Illicit Drug Use and Smell and Taste Dysfunction: A National Health and Nutrition Examination Survey 2013–2014

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Abstract: Taste and smell dysfunction are suspected to be associated with substance use. However, representative epidemiological studies remain insufficient. This cross-sectional study explored the relationship between drug use (including cannabis or hashish, cocaine, heroin, and methamphetamine) and olfactory/gustatory dysfunction using data from the 2013–2014 National Health and Nutrition Examination Survey. In this study, participants who completed the smell examination with mean age of 59 were classified into four groups: cannabis users (n = 845), participants without cannabis use (n = 794), illicit drug users (n = 450), and participants without illicit drug use (n = 2000). Participants who completed the taste examination with mean age of 58 were also categorised into four groups: cannabis users (n = 810), participants without cannabis use (n = 714), illicit drug users (n = 428), and participants without illicit drug use (n = 1815). Logistic regression models investigated the association between cannabis or illicit drug use and smell or taste dysfunctions among study participants. Odds ratios and 95% confidence intervals were calculated. Finally, we did not find correlations between illicit drug use and dysfunction of taste or smell senses; our findings were consistent in many subgroup analyses. We recommend that further studies explore the mechanism and dose of illicit drug use that could have chemosensory impacts.

Keywords: illicit drug; cannabis; smell; taste; NHANES

1. Introduction

Increasing evidence indicates that illicit drug use may lead to a substantial loss of life and disabilities [1]. Up until 2019, it was estimated that 5.4% of the global population used illegal drugs, and around 36.3 million people worldwide could be considered problematic drug users [2,3]. Additionally, according to the United Nations Office on Drugs and Crime report, cannabis is the most used drug, followed by opioids and amphetamines [2]. Moreover, drug abuse has noted tremendous impacts and health problems, including socioeconomic burdens, social and legal consequences, poverty and mental disorders, etc. [4,5]. Previous research indicated the need for excessive sensory stimulation as a predisposition to addictive behaviors. Exploring more sensory characteristics in people with addictive behaviors might provide the governments and policymakers with more information on this population [1,6,7].
Generally, olfactory dysfunction has been recognised as a heterogeneous condition, commonly caused by infection and trauma [8]. Olfactory loss is divided into two types: conductive and sensorineural dysfunction [9]. Impaired olfaction is disabling because it results in nutritional alterations in patients, increases the risk of injury, and lowers social relationships with reduced quality of life [10,11]. To date, taste and smell dysfunction are suspected to be associated with substance use. However, representative epidemiological studies remain insufficient. Smell and taste dysfunctions involve ageusia, hypogeusia, anosmia, hyposmia, etc. Ageusia refers to an absence of the sense of taste and hypogeusia refers to decreased taste sensitivity [12]. Furthermore, qualitative gustatory dysfunction is more frequent than quantitative dysfunction [13]. Moreover, anosmia and hyposmia, referring to a total and partial loss of the senses of smell, affect up to 25% of adults who are 50 years or older in America [14–17].

Currently, most studies explored the association of smell and taste dysfunction in substance users with alcohol use and smoking [18–21]. Some studies have shown a preserved level of olfaction without odour detection thresholds or discrimination deficits in alcoholic participants. Still, some even revealed impaired olfactory event-related potentials and olfactory dysfunction in patients with alcohol dependence [22,23]. However, only a few case series and animal models have reported and investigated the effects of chemosensory impairment in cannabis use [24,25]. Some studies also noticed that heroin addicts might be associated with a change in smell and taste function [26,27]. Nevertheless, there were equivocal results in reporting the connection between cocaine use and smell/taste dysfunction from animal models and humans [28,29].

Accordingly, relevant findings in previous studies have remained inconsistent. The research design investigating the association between chemosensory dysfunction and substance use has included cell research, animal models, and case-control studies. However, although the research focused on one illicit drug, the collected data were limited by small sample sizes and patient reluctance to discuss illicit drug use or resulting harms. Moreover, comprehensive epidemiological studies investigating the relationship between illicit drug use and smell and taste dysfunction have remained deficient. Therefore, this study explored the relationship between drug use (including cannabis or hashish, cocaine, heroin, and methamphetamine) and olfactory/gustatory dysfunction using information from a large-scale cross-sectional database in the United States.

