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Drivers who tested positive for cannabis in oral fluid: a longitudinal analysis of administrative data for Spain between 2011 and 2016

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ABSTRACT

Objectives This study aimed to assess the association between positive roadside tests for delta-9-tetrahydrocannabinol (THC) and other driving-impairing substances and THC concentrations and the age and gender of THC-positive drivers.

Design This study is based on administrative data.

Setting, participants and exposures National administrative data on drivers who tested positive in confirmation analysis of driving-impairing substances in oral fluid were assessed (2011–2016, 179 645 tests).

Primary and secondary outcome measures Frequencies of positivity for THC, THC alone and THC plus non-THC substances (stratification by age and gender in 2016) and THC concentration were obtained. Comparisons and univariate and multivariate regression analyses were performed.

Results Of the 65 244 confirmed drug-positive tests, 51 869 were positive for THC (79.5%). In 50.8% of the THC-positive tests, cocaine and amphetamines were also detected. Positivity for THC and non-THC substances predominated among drivers with low THC concentrations and represented 58.6% of those with levels lower than 25 ng/mL. The mean±SD for age was 29.6±7.7 years (year 2016, n=24 941). Men accounted for 96.3% of all THC-positive drivers. With increasing age, positivity for THC decreased (OR 0.948; 95% CI 0.945 to 0.952; p<0.0001), and positivity for THC and non-THC substances increased (OR 1.021; 95% CI 1.017 to 1.024; p<0.0001). Men were associated with higher THC concentrations (OR 1.394; 95% CI 1.188 to 1.636; p<0.0001).

Conclusions Cannabis positivity is frequent among drivers, and polysubstance use is common. Hence, focusing on younger drivers and those with low THC concentrations is encouraged. This study provides evidence on the current implementation of roadside drug testing in Spain and aims to characterise driving under the influence (DUI) of cannabis to increase the awareness of all involved to help them avoid DUI.

INTRODUCTION

Driving under the influence (DUI) of cannabis is common among the driving population according to surveys, blood and oral fluid (OF) analysis data, and studies of seriously injured or killed car drivers.[1–5] The European Union's Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) project reported a weighted mean prevalence of delta-9-tetrahydrocannabinol (THC) of 1.32% (range 0.0%–5.99%) across Belgium, the Czech Republic, Denmark, Spain, Italy, Lithuania, Hungary, the Netherlands, Poland, Portugal, Finland, Sweden and Norway.[3] Despite the marked difference in prevalence between Northern and Southern Europe, when alcohol was excluded, THC ranked third among all investigated substances in the general driver population, second for seriously injured drivers (0.5%–7.6%) and fourth for killed drivers (0.0%–6.1%).[3]

The DUI of cannabis is a public health concern.[1 3 6] Cannabis impairs cognition, psychomotor function and driving performance.[7] The driver's initial compensation ability is lost with increasing doses and task complexity.[8] Various meta-analyses have confirmed that cannabis use is associated with an increased risk of car crashes,[9 10] although the reported risk magnitude is mostly influenced by alcohol use,[11] methodological flaws in the included studies[12] and interaction effects in the estimates.[13] In any case, the risk of being involved in a car crash while under the influence of cannabis must be considered

to some degree (relative risk 1–3) if no other substances are consumed.[3]

Worldwide, in 2013, alcohol was estimated to be responsible for 188 151 road traffic deaths, and illicit drug use was estimated to be responsible for 39 625 road traffic deaths: cannabis caused one-fifth of all illicit drug-related road traffic deaths.[1] Figures reported in France and the USA are consistent with this finding.[14–16] Importantly, the problem of DUI of cannabis could worsen dramatically with the current trend in global cannabis legalisation initiatives. This may be very disquieting considering that a heterogeneous population is currently taking cannabis and/or products containing cannabinoids (ranging from healthy users of recreational cannabis to polymorbid and polymedicated patients using cannabinoid-based medicines and, probably, raw herbal cannabis). The medical use of cannabis and cannabinoids must, therefore, be defined appropriately.[17] However, in parallel to the implementation of adequate legal measures, awareness must be promoted among all individuals involved in preventing DUI of cannabis (road safety and health authorities, the public at large, practitioners and other healthcare providers).

