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ORIGINAL ARTICLE

Synthetic Cannabinoids and Cannabis: How the Patterns of Use Differ: Results from the European Web Survey on Drugs

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Abstract
The aim of the current study is to assess if the patterns of use, socio-demographic characteristics, and use of other drugs differ among people who only use cannabis and those that use synthetic cannabinoids. Data from the second wave of the European Web Survey on Drugs, a web-based cross-sectional survey from 10 different European countries including individuals aged 18 and over ($n = 37{,}109$). Participation was anonymous, self-selecting, and voluntary. Cannabinoid exposure was taken as the dependent variable and categorized into the four following variables: (1) neither last year use of cannabis nor of synthetic cannabinoids (SC) independently of lifetime use, (2) cannabis use, (3) synthetic cannabinoids use, and (4) use of both, in the last 12 months. Independent variables included socio-demographic data, other drug use in the last month, and patterns of cannabis use. The use of SC was associated with higher odd of polysubstance use in the last year (OR 2.17; 95%CI 1.27–3.72) and use of other drugs during the last month. Low income (OR 2.34; 95%CI 1.20–4.58) and unemployment (OR 3.02; 95%CI 1.34–6.83) were related to SC use alone and cannabis plus SC use (OR 1.53; 95%CI 1.13–2.05) (OR 4.12; 95%CI 3.45–4.91). Social vulnerabilities were associated with the use of cannabis in the last year, but more markedly with synthetic cannabinoids use. Those who used synthetic cannabinoids reported using other drugs more often than those who used or did not use cannabis. The findings highlight the importance of social vulnerabilities and poly-drug use when assessing the use of new psychoactive substances such as SC and how these differ when compared to cannabis.

Keywords Synthetic cannabinoids · Cannabis · European Web Survey on Drugs · New psychoactive substances

Abbreviations

EMCDDA	European Monitoring Center for Drugs and Drug Addiction
NPS	New psychoactive substances
OR	Odds ratio

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SC	Synthetic cannabinoids
SCRA	Synthetic cannabinoid receptor agonists

Background

Cannabis is the third most used substance worldwide, in Europe one in every five people in the 15–24 age group report having used in the last year (European Monitoring Centre for Drugs and Drug Addiction (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2021), with an estimated 192 million users worldwide (United Nations Office on Drugs and Crime (United Nations Office on Drugs and Crime (UNODC), 2021). During the past decades, policies surrounding cannabis have challenged governments and changed drastically, with some countries legalizing its medical use or decriminalizing its recreational use (Hughes et al., 2017). Moreover, rapid emergence of New Psychoactive Substances (NPS) imposes a significant burden on public health and raises new challenges for drug policy making. According to the European Monitoring Center for Drugs and Drug Addiction (EMCDDA), by the end of 2020, the EU Early Warning System on NPS was monitoring around 830 new psychoactive substances that have appeared on Europe's drug market since monitoring began in 1997. In Europe, seizures of NPS are typically dominated by synthetic cannabinoids (SC) and cathinones, with SC accounting for 28% of all seizures reported in 2020 (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2020)).

Although initially synthesized in the 1970s, a series of SC have been available in the illicit drug market for consumption since at least 2006, with metadata suggesting it could have been as early as 2004 (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) 2009). Since then, their presence has steadily increased (European Monitoring Center for Drugs and Drug Addiction (European Monitoring Center for Drugs and Drug Addiction (EMCDDA), 2017). This group of Synthetic Cannabinoid Receptor Agonists (SCRA) is structurally different from plant-derived cannabinoids. Albeit they bind to the same receptors, they have much greater affinity, rendering them full agonists of the CB1 receptor (Alves et al., 2020; Fattore & Fratta, 2011). The endocannabinoid system modulates a myriad of processes involved in the regulation of cell, tissue and organism homeostasis, brain development, neurotransmitter release, and synaptic plasticity and cytokine release from microglia (Cristino et al., 2020). Although cannabis consumption is widely perceived as having a lower toxicity compared to some other illicit substances, evidence points out that it can lead to a variety of adverse health effects, many of which are related to long term and heavy use and ranging from physical consequences of smoking (e.g., cardiovascular disease, chronic bronchitis), poor psychosocial functioning, use and dependence of cannabis and other drugs, psychotic disorders, and other mental health problems (Campeny et al., 2020; Collins, 2014). The higher affinity for CB1 receptors by/of SCRA is translated into a higher potency and greater adverse effects including anxiety, depersonalization, paranoia, psychomotor retardation or agitation, hypertension, tachycardia, respiratory depression, and seizures (Alves et al., 2020; Assi et al., 2020; Castaneto et al., 2014; Gounder et al., 2020; Le Boisselier et al., 2017). Because of changes in the production tactics of organized crime groups as well as access to cheaper and novel precursor, chemicals and processing equipment are part of the reason for changing trends on how cannabis and its derivates are used. The production of illicit drugs is now based on a more diverse set of chemicals, which are both difficult to respond to under European and international laws

and challenging to monitor (European Monitoring Centre for Drugs and Drug Addiction (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2020). Therefore, it has become an imperative need to understand the potential differentiation among cannabis users to give adequate guidance to both health care providers and policymakers.