2. Materials and Methods

2.1. Database

Data from the National Health and Nutrition Examination Survey (NHANES) in the United States were used in this cross-sectional study. NHANES, a vital programme of the National Center for Health Statistics (NCHS), contains interviews and physical examination data of health and nutrition measurements. The database also includes information on about 5000 people from counties across the U.S. as a national and yearly representative sample. The research protocols for the NHANES received approval from the NCHS Research Ethics Review Board and written informed consent was obtained from each participant (https://www.cdc.gov/nchs/nhanes/irba98.htm, accessed on 1 April 2022). This study was exempted from a full review of the Institutional Review Board because the data used were de-identified secondary data from NHANES.

2.2. Study Sample Selection

This study investigated illicit drugs and cannabis use associated with smell and taste dysfunction. Therefore, participants who underwent the Taste and Smell Examination and filled out the Drug Use Questionnaire from 2013 to 2014 were included. Those with incomplete smell and taste, as detected from the examination results, or those with incomplete responses to related drug use questions, were excluded from this study. Finally, participants who completed the smell examination were classified into four groups: cannabis users ($n = 845$), participants without cannabis use ($n = 794$), illicit drug users ($n = 450$),
and participants without illicit drug use ($n = 2000$). Participants who completed the taste examination were also categorised into four groups: cannabis users ($n = 810$), participants without cannabis use ($n = 714$), illicit drug users ($n = 428$), and participants without illicit drug use ($n = 1815$). Cannabis and illegal drug users were identified based on their answers to the relevant questions in the Drug Use Questionnaire. Therefore, cannabis users were defined as participants who answered that they had ever used marijuana or hashish, and illicit drug users were identified as participants who responded that they had ever used cocaine, heroin, or methamphetamine. Flow diagram for study sample selection is displayed in Figure 1.

![Flow Diagram for Study Sample Selection](image)

**Figure 1.** Flow Diagram for Study Sample Selection.

2.3. Outcome Measurements

The definitions of smell and taste dysfunction were based on the smell and taste examination results. An odour identification test examined the ability to smell, and the tasting ability was measured using salt and quinine taste testing.

2.3.1. Smell Dysfunction Definition

An eight-item odour identification test was used to identify the participants’ ability to smell. First, participants were presented with eight specific odours via scratching of test strips. Then, eight specific scents were presented in a fixed sequence of chocolate, strawberry, smoke, leather, soap, grape, onion and natural gas. Participants were finally requested to choose the correct odour of the four listed options for each scent. Those who failed to identify six or more odours were defined as participants with smell dysfunction.

2.3.2. Taste Dysfunction Definition

The 1-mM quinine whole-mouth taste test was used to determine participants’ taste ability [30]. The participants were first asked to take the 10-mL quinine solution into their mouths without swallowing, after which they were asked to swish and spit out the solution. Subsequently, each participant identified the taste of the solution, and their mouths were rinsed with water afterward. Those who failed to identify the bitter taste of quinine in the 1-mM quinine whole-mouth taste test were defined as participants with taste dysfunctions.

2.4. Covariate Measurement

We reduced the influence of potential confounders by considering participants’ age, gender, ethnicity, hypertension status, diabetes mellitus status, coronary heart disease
history, angina pectoris, heart attack susceptibility, stroke, persistent cold/flu over the last 12 months before the study, head injury/loss of consciousness, broken nose/serious injuries to the face or skull, two or more sinus infections, smoking status, heavy alcohol use, and overweight in the regression models. Ethnicity was categorized as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, non-Hispanic Asian and other races. Participants were defined as being overweight or having a medical history of hypertension, diabetes mellitus, coronary heart disease, angina pectoris, heart attack and stroke, based on their self-report of doctors’ diagnosis. Those taking insulin and diabetic pills were also defined as having diabetes mellitus. Furthermore, participants who smoke and heavily take alcohol, or those with persistent cold/flu over the last 12 months before the study, head injury/loss of consciousness, broken nose/serious injury to the face or skull and those with two or more sinus infections, were identified using self-reported questionnaires.