Worldwide, DUI is not allowed, and prohibitions follow three well-defined legal approaches: (1) zero tolerance, that is, laws against driving with any amount of driving-impairing substances in the body; (2) impairment, that is, laws against driving when one is impaired by such drugs, or 'under the influence'; and (3) per se, that is, the definition of a maximum established concentration above which it is unlawful to drive.[1]

In Spain, we have a dual legal approach: zero-tolerance and impairment laws apply.[18] According to our zero-tolerance system, the driver is punished when any amount of drug is detected (except prescribed medicines according to medical indications), regardless of whether his/her driving abilities are impaired. In the absence of impairment, only administrative sanctions are imposed on the infringing driver (a fine of €1000, along with the loss of six driving license points). Additionally, when signs of impairment due to the use of psychoactive drugs are observed, the driver is punished as a criminal offender (imprisonment for 3–6 months, a fine or community service of 31–90 days, with, driving disqualification for 1–4 years in all cases).

Roadside alcohol and drug testing is one means of enforcing laws against DUI. Although guaranteeing safe driving is the main objective,[19 20] the accurate quantification of drugs detected at the roadside with the intention of punishing all drivers–consumers requires a two-step drug detection procedure: on-road screening testing, followed by confirmation analysis in toxicology laboratories. In this sense, the current OF THC cut-off of 25–30 ng/mL set in the available screening devices in our country (see online supplementary table S1) is not taken into account in confirmation analysis, in which punishable THC concentrations are very low (see online supplementary table S2).

Worldwide, consumers of cannabis account for an important proportion of drivers,[1–5] but the profile of such drivers may differ from one region to another. What is the average age of cannabis consumers who drive? Do men or women consume more? Which other driving-impairing substances are used by such drivers? What amounts are consumed? The deterrent effects of measures to prevent DUI (roadside drug testing in association with regulations) must be monitored.[21] These measures may need to be adapted to the evidence.[3 6] Although this study may not be an authentic monitoring tool, it provides real-world evidence on the current implementation of roadside drug testing in Spain, with the aim of characterising DUI of cannabis to improve the awareness of all parties involved in controlling it (ie, healthcare providers, authorities and the public at large).

Australia, a pioneering country in the adoptions of roadside testing, has also reported the profile of cannabis-positive drivers[22 23] with the aim of evaluating this and other deterrent measures.[24]

This study aimed to comprehensively assess the association between confirmed positive roadside tests for THC and other driving-impairing substances and THC concentrations and the age and gender of THC-positive drivers.

METHODS
Study design, data source and target population
A study based on national administrative data of drivers who tested positive on confirmation analyses for licit/illicit driving-impairing substances was conducted, and its results are presented here according to the REporting of studies Conducted using Observational Routinely collected health Data statement.[25]

The drug-positive roadside tests accessed were sent for confirmation analysis according to current legislation, and they corresponded to the following: (1) drivers involved in road traffic accidents, (2) drivers involved in traffic violations, (3) random testing and (4) special circumstances, also called 'targeted testing' (eg, when the traffic police suspect the driver is under the influence of drugs or in road safety campaigns).[26]

As in our previous study,[26] the entire nationwide database on drivers with confirmed positive results for specific psychoactive substances was accessible. Since 2011, confirmation analysis information has been routinely collected and recorded at the Dirección General de Tráfico (the Spanish National Traffic Agency).[27] For this study, any confirmed positive result for drugs, that is, the presence of concentrations equal to or greater than the lower limit of quantification (see online supplementary table S2), was considered a drug-positive case and recorded as such. Other than the number of cases, no information on drivers who tested negative at roadside was available (see online supplementary methods). Anonymisation of the database was guaranteed, but the age and gender of many drug-positive drivers were retained (information was systematically recorded and available starting in 2016).

Following our nationwide-regulated procedure of detection of drugged driving (see online supplementary methods), 65 244 drug-positive roadside tests out of the total 179 645 tests performed between 01 January 2011 and 31 December 2016 were sent for confirmation analysis (see online supplementary table S3) and were distributed as follows (year, n): 2011/62, 2012/1087, 2013/2017, 2014/9991, 2015/25 966 and 2016/26 121. At the time of testing, the individuals were men and women aged 16 years and older who had a driving license.

Driving-impairing drugs

Information on the following groups of DRUID[3] driving-impairing substances and some of their metabolites that were assessed in the confirmation analysis were accessed: (1) amphetamines (amphetamine, 3,4-methylenedioxymethamphetamine, 3,4-methylenedioxyamphetamine, 3,4-methylenedioxy-N-ethylamphetamine and methamphetamine), (2) cocaine (benzoylecgonine), (3) THC, (4) opioids (6-acetylmorphine, morphine, codeine, methadone and tramadol), (5) benzodiazepines (hypnotics, flunitrazepam, 7-aminoflunitrazepam, anxiolytics, alprazolam, clonazepam, 7-aminoclonazepam, diazepam, lorazepam, nordiazepam and oxazepam) and (6) Z-drugs (zolpidem and zopiclone).