There is a lack of information regarding a wide range of aspects about NPS (prevalence, patterns of use, risk profiles, etc.…). Previous evidence, although limited, seems to point out that low income increases the odds of using both cannabis and SC (Elliott et al., 2019; Monte et al., 2017), also among full-time students who use cannabis, there is an increased likelihood of consuming SC (Tai et al., 2021), and unemployment increases the odds for SC use and for cannabis plus SC use (Specka et al., 2020). More so, the evidence seems to point out that some users report preference of SC over cannabis due to cost and accessibility (Castaneto et al., 2014).

In the past, comparative drug policy analyses were done mainly based on information obtained from general population surveys or treatment samples. Targeted web surveys have proven to be a reliable and valuable complementary tool for collecting information on sensitive topics such as drug use by providing a sense of anonymity (Burkill et al., 2016; Miller & Sønderlund, 2010; Waldron et al., 2020). The European Web Survey on Drugs (EWSD) is an example of such a web survey strategy that offers the possibility of collecting information from large numbers of people and helps to fill out the knowledge gaps about drug use, supplementing the already established data collection tools (Matias et al., 2019; Škařupová et al., 2019). The EWSD was initially conceived to collect data from international samples of people who use drugs and their consumption and purchasing behaviors. There is a considerable gap in the knowledge about the public health impact of NPS use in Europe, for this reason, the use of national probabilistic surveys with harmonized data collection instruments such as the EWSD provides valuable and novel data on this important and understudied subject. The aim of the current study is to evaluate whether the patterns of use, socio-demographic characteristics, and use of other drugs differ among people who use cannabis and those who use cannabis and/or synthetic cannabinoids.

Methods

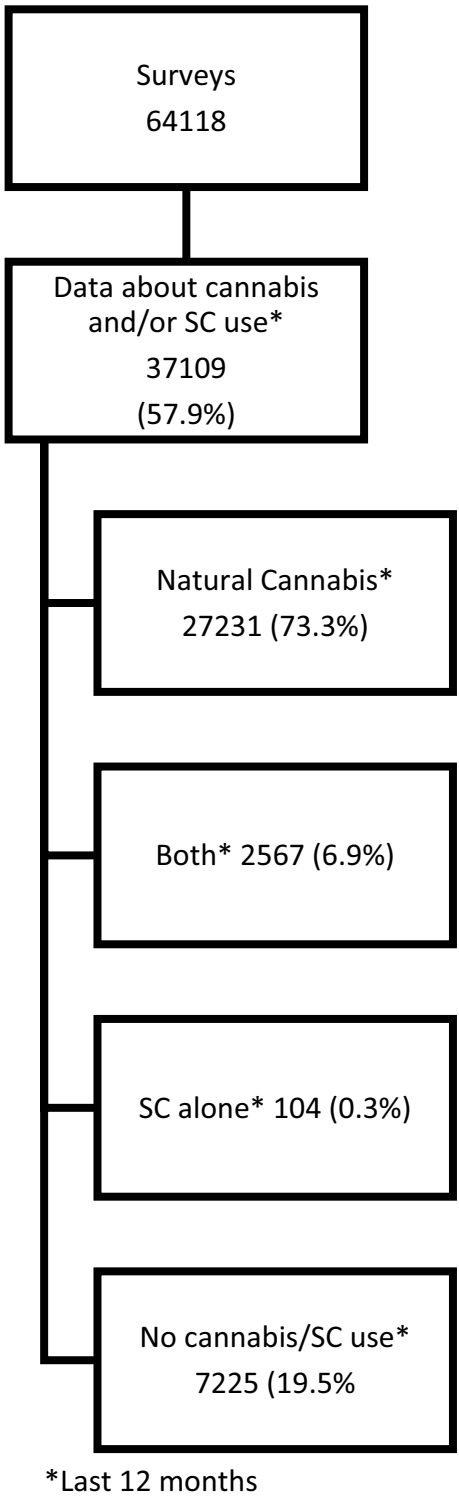
The EWSD collected information about patterns of use and purchase of the most frequently used illicit drugs (i.e., cannabis, opioids, stimulants, hallucinogens, NPS). The analysis presented is based on data about amounts and frequency of the different drugs used and purchased in 10 different European countries: Austria, Belgium, Cyprus, Estonia, Finland, Italy, Latvia, Lithuania, Luxembourg, and Poland participated in second wave of the EWSD initiative in 2017/18 (Matias & Singelton, 2018). For this study, only subjects for whom data about cannabis and SC use in the last 12 months was available were included (Fig. 1).

Individuals aged 18 and over who had used one or more of the drugs covered by the survey and who were resident in the participant countries were eligible to take part. Participation was anonymous, self-selecting, and voluntary.