2.5. Statistical Analysis

This study used the SAS system (SAS System for Windows, V9.4, SAS Institute Inc., Cary, NC, USA) to conduct all analyses. Chi-squared tests were first applied to investigate differences in gender, ethnicity, hypertension, diabetes mellitus, coronary heart disease, angina pectoris, heart attack, stroke, persistent cold/flu last 12 months before the study, head injury/loss of consciousness, broken nose/serious injury to face or skull, two or more sinus infections, smoking status, heavy alcohol use, and overweight, between participants with and without smell or taste dysfunction. Next, the independent t-test was performed to compare the difference in age between participants with and without smell or taste dysfunctions. Finally, logistic regression models investigated the association between cannabis or illicit drug use and smell or taste dysfunctions among study participants, after which odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A two-sided p-value < 0.05 was used to define the statistical significance of this study.

3. Results

This study contained smell and taste dysfunction study groups. Table 1 displays study participants’ demographic characteristics and comorbidities with and without smell dysfunctions. The relevant findings showed significant differences in age, gender, ethnicity, hypertension, diabetes mellitus, coronary heart disease, angina pectoris, heart attack, stroke, two or more sinus infections, smoking status, and overweight between participants with and without smell dysfunction. The results (Table 1) also showed significant differences between the participants with and without taste dysfunction based on age, ethnicity, and smoking status. Therefore, we considered all these factors in the regression model to eliminate potential bias.

Table 2 presents the prevalence of cannabis and illicit drug use among participants with and without smell dysfunction to further investigate the cannabis and illicit drug use association with smell dysfunction. Participants with and without smell dysfunction comprised 40.8% and 52.7% of cannabis users, respectively. After adjustments, the adjusted OR for cannabis use was 0.67 (95% CI, 0.43–1.03) among participants with and without smell dysfunction. Furthermore, individuals with and without smell dysfunction included 15.6% and 18.8% of illicit drug users, respectively. However, the adjusted OR for illicit drug use was 0.85 (95% CI, 0.59–1.25) among study participants with and without smell dysfunction, respectively. Subsequently, we further estimated the adjusted ORs for cocaine (OR, 0.85; 95% CI, 0.58–1.26), heroin (OR, 0.69; 95% CI, 0.30–1.56), and methamphetamine (OR, 0.84; 95% CI, 0.47–1.50) use of the understudied participants, respectively. Overall, there was no significant difference in smell dysfunction between cannabis or illicit drug users and those who did not use cannabis or illicit drugs.
Table 1. Baseline characteristics based on smell and taste dysfunction among study participants.