Variables

The following information was available for each drug-positive case: (1) date of the roadside drug test, (2) age and gender for the year 2016 (age and gender (n) 24 941/24 748) and (3) THC concentration (in ng/mL) and concentration of other drugs (but this information is not presented in this manuscript). No information was available for alcohol breath tests.

Ethics approval

The database provided by the Dirección General de Tráfico was anonymised, and no personal data were accessible to us.

Patient and public involvement

Patients and members of the public were not involved.

Statistical analyses

The frequencies (percentages) of positive cases for THC, THC alone, and THC and non-THC substances were calculated. Mean and SD were calculated for age and THC concentration. Medians with quartiles 1 and 3 were also obtained for THC concentration. Stratification by age and gender for the year 2016 was performed.

Differences between groups were determined for categorical variables (percentage of THC-positive cases) using the χ^2 test and for continuous variables (THC concentration) using the Mann-Whitney U test or Kruskal-Wallis H test. The Kolmogorov-Smirnov Z test was used to assess whether the THC concentration was normally distributed. Cohen's d effect sizes corresponding to comparisons of THC concentrations were calculated. Relationships observed in a univariate regression were confirmed in a multivariate regression. Multivariate regression analyses were performed to evaluate the relationships of (1) positivity for THC and (2) positivity for THC and non-THC substances (dependent variables) and the age or gender of THC-positive drivers (independent variables), from which ORs with their corresponding 95% CIs were determined. The relationships between (1) THC concentrations of 25 ng/mL or over and (2) THC concentrations less than 25 ng/mL (dependent variables) and the age or gender of THC-positive drivers (independent variables) were also assessed in the multivariate logistic regression. Multiple linear regression analysis was performed to assess the association between THC concentration and the age and gender of THC-positive drivers, from which the slope of the line (b) and the corresponding 95% CIs are presented.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS V.23.0). For statistical significance testing ($p \leq 0.05$), two-tailed tests were used.

RESULTS

A total of 51 869 out of the 65 244 drug-positive cases were positive for THC (79.5%). In 50.8% of all THC-positive cases (26 353 out of 51 869), other substances were detected: cocaine (43.7%, n=22 666) and amphetamines (15.5%, n=8040) were the most frequently detected (table 1).

Despite its marked dispersion (Kolmogorov-Smirnov Z test, p corresponding to THC concentration for all THC-positive cases, men and women: 0.164, p<0.0001/0.164, p<0.001/0.178, p<0.0001; figure 1 and online supplementary table S4, figure S1), THC concentrations were higher in drivers who tested positive for THC alone compared with those who tested positive for THC plus another driving-impairing substance (table 1). Indeed, differences between these two groups of drug-positive drivers were evident in all THC concentration deciles (χ^2=748.2, p<0.0001; see online supplementary table S5): positivity for THC and non-THC substances predominated in THC concentration deciles 1 and 2 and represented 58.6% of those with levels lower than 25 ng/mL.

Based on the data for the year 2016, the average age (mean±SD) of the THC-positive men and women was 29.6±7.7 years, with a peak age range of 20–30 years (figure 2). THC-positive cases accounted for 77.9% of the men and 75% of the women who tested positive for any substance (χ^2=4.5, p<0.034), but in all THC-positive cases, men accounted for 96.3%. In the multivariate logistic regression analysis, the frequency of THC-positive cases decreased with age (OR 0.948; 95% CI 0.945 to 0.952; p<0.0001) but did not differ regarding gender (OR 1.163; 95% CI 0.998 to 1.355; p=0.054), and the frequency of drivers who tested positive for THC and non-THC substances increased with age (OR 1.021; 95% CI 1.017 to 1.024; p<0.0001) but did not differ regarding gender (OR 0.909; 95% CI 0.782 to 1.056; p=0.21). In the multiple

Table 1 Presence of tetrahydrocannabinol and other driving-impairing substances in the oral fluid of Spanish drivers according to confirmation analysis data (years 2011–2016)

Category	THC positivity N=51 869 (n/%)	Median/Q1–Q3 of THC concentration (ng/mL)
THC alone	25 516/49.2	119.1/37.3–351.8*
THC in combination with	26 353/50.8	108.2/24.1–368.4*
Cocaine	22 679/43.7	108.6/23.9–372.8**
Amphetamines	8048/15.5	112.4/23.5–391.1**
Opioids	2936/5.7	63.6/11.7–257.8**
Benzodiazepines	1731/3.3	90.9/17.8–357.6**
Z-drugs	27/0.1	85.3/5.9–400.0**
*Mann-Whitney U test (p) for THC alone versus THC in combination with **Kruskal-Wallis H test (p) across cocaine, amphetamines, opioids, benzodiazepines and Z-drugs Cohen's d effect size (judgement)		427.4 (0.0001) 453.1 (0.02) 0.746 (moderate)