Data Collection

The EWSD questionnaire was based on a previous European study (Report of consortium of Trimbos Institute RAND Europe & ICPR for European Commission- Directorate-General

Fig. 1 Flow diagram



for Justice, 2013) and comprised of128 questions on the patterns of use of cannabis (resin and herbal), amphetamines, methamphetamine, cocaine and MDMA (ecstasy), and NPS. The survey ran in 2017/2018 by using LimeSurvey©. For each participation country, a national partner connected to the Reitox national focal points and/or a harm reduction NGO was responsible for translating the survey for national audience and testing the questionnaire. Each participating country devised its own sampling strategy based on their networks and experience. Recruitment was done through multiple channels in order to attract a heterogeneous population of people who use drugs, among others by using online advertisements on Facebook/Instagram and websites associated with nightlife or via cannabis legalization initiatives forums (Matias et al., 2019).

The questionnaire covered questions on patterns of use of a range of substances for different timeframes, some attitude questions, and general demographics. Based on the European Model Questionnaire for surveys on drug use among the general population (European Monitoring Centre for Drugs and Drug Addiction (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2002), the attitude questions were added as introductory questions in order to avoid starting with more sensitive questions regarding drug using patterns. The web survey was organized into nine question groups: (1) information and consent; (2) age, gender, prevalence questions, and opinions; (3) cannabis module; (4) cocaine module; (5) ecstasy/MDMA module; (6) amphetamine module; (7) methamphetamine module; (8) NPS module (in turn split up into four submodules depending on the format of substance); (9) socio-demographic questions. At any point in time, a participant could opt out. Modules regarding drug use were displayed in a random order to respondents who reported having used the respective drug(s) in the last 12 months. At the end of each module, if they had used more than one drug, respondents were asked whether they wished to answer another drug module or finish the questionnaire. This procedure aimed to reduce the burden for users of multiple drugs and to reduce drop out due to time constraints and/or boredom. Randomization of the drug modules was based on the experience of the web survey that inspired the EWSD (Trautmann et al., 2013). In this web survey, they concluded that people were mostly replying to the cannabis module (the drug mostly used) and not so much to the other modules, as this was displayed always in the first place. Hence, they made a recommendation of randomizing all the drug-specific modules in order to have more respondents to all the modules.

Variables

Cannabinoid exposure was taken as the dependent variable and categorized into (1) no last year use of cannabis or SC independently of lifetime use, (2) cannabis use, (3) synthetic cannabinoids use, and (4) use of both in the last 12 months. Independent variables included socio-demographic data and cannabis use patterns including age, gender, employment status, income, average number of days of cannabis use in the past year, average quantity of cannabis used per occasion in the last year, mode of use, and use of other drugs. Substance use prevalence was generally assessed for the last 30 days, except for poly-drug use assessed only for the last 12 months and cannabis and SC use assessed for the last 30 days and last 12 months. We have prioritized the prevalence of substance use during the last month as it is a more direct measure of current consumption and a better indicator of a possible risky behavior. On the other hand, as the scope of this paper is based mainly on cannabinoid exposure, we assessed its use with a wider time frame (12 months).

Statistical Analysis

Univariate linear regression analysis was used to evaluate the unadjusted odds ratio (OR) of socio-demographic factors according to the type of cannabis used in the last year. The "no cannabis use exposure group" was the reference category for the main analysis (and the "cannabis use group" was the reference category for supplementary analysis).

Univariate analyses were also used to assess and compare the prevalence of last month use according to the type of cannabis used in the last year trough unadjusted OR. The "no cannabis use exposure group" was the reference category for the main analysis (and the cannabis use group for supplementary analysis). The odds of other drug use (last month) according to type of cannabis used in the last year were plot.

Characterization of the patterns of cannabis use alone and the use of both synthetic cannabinoids and cannabis during last year was assessed through the median and interquartile range. All statistical analyses were done using SPSS v24. The significance threshold was set to $\alpha < 0.05$.

Ethics

Only participants aged 18 and older who provided informed consent were allowed to participate in the study. Anonymity and confidentiality were ensured for all participants. Ethical approval was requested by the participating countries, where applicable.

Results

Socio-demographic characteristics and impact on type of cannabis used in the last year, using as the control group "no cannabis and no SC use" can be seen in Table 1. The most frequent pattern of use was "only cannabis use" (73.3%), with those who only used SC being a minority (0.3%) (see Fig. 1). Individuals who reported using both substances (cannabis and SC) during the last year had a tendency towards being younger (19 years; IQR 18–22) than only SC use (23 years; IQR 19–32.8) or only cannabis use (21 years; IQR 19–26).

Being male seems to be more likely related (OR 1.45; 95%CI 1.32–1.64) to cannabis use and females being less likely associated (OR 0.69; 95%CI 0.61–0.77), while being transgender did not seem to have an effect on cannabis use. On the other hand, gender did not seem to have an effect on the use of "SC only" and "both."