| Variable                              | Participants with Smell Dysfunction (n = 630) | Participants without Smell Dysfunction (n = 2889) | p Value | Participants with Taste Dysfunction (n = 540) | Participants without Taste Dysfunction (n = 2574) | p Value |
|---------------------------------------|-----------------------------------------------|--------------------------------------------------|---------|-----------------------------------------------|--------------------------------------------------|---------|
|                                      | No. %                                        | No. %                                            |         | No. %                                        | No. %                                            |         |
| Age (Mean ± SD)                       | 65.9 ± 12.2                                  | 57.5 ± 11.5                                      | <0.001  | 67.0 ± 11.7                                  | 58.8 ± 12.0                                      | 0.002   |
| Gender                                |                                               |                                                  |         |                                               |                                                  |         |
| Male                                  | 368 58.4                                     | 1311 45.4                                       |         | 259 48.0                                     | 1251 48.6                                       | 0.787   |
| Female                                | 262 41.6                                     | 1578 54.6                                       |         | 281 52.0                                     | 1323 51.4                                       |         |
| Ethnicity                             |                                               |                                                  |         |                                               |                                                  |         |
| Mexican American                      | 80 12.7                                      | 380 13.2                                        | 0.030   | 60 11.1                                      | 336 13.1                                        | <0.001  |
| Other Hispanic                        | 61 9.7                                       | 249 8.6                                         |         | 46 8.5                                       | 214 8.3                                         |         |
| Non-Hispanic White                    | 248 39.4                                     | 1316 45.6                                       |         | 253 46.9                                     | 1187 46.1                                       |         |
| Non-Hispanic Black                    | 153 24.3                                     | 574 19.9                                        |         | 138 25.6                                     | 494 19.2                                        |         |
| Non-Hispanic Asian                    | 78 12.4                                      | 307 10.6                                        |         | 26 4.8                                       | 297 11.5                                        |         |
| Other Race—Including Multi-Racial     | 10 1.6                                       | 63 2.2                                          |         | 17 3.2                                       | 46 1.8                                          |         |
| Ever had diagnosis                    |                                               |                                                  |         |                                               |                                                  |         |
| Hypertension                          | 365 57.9                                     | 1365 47.3                                       | <0.001  | 266 49.4                                     | 1240 48.2                                       | 0.625   |
| Diabetes mellitus                     | 146 23.2                                     | 490 17.0                                        | <0.001  | 85 15.8                                      | 444 17.3                                        | 0.406   |
| Coronary heart disease                | 50 8.0                                       | 157 5.5                                         | 0.013   | 35 6.5                                       | 146 5.7                                         | 0.468   |
| Angina pectoris                       | 33 5.3                                       | 89 3.1                                          | 0.007   | 14 2.6                                       | 97 3.8                                          | 0.182   |
| Heart attack                          | 53 8.4                                       | 151 5.2                                         | 0.002   | 35 6.5                                       | 137 5.3                                         | 0.280   |
| Stroke                                | 65 10.3                                      | 109 3.8                                         | <0.001  | 24 4.5                                       | 112 4.4                                         | 0.922   |
| Persistent cold/flu last 12 months    | 48 7.6                                       | 188 6.5                                         | 0.314   | 32 5.9                                       | 175 6.7                                         | 0.503   |
| Head Injury/Loss of consciousness     | 86 13.7                                      | 404 14.0                                        | 0.823   | 81 15.0                                      | 364 14.2                                        | 0.619   |
| Broken Nose/Serious Injury to Face/Skull | 91 14.5                               | 412 14.3                                        | 0.875   | 87 16.1                                      | 371 14.4                                        | 0.318   |
| Two or more sinus infections          | 155 24.8                                     | 1040 36.1                                       | <0.001  | 185 34.6                                     | 903 35.1                                        | 0.811   |
| Smoking status a                      |                                               |                                                  | 0.039   |                                               |                                                  | 0.004   |
| Current smoker                        | 98 15.6                                      | 543 18.8                                        |         | 125 23.2                                     | 442 17.2                                        |         |
| Former smoker                         | 201 32.0                                     | 796 27.6                                        |         | 153 28.3                                     | 744 28.9                                        |         |
| Never                                 | 330 52.5                                     | 1540 54.6                                       |         | 262 48.5                                     | 1387 53.9                                       |         |
| Heavy alcohol use                     | 95 15.7                                      | 422 18.1                                        | 0.079   | 86 19.1                                      | 389 18.7                                        | 0.864   |
| Overweight                            | 214 34.0                                     | 1160 40.2                                       | 0.004   | 204 37.8                                     | 1015 39.4                                       | 0.474   |

Note: SD, standard deviation. a The sum of n did not equal to the total number because of the missing data.

The prevalence and ORs for cannabis and illicit drug use among study participants with and without taste dysfunction are displayed in Table 2. Study participants with and without taste dysfunction comprised 57.0% and 52.2% of cannabis users, respectively. However, the adjusted OR for cannabis use was 0.98 (95% CI, 0.71–1.35) among participants with and without taste dysfunction. Furthermore, although participants with and without taste dysfunction comprised 20.5% and 18.8% of illicit drug users, respectively, the adjusted OR for illicit drug use was 0.85 (95% CI, 0.63–1.15) among participants with and without taste dysfunction. We further evaluated the adjusted ORs for cocaine (OR, 0.92; 95% CI, 0.68–1.26), heroin (OR, 0.64; 95% CI, 0.32–1.27), and methamphetamine (OR, 0.79; 95% CI, 0.50–1.25) use of the participants. Summarily, no significant difference in taste dysfunction was observed between cannabis or illicit drug users and participants who did not use cannabis or illicit drugs.

Subsequently, to reduce the effect of gender, we performed stratified analyses to explore the relationship between cannabis or illicit drug use and smell or taste dysfunction in males and females (Table 3). After adjusting for various confounders, findings indicated no significant association between cannabis or illicit drug use and smell or taste dysfunctions in the male or female population. Then, due to the influence of age on smell and taste dysfunction, we further investigated the association between cannabis or illicit drug use and smell or taste dysfunctions among study participants according to the different age groups (Table 4). The study results remained unchanged after adjusting for demographic characteristics and comorbidities. Additionally, there was no significant difference in smell or taste dysfunction between cannabis or illicit drug users and those who did not use cannabis or illicit drugs in participants aged 40–49, 50–59, and 60–69 years.
### Table 2. Prevalence and odds ratios for cannabis and illicit drug use among study participants with and without smell and taste dysfunction.