Q, quartile; THC, delta-9-tetrahydrocannabinol; Z-drugs, zopiclone and zolpidem.

linear regression analysis, THC concentration (ng/mL) did not differ with age (slope=b; b=0.165; 95% CI −0.117 to 0.446; p=0.251), but it was higher in men than in women (b=29.5; 95% CI 18.0 to 41.0; p<0.0001).

Multivariate logistic regression analysis also revealed that the occurrence of THC concentrations of 25 ng/mL or over, compared with THC concentrations less than 25 ng/mL, decreased with age (OR 0.993; 95% CI 0.989 to 0.997;
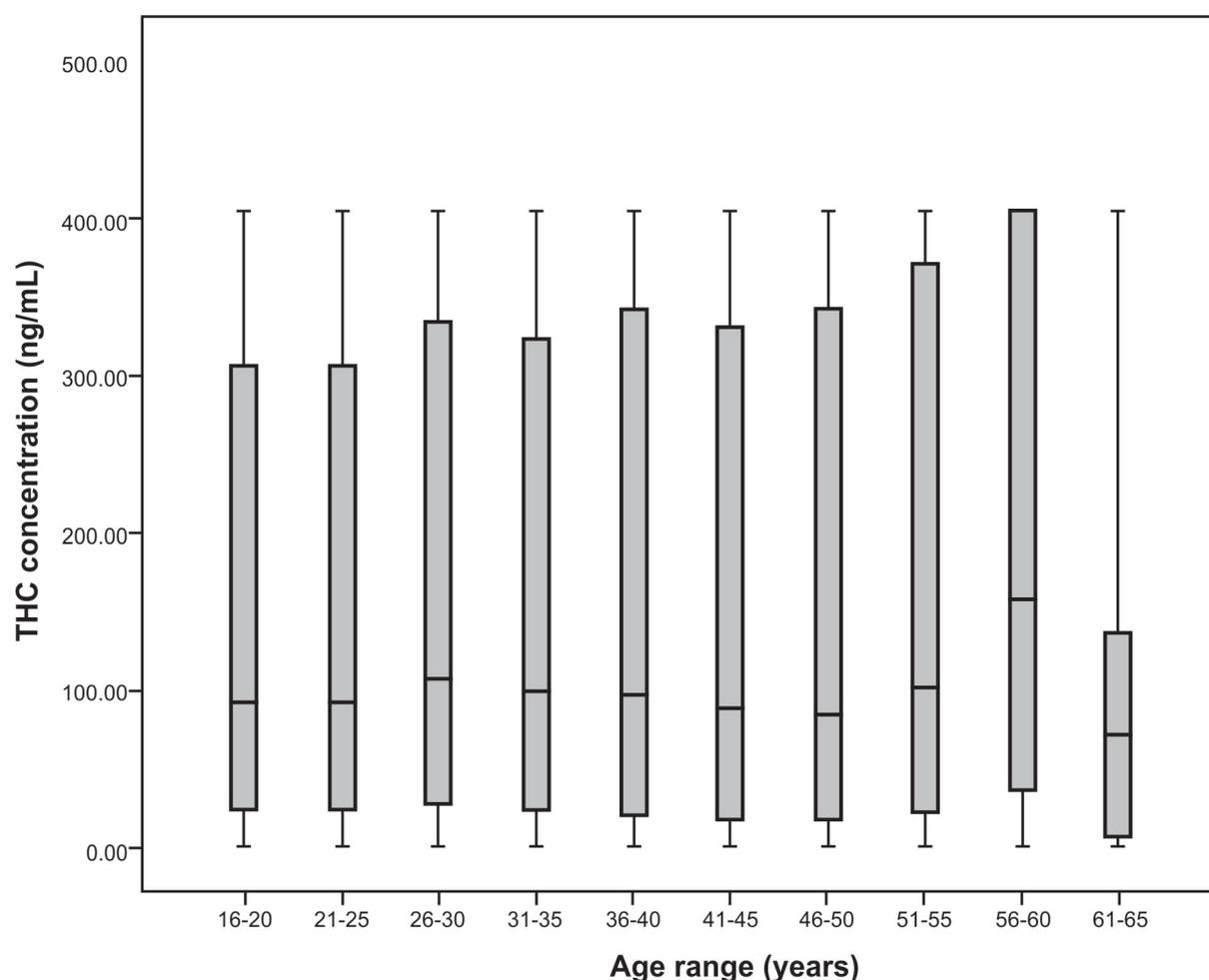
Figure 1 Distribution of medians and IQRs of tetrahydrocannabinol concentration in the oral fluid of the THC-positive drivers by age. X-axis=5-year age distribution. Y-axis=THC concentration (ng/mL). THC, delta-9-tetrahydrocannabinol.
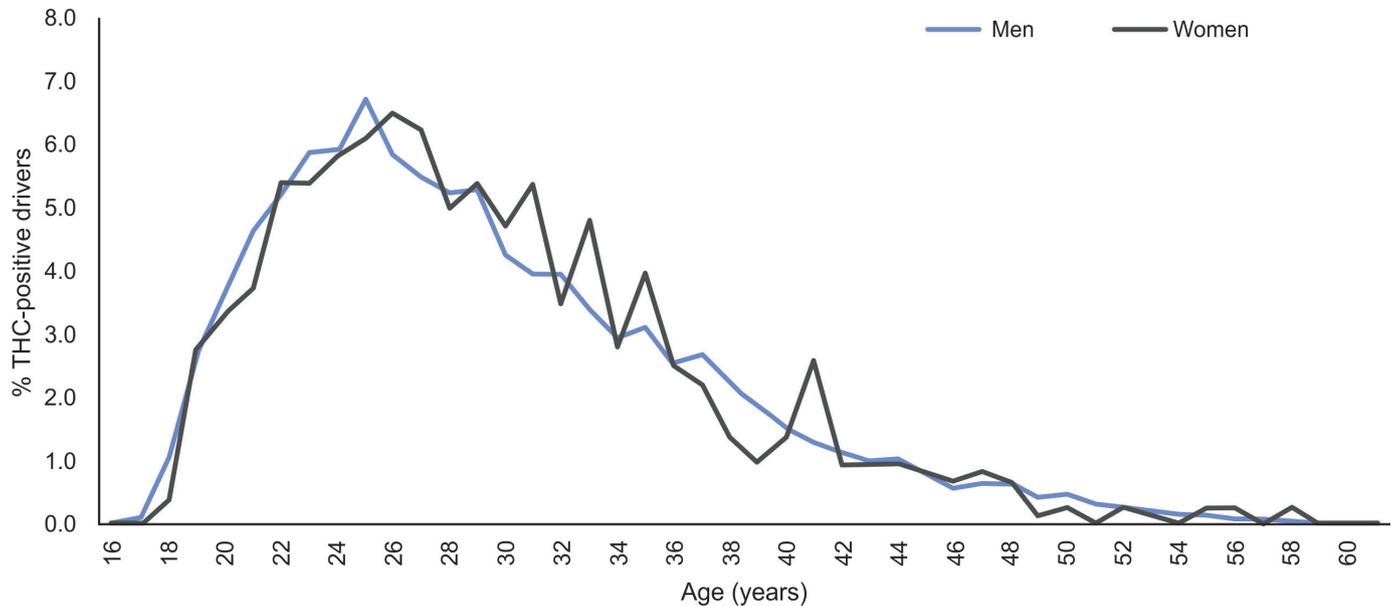
Figure 2 Distribution of the percentage of THC-positive men and women by age. X-axis=2-year age distribution. Y-axis=% THC-positive drivers. THC, delta-9-tetrahydrocannabinol.