Having a full-time job seems to be less likely related to cannabis use (OR 0.56; 95%CI 0.49–0.64) as well as for cannabis plus SC use (OR 0.34; 95%CI 0.28–0.41) while full-time student seems to be more likely in those who report cannabis use (OR 2.09; 95%CI 1.7–2.46) and cannabis plus SC use (OR 2.92; 95%CI 2.39–3.56). Unemployment seems to be related to higher odds of SC use (OR 3.02; 95%CI 1.34–6.83) and cannabis plus SC use (OR 1.53; 95%CI 1.13–2.05).

Low income (< 2000€ per month) is associated with an increased probability of cannabis use (OR 3.00; 95%CI 2.68–3.37), SC use (OR 2.34; 95%CI 1.20–4.58), and both (OR 4.12; 95%CI 3.45–4.91). High income (> 5000€ per month) is less likely to be related to cannabis use (OR 0.03; 95%CI 0.02–00.4), SC use (0.08; 95%CI0.01–1.38), and both (OR 0.05; 95%CI 0.02–0.09), while medium income (2000–5000€) is less likely to be related

Table 1 Socio-demographic characteristics and impact on type of cannabis used in the last year (control group is "no cannabis use, no synthetic cannabinoid use"*)

	No cannabis* ($n=7225$)		Cannabis ($n=27,213$)			Synthetic cannabinoids ($n=104$)			Both ($n=2567$)			Stastics (p)
	Cases n (%)	Valid response	Cases n (%)	Valid response	OR (CI 95%)	Cases n (%)	Valid response	OR (CI 95%)	Cases n (%)	Valid response	OR (CI 95%)	
Gender (female)	577 (41.6)	1386	8766 (32.8)	26,689	0.69 (0.61–0.77)	30 (34.5)	87	0.7 (0.47–1.16)	981 (41.2)	2383	0.98 (0.86–1.1)	213,346 (<0.001)
Gender (trans)	13 (0.9)	1386	191 (0.7)	26,689	0.76 (0.43–1.33)	4 (4.6)	87	5.09 (1.62–15.95)	60 (2.5)	2383	2.73 (1.49–4.99)	
Gender (male)	796 (57.4)	1386	17,732 (66.4)	26,689	1.45 (1.32–1.64)	53 (60.9)	87	1.16 (0.74–1.80)	1342 (56.3)	2383	0.96 (0.84–1.09)	
Full-time job	543 (59.5)	912	7827 (45.0)	17,381	0.56 (0.49–0.64)	18 (47.4)	38	0.61 (0.32–1.17)	382 (33.3)	1146	0.34 (0.28–0.41)	202.146 (<0.001)
Partial-time job	84 (9.2)	912	1881 (10.8)	17,381	1.2 (0.95–1.51)	3 (7.9)	38	0.85 (0.25–2.81)	109 (9.5)	1146	1.03 (0.77–1.40)	
Full-time student	186 (20.4)	912	6054 (34.8)	17,381	2.09 (1.7–2.46)	8 (21.1)	38	1.04 (0.47–2.31)	490 (42.8)	1146	2.92 (2.39–3.56)	
Unemployed	74 (8.1)	912	1249 (7.2)	17,381	0.88 (0.69–1.12)	8 (21.1)	38	3.02 (1.34–6.83)	136 (11.9)	1146	1.53 (1.13–2.05)	
Other working status	25 (2.7)	912	370 (2.1)	17,381	0.77 (0.51–1.16)	1 (2.6)	38	0.96 (0.13–7.27)	29 (2.5)	1146	0.92 (0.54–1.58)	
Income < 2000€	582 (47.0)	1238	13,571 (72.7)	18,663	3.00 (2.68–3.37)	27 (67.5)	40	2.34 (1.20–4.58)	961 (78.5)	1224	4.12 (3.45–4.91)	1713.382 (<0.0001)
Income 2000–5000€	498 (40.2)	1238	5009 (26.9)	18,633	0.55 (0.49–0.62)	13 (32.5)	40	0.72 (0.37–1.40)	255 (20.8)	1224	0.39 (0.33–0.47)	
Income > 5000€	158 (12.8)	1238	83 (0.4)	18,633	0.03 (0.02–00.4)	0 (0.0)	40	0.08 (0.01–1.38)	8 (0.7)	1224	0.05 (0.02–0.09)	

to cannabis use (OR 0.55; 95%CI 0.49–0.62) and both (OR 0.39; 95%CI 0.33–0.47) but no statistical difference for SC use alone. Statistical significance and directionality of the effect was consistent when using cannabis use as the reference group (see supplementary table 1).

