 to −0.25)
Nausea and vomiting	0	489 (96.1)	Ref.	Ref.
	1–6	14 (2.8)	− 0.10 (− 0.19 to − 0.01)	− 0.11 (− 0.20 to − 0.02)
	≥ 7	6 (1.2)	− 0.29 (− 0.42 to − 0.15)	− 0.27 (− 0.45 to − 0.08)

The comparison population is omitted from this analysis, as all patients in that group are non-users of MC

CI confidence interval, *MC* medicinal cannabis, *QALY* quality-adjusted life years

[a]Adjusted for age, gender, region of residence, education, income, employment status, civil status, Charlson comorbidity index, and patients belonging to more than one indication

Region. This was especially evident for the patients with nausea and vomiting, and patients with other diagnostic indications, where more than half of each group were residing in the Capital Region and < 4% in the North Denmark Region. For the patients with other diagnostic indications, this could stem from an uneven distribution of MC prescribing by GPs across the regions, as the Capital Region has the highest number of unique MC-prescribing GPs. The Capital Region also has the highest number of GPs compared with the other regions [31, 32]. Earlier research has further documented that there exists geographic variation in use of medication in general between the regions, though the Capital Region was using less medication than Region Zealand, Region of Southern Denmark, and the North Denmark Region at the time of study, but the differences were modest [33].

4.3 Comparisons with Other Studies

A systematic review of 14 studies on cannabinoids with distinct formulations yielded inconclusive evidence on the HRQoL relationship with patients' medical conditions. While some studies reported improvements in treated patients compared with placebo, most did not find significant differences [5]. A retrospective case series study assessing the relationship between MC and HRQoL on 3148 patients showed sustained HRQoL improvements over time and common but rarely serious adverse events [7]. The existing studies show that the current evidence base is mixed. Our study contributes to current literature by comparing the HRQoL of MC users versus non-users grouped across different diagnostic indications, which has not been documented to the same extent in previous studies. This needs to be backed by follow-up surveys asking the same questions to the same population, in order to detect changes in MC users' HRQoL over time.

4.4 Methodological Considerations

4.4.1 Strengths

We invited a large national sample comprising both users and non-users with diagnostic indications recommended for prescription by the Danish Medicines Agency, as well as users with other diagnostic indications and non-users in a comparison group of the adult population [12]. This allowed for a comparison of HRQoL between patient groups and examination of associations between HRQoL and use of MC within these groups.

4.4.2 Weaknesses

Our cross-sectional survey study design cannot determine causality, meaning that we cannot determine whether the use of MC lowers the HRQoL of patients, or whether patients with the lowest HRQoL are using MC because, for instance, they have tried all conventional medication with no effect or unacceptable adverse effects. Healthy user bias could also be evident in our survey, as survey responders are expected to be healthier than non-responders. This is a known challenge when conducting surveys that can challenge our study's external validity towards our target population [34]. It could be argued that this bias is evident here when interpreting the

relatively high percentage of patients with CCI scores < 1. However, when comparing the CCI scores with those of a sample of the general Danish adult population from a recent Danish study, the patients in our study are, as expected, more severely ill [35]. We examined self-reported use of MC rather than examining the patient's medical records, which would have provided us with a more objective measure. Recall bias is another known weakness of survey data, as people tend to either overestimate or underestimate experiences from the past. They are therefore potentially skewing their answers, which in turn decreases the validity of the survey data [36].

5 Conclusion

Patients with multiple sclerosis, paraplegia, neuropathy, or nausea and vomiting after chemotherapy, had a significantly lower HRQoL than individuals from the general adult population. The HRQoL was significantly lower among users of MC compared with non-users in all diagnostic indications. We also observed that patients redeeming the highest number of MC prescriptions had a lower HRQoL compared with patients redeeming fewer prescriptions and non-users, except for patients diagnosed with paraplegia. However, it should be noted that the number of users was quite small compared with non-users in the diagnostic indications.

6 Perspectives

The results provide knowledge relevant for current patients in the examined diagnostic indications as well as future potential users of MC. Clinicians will benefit from the results by getting a clear view of the differences in HRQoL at a group level between diagnostic indications and MC users compared with non-users. Future studies should follow up on our survey in order to detect changes in MC users' HRQoL over time, and investigate patients' experienced effects and adverse effects, and their reasons to continue or discontinue treatment with MC.

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Declarations

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Conflict of interest All authors declare that they have no competing interests.

Ethics approval and consent to participate The study protocol received approval from the Danish Data Protection Agency (journal number: 2015-57-0008) and the University of Southern Denmark's Research & Innovation Organization Institutional Review Board (journal number 10.335). No approval from the Regional Scientific Ethical Committees for Southern Denmark was needed according to Danish legislation. Moreover, answers to the questionnaire were anonymous to everyone except the research group, which obtained informed consent about participation and publishing of data from all participating individuals. All methods were carried out in accordance with the Helsinki declaration [37].

Consent for publication Not applicable.

Availability of data and materials The dataset generated and analyzed in the current study are available from the corresponding author on reasonable request, but restrictions apply to the availability of these data due to the data protection regulations from the Danish Data Protection Agency, and so are not publicly available. Access to data is strictly limited to the researchers who have obtained permission for data processing. This permission was given to the Research Unit of General Practice, Department of Public Health, University of Southern Denmark.

Code availability Not applicable.

Author contributions Each author has made substantial contributions according to the recommendations by the International Committee of Medical Journal Editors (ICMJE). All authors contributed to the design of the work, while FR in collaboration with SW performed the statistical analyses. All authors contributed to the interpretation of the data. FR drafted the manuscript. All authors revised the manuscript critically, and they have read and approved the final manuscript.

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