p<0.0001) and were more common in men (OR 1.394; 95% CI 1.188 to 1.636; p<0.0001).

DISCUSSION

Our study presents data for confirmed positive roadside tests for THC and other licit/illicit driving-impairing substances in Spain between 2011 and 2016. Cannabis was found in four out of five drivers who were positive for drugs. In half of the THC-positive drivers, cocaine and amphetamines were detected. Most of those who tested positive for THC were young men, although no association between positivity for THC or THC plus non-THC substances and driver gender was found. Positivity for THC was associated with age. Higher THC concentrations were predominantly observed in men.

DUI of cannabis is a huge burden worldwide.[1–6] Although cannabis cases have decreased in Spain after the implementation of roadside drug testing and the most recent regulation amendments,[28] the weighted mean prevalence in Spain (5.99%) is still more than four times that of the weighted European Union mean prevalence (1.32) and almost twice that of the weighted Southern Europe mean prevalence (3.06).[3] In Australia, cannabis is also reported as a common driving-impairing substance (29.8%).[23] Cannabis consumption could be the illegal equivalent of the use of benzodiazepines, the most frequently dispensed driving-impairing medicine in our country (dispensing to 10.97% of drivers).[29] In any case, worldwide, in 2013, cannabis caused one-fifth of all illicit drug-related road traffic deaths.[1] Therefore, considering the current momentum and enthusiasm for cannabis legalisation, the assessment of current measures to prevent DUI of cannabis is a priority, and the improvement of these measures is necessary.[21]

Most importantly, polysubstance use in Spain is alarming.[18 26] It should not be forgotten that the risk of being seriously injured or killed in an accident while DUI of psychoactive substances increases substantially with the use of multiple drugs and/or alcohol.[1 3] Cannabis alone only slightly impairs drivers,[9–12] but the risk can increase from moderate (relative risk 2–10) to extreme (relative risk 20–200) when alcohol levels increase from 0.5 g/L to more than 1.2 g/L and multiple drugs are used.[3] Additionally, the use of recreational drugs (mostly illicit) is consistent with the well-known differences between Northern and Southern Europe[3]: cocaine, amphetamines, opioids, benzodiazepines and Z-drugs were detected concomitantly with THC.

Whatever way we look at it, the problem of polysubstance use is tangible. Although there was a great range of THC concentrations detected, low levels mostly corresponded to results positive for the use of multiple substances. Worldwide, there is a lively debate regarding whether per se limits or zero tolerance is better for preventing DUI.[1 3 21] According to our results, if confirmation analysis of roadside drug tests had only been conceived to detect THC and measuring THC concentrations higher than 25 ng/mL, one out of five THC-positive drivers would not have been identified. Evidently, drivers who tested positive for THC alone with levels lower than 25 ng/mL can be unimpaired, but it should not be forgotten that multiple factors influence the concentration–effect relationship[30]: at least half of THC-positive cases were positive for other driving-impairing substances, and drivers who tested positive for multiple substances typically had low THC concentrations.

THC-positive cases were common among drivers aged 20–30 years. The figures reported for Spain by the DRUID project confirm these findings.[3] These findings are also

in line with those reported for Australia,[22] [23] although cannabis is the second most commonly detected drug there. In Spain, a possible explanation for the number of women who tested positive for cannabis may be the increase in drug use among women over the last 20 years.[31] [32] Polysubstance use in strata of drivers older than 30–40 years and increased amounts consumed among men are also alarming.

This study provides real-world evidence on DUI of cannabis among Spanish drivers. Real-world data allow the evaluation of patterns of and changes in drug use.[33] Particularly in the context of substance abuse, administrative data are increasingly being used as 'official' records and can contribute to the characterisation of substance abusers.[34] In this sense, polysubstance use is the main characteristic or 'phenotype' of drivers who tested positive for cannabis in Spain.[34] Importantly, the findings presented here are derived from 'emerging sources' outside research environments.[33] Thus, questions about the quality of the evidence may arise. The management of an enormous volume of messy data sets requires a step-by-step treatment (statistical analyses performed after the harmonisation of the database). A clear definition of the intended application of the data (eg, the definition of a driver who is positive for drugs) is also a key aspect.[34]

This study has some limitations. First, information on alcohol positivity was not available. In the current practice of Spain's traffic police, if an alcohol breath test is positive, screening for drugs is not performed (but this is not always the case).[26] In any case, difficulties in discerning between positivity for alcohol alone and positivity for alcohol and other substances are a common limitation of epidemiological studies on drug abuse. Second, systematic information on age and gender was available only for the year 2016. Initially, data were not collected with the goal of supporting research. The collection of demographic data, anonymisation of records and a unified electronic format for codified records were needed. Finally, an increase in the yearly number of roadside drug tests was observed. This increase is explained by the increases in the budget allocated for roadside drug testing nationwide, the increasing number of traffic police officers trained in the use of testing devices and detection kits, and the progressively increasing availability of accredited toxicology laboratories for confirmation analyses. An increase in the number of impaired drivers can also explain the increase in THC-positive tests. In any case, this year-to-year increase in tests could contribute to response bias.