Relationship with the Use of Other Drugs

The prevalence of last month drug use according to the type of cannabis used in the last year, using as the control group "no cannabis and no SC use" is shown in Table 2 and Fig. 2. The use of SC in the last year seems to be associated with a higher odd of polysubstance use in the last year (OR 2.17; 95%CI 1.27–3.72). The use of both cannabis and SC seems to be highly associated with consuming NPS as a whole (OR19.41; 95%CI 16.21–23.23) and alcohol (OR 2.53; 95%CI 2.22–2.88) while showing a similar risk for MDMA use last month. The likelihood of consuming new opiates (OR 73.58; 95%CI 44.68–121.18), cathinones (OR 42.7; 95%CI 26.69–68.44), and other NPS (OR 47.6; 29.72–76.28) is especially higher in the group who reported using only SC. Statistical significance was achieved for all cases except for heroin use last month in last year cannabis users ($p > 0.05$, CI95% 0.95–1.61). Supplementary table 2 shows the prevalence of last month drug use according to the type of cannabis used in the last year, using as the control group "cannabis use."

Patterns of Use

The pattern of cannabis use only versus both cannabis plus SC use during the last year is shown in Table 3. When compared to only cannabis users, those who used both cannabis and SC in the last year reported having used cannabis resin (3 [IQR 1–12] vs. 7 [IQR 2–25]; $p < 0.001$), herbal cannabis (14 [IQR 4–25] vs. 20 [IQR 6–29]; $p < 0.001$), and the sum of resin and weed (25 [IQR 11–30] vs. 30 [IQR 19–30]; $p < 0.001$) more days during last month. Furthermore, they reported smoking more joints (resin + weed) (2.0 [IQR 1–3] vs. 2.8 [1.9–4]; $p < 0.001$), weed joints (2 [IQR 1–3] vs. 3 [IQR 2–4]; $p < 0.001$), and resin joints (2 [IQR 1–3] vs. 3 [IQR 2–4]; $p < 0.001$) per day during the last month.

The pattern of use of synthetic cannabinoids versus both cannabis plus SC during last year is shown in Table 3. When compared to those who use both cannabis and SC, individuals who use only SC reported using more powder SC (2 [IQR 0–4] vs. 1 [IQR 0–3]; $p = 0.01$) and blotters NPS (3.5 [IQR 0–7] vs. 1 [IRQ 0–1.25]; $p = 0.018$) per day during the last month. However, those who used both substances last year trended to use more powder per day (0.75 [IQR 0.2–1.0] vs. 1 [IQR0.5–2]; $p < 0.001$).

Discussion

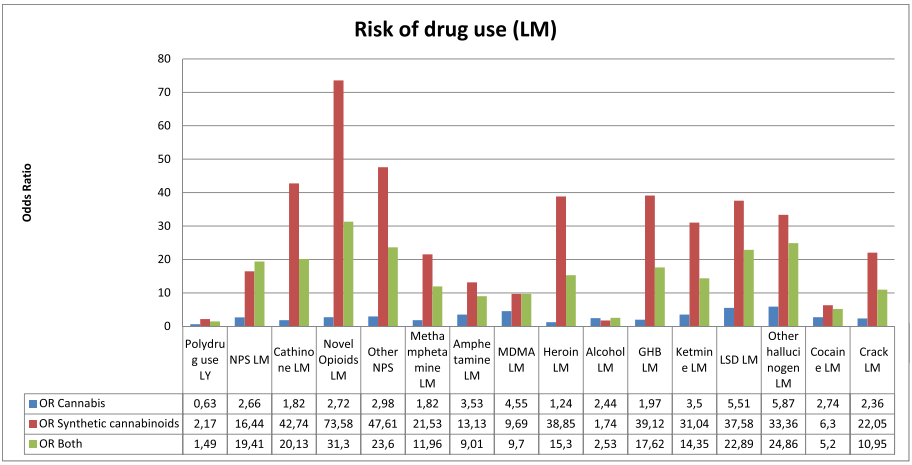
The present exploratory analysis of the EWSD found that the most common pattern of use was only cannabis, while those who use only SC represent only a minority of the sample; furthermore, those reporting the use of both substances during the last year were younger. Similarly, to what has been previously highlighted, it seems that men are more likely to consume cannabis than women (M. B. Forrester et al., 2012; Mathias B. Forrester et al., 2011; Hoyte et al., 2012; Salas-Wright et al., 2019; Sznitman et al., 2020).

Table 2 Prevalence of last month use according to the type of cannabis used in the last year (control group is "no cannabis use, no synthetic cannabinoid use")