In conclusion, positivity for THC was very common among Spanish drivers who tested positive for drugs: polysubstance use was observed in half of the THC-positive cases, and THC concentrations below 25 ng/mL accounted for a large proportion of those who tested positive for THC and other driving-impairing substances. The implementation of roadside drug testing in association with an efficient punitive system could be an efficacious public health intervention for maintaining safe driving. One can accept that the testing regulation package has been a contributing factor to the initial decrease in drugged driving cases in Spain in the last few years.[28] However, the deterrent effects necessary to avoid DUI require constant monitoring.[21] Indirectly, this study contributes to the assessment of how effective measures are implemented to date, but its main aim is to increase the awareness of those who can avoid DUI in everyday life by focusing on young men who drive (eg, using a targeted deterrence strategy that follows the Australian approach)[35] and on those who tested positive for THC and other psychoactive substances (eg, drivers must undergo tests of behavioural impairment regardless of whether the use of more than one substance is detected)[36] is encouraged. Drivers who use cannabis and other drugs must continue to perceive that the risk of detection is high, even if they 'erroneously' believe that there is no impairment risk and refuse to change their consumption habits.[6] This factor is particularly important if polysubstance use is taken into account.[26] The implementation of measures to prevent DUI should be based on objective scientific evidence.[37] This study provides the evidence needed as any epidemiological research study that aims to improve quality of life does.[38]

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Patient consent for publication Not required.