	No cannabis LY ($n=7225$)		Natural cannabis LY ($n=27,213$)			Synthetic cannabinoids LY ($n=104$)			Both LY ($n=2567$) OR (CI 95%)			Stastics (p)
	Cases n (%)	Valid responses	Cases n (%)	Valid responses	OR (CI 95%)	Cases n (%)	Valid responses	OR (CI 95%)	Cases n (%)	Valid responses	OR (CI 95%)	
Poly-drug use LY	932 (67.0)	1391	15,072 (56.2)	26,803	0.63 (0.56–0.71)	75 (78.9)	95	2.17 (1.27–3.72)	2391 (100.0)	2391	1.49 (1.44–1.55)	1,801,294 (<0.001)
NPS LM	156 (2.2)	7183	1513 (5.6)	27,124	2.66 (2.25–3.14)	27 (26.7)	101	16.44 (10.29–26.25)	769 (30.1)	2554	19.41 (16.21–23.23)	2,627,357 (<0.001)
Cannabis LM	0 (0.0)	7152	21,533 (79.1)	27,213	N/A	0 (0.0)	101	N/A	2247 (87.5)	2567	N/A	17,064,253 (<0.001)
SC LM	0 (0.0)	7120	2 (<0.1)	26,868	N/A	54 (51.9)	104	N/A	1572 (61.2)	2567	N/A	2,1923,567 (<0.001)
Cathinone LM	81 (1.2)	7009	550 (2.1)	26,826	1.82 (1.44–2.30)	33 (33.0)	100	42.74 (26.69–68.44)	474 (18.8)	2517	20.13 (15.82–25.61)	2,542,703 (<0.001)
Novel opiates LM	51 (0.7)	7115	517 (1.9)	26,818	2.72 (2.04–3.64)	34 (34.7)	98	73.58 (44.68–121.18)	463 (18.4)	2512	31.30 (23.34–41.97)	2,692,743 (<0.001)
Other NPS LM	75 (1.0)	7112	827 (3.0)	26,836	2.98 (2.35–3.78)	34 (33.7)	101	47.61 (29.72–76.28)	510 (20.1)	2538	23.60 (18.43–30.22)	2,193,520 (<0.001)
Methampheta-mine LM	123 (1.7)	7184	832 (3.1)	27,112	1.82 (1.50–2.20)	27 (27.3)	99	21.53 (13.36–34.68)	440 (17.2)	2552	11.96 (9.74–14.69)	1,561,055 (<0.001)
Amphetamine LM	399 (5.6)	7184	4667 (17.2)	27,125	3.53 (3.18–3.93)	44 (43.6)	101	13.13 (8.75–19.70)	886 (34.6)	2558	9.01 (7.92–10.26)	1,314,858 (<0.001)
MDMA LM	363 (5.0)	7192	5286 (19.5)	27,135	4.55 (4.08–5.08)	34 (34.0)	100	9.69 (6.32–14.85)	872 (34.1)	2559	9.7 (8.51–11.11)	1,379,886 (<0.001)

Table 2 (continued)

	No cannabis LY ($n=7225$)		Natural cannabis LY ($n=27,213$)			Synthetic cannabinoids LY ($n=104$)			Both LY ($n=2567$) OR (CI 95%)			Stastics (p)
	Cases n (%)	Valid responses	Cases n (%)	Valid responses	OR (CI 95%)	Cases n (%)	Valid responses	OR (CI 95%)	Cases n (%)	Valid responses	OR (CI 95%)	
Heroin LM	67 (0.9)	7104	313 (1.2)	26,898	1.24 (0.95–1.61)	27 (27.0)	100	38.85 (23.50–64.23)	323 (12.7)	2551	15.30 (11.71–19.98)	1,964,676 (<0.001)
Alcohol LM	5281 (73.9)	7142	23,589 (87.4)	26,993	2.44 (2.29–2.60)	84 (83.2)	101	1.74 (1.03–2.94)	2234 (87.8)	2545	2.53 (2.22–2.88)	821,714 (<0.001)
GHB LM	64 (0.9)	7094	473 (1.8)	26,804	1.97 (1.52–2.57)	26 (26.3)	99	39.12 (23.47–65.20)	348 (13.8)	2518	17.62 (13.44–23.10)	1,690,649 (<0.001)
Ketamine LM	100 (1.4)	7108	1278 (4.8)	26,872	3.50 (2.85–4.30)	31 (30.7)	101	31.04 (19.46–49.49)	431 (16.7)	2536	14.35 (11.48–17.93)	1,106,080 (<0.001)
LSD LM	80 (1.1)	7095	1586 (5.9)	26,842	5.51 (4.39–6.90)	30 (30.0)	100	37.58 (23.23–60.80)	527 (20.7)	2546	22.89 (18.00–29.11)	1,381,165 (<0.001)
Other hallucinogen LM	108 (1.5)	7101	2224 (8.3)	26,778	5.87 (4.83–7.13)	34 (34.0)	100	33.36 (21.16–52.59)	699 (27.7)	2520	24.86 (20.17–30.64)	1,338,836 (<0.001)
Cocaine LM	398 (5.5)	7178	3757 (13.8)	27,137	2.74 (2.46–3.05)	27 (27.0)	100	6.30 (4.01–9.91)	599 (23.4)	2560	5.20 (4.54–5.96	690,838 (<0.001)
Crack LM	112 (1.6)	7140	977 (3.6)	26,963	2.36 (1.94–2.87)	26 (26.0)	100	22.05 (13.59–35.78)	378 (14.9)	2545	10.95 (8.82–13.59)	1,021,223 (<0.001)