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REFERENCES

1. World Health Organization (WHO). *Drug use and road safety: a policy brief* [internet]. Geneva, Switzerland: WHO, 2016. Available: http://apps.who.int/iris/bitstream/10665/249533/1/WHO-MSD-NVI-2016.01-eng.pdf [Accessed 30 Jun 2018].
2. Substance Abuse and Mental Health Services Administration (SAMHSA). Rockville, USA: SAMHSA*Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings* [internet], 2016. Available: https://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf [Accessed 30 Jun 2018].
3. Schulze H, Schumacher M, Urmeew R, *et al*. *Driving under the influence of drugs, alcohol and medicines in Europe – findings from the DRUID project [internet]*. Lisbon, Portugal: European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2012.
4. Mallick J, Johnston J, Goren N, *et al*. *Drugs and driving in Australia: a survey of community attitudes, experience and understanding [internet*. Melbourne, Australia: Australian Drug Foundation, 2007.
5. New Zealand Drug Foundation. Drug Driving in New Zealand: A survey of community attitudes, experience and understanding [internet]. Neuseeland, New Zealand: New Zealand Drug Foundation, 2009. Available: http://images.tvnz.co.nz/tvnz_images/news2009/drugs-alcohol-tobacco/drugdrivinginnewzealand.pdf [Accessed 30 Jun 2018].
6. Ramaekers JG. Driving under the influence of cannabis: an increasing public health concern. *JAMA* 2018;319:1433–4.
7. Ramaekers JG, Berghaus G, van Laar M, *et al*. Dose related risk of motor vehicle crashes after cannabis use. *Drug Alcohol Depend* 2004;73:109–19.
8. Hartman RL, Huestis MA. Cannabis effects on driving skills. *Clin Chem* 2013;59:478–92.
9. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ* 2012;344:e536.
10. Li M-C, Brady JE, DiMaggio CJ, *et al*. Marijuana use and motor vehicle crashes. *Epidemiol Rev* 2012;34:65–72.
11. Rogeberg O, Elvik R. The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction* 2016;111:1348–59.
12. Hostiuc S, Moldoveanu A, Negoi I, *et al*. The association of unfavorable traffic events and cannabis usage: a meta-analysis. *Front Pharmacol* 2018;9:99.
13. Elvik R. Interpreting interaction effects in estimates of the risk of traffic injury associated with the use of illicit drugs. *Accid Anal Prev* 2018;113:224–35.
14. Martin J-L, Gadegbeku B, Wu D, *et al*. Cannabis, alcohol and fatal road accidents. *PLoS One* 2017;12:e0187320.
15. Laumon B, Gadegbeku B, Martin J-L, *et al*. Cannabis intoxication and fatal road crashes in France: population based case-control study. *BMJ* 2005;331.
16. Romano E, Voas RB, Camp B. Cannabis and crash responsibility while driving below the alcohol per se legal limit. *Accid Anal Prev* 2017;108:37–43.
17. Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products - Regulations in Europe and North America. *Eur J Intern Med* 2018;49:2–6.
18. Fierro I, Colás M, González-Luque JC, *et al*. Roadside opioid testing of drivers using oral fluid: the case of a country with a zero tolerance law, Spain. *Subst Abuse Treat Prev Policy* 2017;12:22.
19. Real Decreto Legislativo 6/2015, de 30 de octubre, por el que se aprueba el texto refundido de la Ley sobre Tráfico, Circulación de Vehículos a Motor y Seguridad Vial. [Royal Legislative Decree 339/1990 (30 October) approving the Restated Text of the Law on Traffic, Circulation of Motor Vehicles, and Driving Safety]. Available: https://www.boe.es/boe/dias/2015/10/31/pdfs/BOE-A-2015-11722.pdf [Accessed 10 Dec 2018].
20. Ley Orgánica 5/2010, de 22 de junio, por la que se modifica la Ley Orgánica 10/1995, de 23 de noviembre, del Código Penal [Institutional Act 5/2010 (22 June) amending Criminal Code Institutional Act 10/1995 (23 November)]. Available: https://www.boe.es/boe/dias/2010/06/23/pdfs/BOE-A-2010-9953.pdf [Accessed 10 Dec 2018].
21. Hall W. How should we respond to cannabis-impaired driving? *Drug Alcohol Rev* 2018;37:3–5.
22. Boorman M, Owens K. The Victorian legislative framework for the random testing drivers at the roadside for the presence of illicit drugs: an evaluation of the characteristics of drivers detected from 2004 to 2006. *Traffic Inj Prev* 2009;10:16–22.
23. Davey J, Armstrong K, Martin P. Results of the Queensland 2007-2012 roadside drug testing program: the prevalence of three illicit drugs. *Accid Anal Prev* 2014;65:11–17.
24. Horyniak D, Dietze P, Lenton S, *et al*. Trends in reports of driving following illicit drug consumption among regular drug users in Australia. *2007-2013: Has random roadside drug testing had a deterrent effect? Accid Anal Prev* 2017;104:146–55.
25. Benchimol EI, Smeeth L, Guttmann A, *et al*. The reporting of studies conducted using observational Routinely-collected health data (record) statement. *PLoS Med* 2015;12:e1001885.
26. Herrera-Gómez F, García-Mingo M, Colás M, *et al*. Opioids in oral fluid of Spanish drivers. *Drug Alcohol Depend* 2018;187:35–9.
27. La Subdirección General de Análisis y Vigilancia Estadística. [The General Subdirectorate for Statistical Analysis and Surveillance]. Available: http://www.dgt.es/es/ladgt/quienes-somos/estructura-organica/servicios-centrales/subdireccion-generaldeanalisis-y-vigilancia-estadistica.shtml [Accessed 30 Jun 2018].
28. Fierro I, González-Luque JC, Seguí-Gómez M, *et al*. Alcohol and drug use by Spanish drivers: comparison of two cross-sectional road-side surveys (2008-9/2013). *Int J Drug Policy* 2015;26:794–7.
29. Herrera-Gómez F, Gutierrez-Abejón E, Criado-Espegel P, *et al*. The problem of benzodiazepine use and its extent in the driver population: a population-based registry study. *Front Pharmacol* 2018;9:408.
30. Huestis MA, Smith ML. Cannabinoid markers in biological fluids and tissues: revealing intake. *Trends Mol Med* 2018;24:156–72.
31. McHugh RK, Wigderson S, Greenfield SF. Epidemiology of substance use in reproductive-age women. *Obstet Gynecol Clin North Am* 2014;41:177–89.
32. WHO. *Alcohol, Gender and Drinking Problems: Perspectives from Low and Middle Income Countries [internet]. (Accessed 30 June 201)*. Geneva, Switzerland: WHO, 2005.
33. Sherman RE, Anderson SA, Dal Pan GJ, *et al*. Real-World Evidence - What Is It and What Can It Tell Us? *N Engl J Med* 2016;375:2293–7.
34. Richesson RL, Hammond WE, Nahm M, *et al*. Electronic health records based phenotyping in next-generation clinical trials: a perspective from the NIH health care systems Collaboratory. *J Am Med Inform Assoc* 2013;20:e226–31.
35. National Drug Driving Working Group. Australia's second generational approach to roadside drug testing [internet]. Department of Infrastructure, Regional Development and Cities of the Australian Government, 2018. Available: https://infrastructure.gov.au/roads/safety/publications/2018/pdf/second_gen_approach_roadside_drug_testing.pdf
36. *Cannabis and driving: questions and answers for policymaking* [internet]. Lisbon, Portugal: European monitoring centre for drugs and drug addiction (EMCDDA), 2018. Available: http://www.emcdda.europa.eu/system/files/publications/743/TDXA12006ENN_402402.pdf [Accessed 28 Feb 2019].
37. Hartman RL, Brown TL, Milavetz G, *et al*. Effect of blood collection time on measured Δ9-tetrahydrocannabinol concentrations: implications for driving interpretation and drug policy. *Clin Chem* 2016;62:367–77.
38. Epidemiology is a science of high importance. *Nat Commun* 1703;2018.