	Polydrug use LY	NPS LM	Cathinone LM	Novel Opioids LM	Other NPS	Methampheta mine LM	Amphetamine LM	MDMA LM	Heroin LM	Alcohol LM	GHB LM	Ketmine LM	LSD LM	Other hallucinogen LM	Cocaine LM	Crack LM
OR Cannabis	0,63	2,66	1,82	2,72	2,98	1,82	3,53	4,55	1,24	2,44	1,97	3,5	5,51	5,87	2,74	2,36
OR Synthetic cannabinoids	2,17	16,44	42,74	73,58	47,61	21,53	13,13	9,69	38,85	1,74	39,12	31,04	37,58	33,36	6,3	22,05
OR Both	1,49	19,41	20,13	31,3	23,6	11,96	9,01	9,7	15,3	2,53	17,62	14,35	22,89	24,86	5,2	10,95

Fig. 2 Risk of drug use (last month) according to the type of cannabis used in the last year (control group is "no cannabis use, no synthetic cannabinoid use"*). *Statistical significance ($p < 0.05$, CI95% > 1.0) for all cases except for heroin use LM in cannabis users LY ($p > 0.05$, CI95% 0.95–1.61) and poly-drug use LY in cannabis users LY ($p < 0.05$, CI 95% < 1.0)

Moreover, as it has been previously reported (Tai et al., 2021), we also found that among full-time students who use cannabis, there is an increase likelihood of consuming SC. Also, like what previous evidence points out, low income seems to increase the odds of using both cannabis and SC (Elliott et al., 2019; Monte et al., 2017). Furthermore, unemployment increases the odds for SC use and for cannabis plus SC use, another consistent finding with what has been previously described (Specka et al., 2020). Furthermore, it has been found that some users report preference of SC over cannabis due to cost and accessibility (Castaneto et al., 2014). In the light of these findings, public funds and strategies could be more target oriented to prevent the concomitant use of potentially harmful substances. The fact that NPS represent a highly heterogeneous set of substances and their increasing presence in the global market makes it almost impossible to control each new substance individually (European Monitoring Centre for Drugs and Drug Addiction and Eurojust 2016). As part of a response to the alarming health-related issues associated with SC consumption across Europe and the USA, countries have banned and controlled their use (Alves et al., 2020; Caviness et al., 2015). Most EU Member States have decided to manage them under the existing drug legislation, through either modification or extension of preexisting laws with several extending the coverage by listing tightly defined generic groups of substances rather than individual drugs (United Nations Office on Drugs and Crime (United Nations Office on Drugs and Crime (UNDOC), 2020). Nonetheless, despite efforts and initiatives, these substances continue to emerge and thrive in the illegal drug markets. A suitable public health approach, implemented for other substances (e.g., alcohol), focuses on identifiying high-risk groups of having harmful consequenses from substance use. Besides individual non-modifiable or partially modifiable factors, patterns of use (frequency, dose per use, concomitant use of other substances, and route of administration among others) can help identify high-risk users and intervene in a more specific way (Bruguera et al., 2021; Casajuana Kögel et al., 2017). Complementary strategies to reduce impact on health related to cannabis and synthetic cannabinoids use, among which harm

Table 3 Cannabis versus both (synthetic cannabis + cannabis) during last year: patterns of use

	Natural cannabis LY ($n=27,213$)			Both LY ($n=2567$)			Stastics (p)
	Median	IQR	Valid responses	Median	IQR	Valid responses	
Age	21	19–26	26,557	19	18–22	2335	$P<0.001$
No of days used cannabis in the past 30 days	20	5–20	339	22.5	10–30	36	0.343
No. of days used cannabis resin in the past 30 days	3	1–12	5941	7	2–25	506	$P<0.001$
No. of days used cannabis weed/skunk in the past 30 days	14	4–25	15,379	20	6–29	1153	$P<0.001$
Sum of days used resin & weed in the past 30 days	25	11–30	5413	30	19–30	447	$P<0.001$
How many joint(s) do you smoke/consume on a typical day you use resin?	2	1–3	5015	3	2–4	387	<0.001
How many dry pipe(s) or chillum(s) do you smoke/consume on a typical day you use resin?	2	1–3	469	2	1–5	45	0.324
How many water pipe(s) do you smoke/consume on a typical day you use resin?	3.2	2–5	496	5	3–10	44	0.003
How many joint(s) do you smoke/consume on a typical day you use weed/skunk?	2.0	1–3	14,997	3	2–4	1009	<0.001
How many dry pipe(s) or chillum(s) do you smoke/consume on a typical day you use weed/skunk?	2.0	1–3	1212	3	1.25–5	88	<0.001
How many water pipe(s) or chillum(s) do you smoke/consume on a typical day you use weed/skunk?	3.0	2–5	1268	3	2–7	76	0.606
Number of joints consumed on typical day 2 using cannabis (either resin or resin)	2.0	1–3	15,872	2.87	1.92–4	7096	<0.001
Number of dry pipes consumed on typical day using cannabis (either resin or resin)	2	1–3	1531	2	1–5	119	0.001
Number of waterpipes consumed on typical day using cannabis (either resin or resin)	3	2–5	1484	4.81	2–8	95	0.109

reduction programs and onsite analysis like drug checking could be considered, guided by evidence are essential to tackle this concerning matter.

Another very sensitive finding is the fact that the use of SC in the last year is associated with the highest risk of polysubstance use in the last month, a finding consistent with previous reports (Shapira et al., 2020; Specka et al., 2020; Winstock & Barratt, 2013), with the risk being particularly high for co-use of cathinones and synthetic opioids. The fact that a low number of synthetic opioid users participated in the survey is worth mentioning. We hypothesize this finding could be due, at least in part, because both cathinones and SC have similar status, as they have been sold in the same places. We add the fact that until not so long ago they were legally and readily available in convenience stores across Europe (Shapira et al., 2020). On the other hand, it could simply be a secondary phenomenon to the fact that there is just a broader (mainstream) interest for stimulants and cannabis than for opioid substances (European Monitoring Centre for Drugs and Drug Addiction (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2021). Nevertheless, this finding could also be explained by the recruitment strategies applied, with convenience sampling and online format probably reaching mainly people who use drugs in recreational settings and hence aim for the effects of stimulants, hallucinogens, or cannabis rather than sedatives. In addition, these online formats tend to attract to mainly high- and middle-class participants and mainly fail in reaching out to most marginalized populations among which the use of opioids is more prevalent.

Furthermore, interestingly this research points out differences regarding the patterns of use, showing that individuals who smoke cannabis plus SC seem to consume a higher quantity of cannabis in any form when compared to those who smoke only cannabis. One possible explanation for this phenomenon could be the fact that SC has a much stronger affinity for the CB1 receptor (Alves et al., 2020; Castaneto et al., 2014), thus requiring higher doses to achieve a desired effect when compared to those who only use cannabis. This finding is particularly relevant in the light of the fact that heavier use is related to adverse effects in cannabis users (Campeny et al., 2020; Collins, 2014). Another possible explanation is that some individuals might seek more affordable and accessible alternatives; nonetheless, differences in price and routes of purchases were explored and no significant differences found.

Some strengths of the EWSD are that it targeted selected groups with high prevalence of use, using specific sampling and data collection methods, which provides detailed information from users, valuable for the development of specific interventions. On the other hand, there are some noteworthy limitations to this study. First, and most important, the small sample size of SC users compared to the other groups could lead to an under/overestimation of the effect as well as a greater uncertainty (margin of error). This is relevant since a small sample can make statistically significant differences unnoticeable, and by contrast, they could have a big clinical impact (Beta error). Second are limitations specific to the EWSD, in that it does not allow drawing conclusions generalizable to the entire population. Nevertheless, this was likely attenuated by the fact that the same questionnaire was used in all participating countries and resulted in a very large data set. A limitation that should be mentioned is that cannabis strength/purity (THC/CBD levels) differs highly between countries and might have an impact on the results (Freeman et al., 2021; Quattrone et al., 2021). Furthermore, recall bias and confounding effects from other substances are all issues needed to be considered. It is also very possible that the effect profile with synthetic cannabinoids will change with repeated episodes of use and with differing routes of administration (e.g., oral). However, in the early stages of the appearance of a new drug, approaches such as these are often the only initial way of accessing data rapidly and

efficiently. Another noteworthy limitation of the EWSD is the fact that the respondent profiles differed between countries (e.g., the proportion aged 18–24 ranged from 30 to 80%); also, the results relating to use showed both inter-country similarities and differences (e.g., mean daily amounts of cocaine used varied between countries but increases in amounts used with increased frequency of use were similar) (Matias et al., 2019). Furthermore, the fact that there was a randomized distribution of the different sections within the drug modules could lead to a possible bias.

Conclusions

Considering the gap in the knowledge about the public health impact of NPS use in Europe, this study provides novel, valuable, and reliable data by means of the EWSD to further understand the NPS phenomenon. Social vulnerabilities (e.g., low incomes, unemployment) and being male were associated with synthetic cannabinoids use last year compared with no cannabis use or only cannabis use. Those who used synthetic cannabinoids last year tended to use other drugs more often than those who only used cannabis or did not use cannabis. Understanding the patterns of NPS use needs to be focused on the link between gender, social vulnerabilities, and poly-drug use. Considering the limitations, from a clinical point of view, the current findings could encourage and guide clinicians when assessing cannabis use in the described populations, exploring the use of SC among those who seem to be at highest risk.

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Data Availability The datasets generated and/or analyzed during the current study are not publicly available due to confidentiality reasons, but are available from the corresponding author on reasonable request.

Declarations

Ethics Approval and Consent to Participate Only participants aged 18 and older who provided informed consent were allowed to participate in the study. Anonymity and confidentiality were ensured for all participants. Ethical approval was requested by the participating countries, where applicable.

Competing Interests The authors declare no competing interests.

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