| Variables                  | Participants with Smell Dysfunction | Participants without Smell Dysfunction | Participants with Taste Dysfunction | Participants without Taste Dysfunction |
|----------------------------|------------------------------------|----------------------------------------|------------------------------------|----------------------------------------|
|                            | No.  | %     | No.  | %     | No.  | %     | No.  | %     |
| Ever used cannabis or hashish |      |       |      |       |      |       |      |       |
| Yes                        | 64   | 40.8  | 781  | 52.7  | 171  | 57.0  | 639  | 52.2  |
| No                         | 93   | 59.2  | 701  | 47.3  | 129  | 43.0  | 585  | 47.8  |
| Crude OR (95% CI) a         | 0.62 ** (0.44–0.86)               | 1.21 (0.94–1.57)                     | 0.67 (0.43–1.03)                   | 0.98 (0.71–1.35)                     |
| Adjusted OR (95% CI) ab     |      |       |      |       |      |       |      |       |
| Ever used illicit drug c    |      |       |      |       |      |       |      |       |
| Yes                        | 46   | 15.6  | 404  | 18.8  | 83   | 20.5  | 345  | 18.8  |
| No                         | 249  | 84.4  | 1751 | 81.2  | 322  | 79.5  | 1493 | 81.2  |
| Crude OR (95% CI) a         | 0.80 (0.57–1.12)                  | 1.12 (0.85–1.46)                     | 0.85 (0.59–1.25)                   | 0.85 (0.63–1.15)                     |
| Adjusted OR (95% CI) ab     |      |       |      |       |      |       |      |       |
| Type of illicit drug use    |      |       |      |       |      |       |      |       |
| Ever used cocaine           |      |       |      |       |      |       |      |       |
| Yes                        | 42   | 14.2  | 376  | 17.5  | 81   | 20.0  | 317  | 17.3  |
| No                         | 253  | 85.8  | 1787 | 82.5  | 324  | 80.0  | 1520 | 82.7  |
| Crude OR (95% CI) a         | 0.79 (0.56–1.11)                  | 1.20 (0.91–1.57)                     | 0.85 (0.58–1.26)                   | 0.92 (0.68–1.26)                     |
| Adjusted OR (95% CI) ab     |      |       |      |       |      |       |      |       |
| Ever used heroin            |      |       |      |       |      |       |      |       |
| Yes                        | 7    | 2.4   | 69   | 3.2   | 11   | 2.7   | 62   | 3.4   |
| No                         | 288  | 97.6  | 2084 | 96.8  | 394  | 97.3  | 1775 | 96.6  |
| Crude OR (95% CI) a         | 0.73 (0.33–1.61)                  | 0.80 (0.42–1.53)                     | 0.69 (0.30–1.56)                   | 0.64 (0.32–1.27)                     |
| Adjusted OR (95% CI) ab     |      |       |      |       |      |       |      |       |
| Ever used methamphetamine  |      |       |      |       |      |       |      |       |
| Yes                        | 16   | 5.4   | 154  | 7.2   | 30   | 7.4   | 137  | 7.5   |
| No                         | 279  | 94.6  | 2001 | 92.8  | 375  | 92.6  | 1701 | 92.5  |
| Crude OR (95% CI) a         | 0.75 (0.44–1.27)                  | 0.99 (0.66–1.50)                     | 0.84 (0.59–1.40)                   | 0.87 (0.50–1.45)                     |
| Adjusted OR (95% CI) ab     |      |       |      |       |      |       |      |       |

Note: CI = confidence interval; OR = odds ratio; a Logistic regression; b adjusted for age, gender, ethnicity, hypertension, diabetes mellitus, coronary heart disease, angina pectoris, heart attack, stroke, persistent cold/flu last 12 months, head injury/loss of consciousness, broke nose/serious injury to face/skull, two or more sinus infections, smoking status, heavy alcohol use, and overweight; c Study participants who ever used cocaine/heroin/methamphetamine. ** p ≤ 0.01

### Table 3. Association between cannabis/illicit drug use and smell/taste dysfunction among study participants according to gender.

| Variables                  | Participants with Smell Dysfunction | Participants without Smell Dysfunction | Participants with Taste Dysfunction | Participants without Taste Dysfunction |
|----------------------------|------------------------------------|----------------------------------------|------------------------------------|----------------------------------------|
|                            | No.  | %     | No.  | %     | No.  | %     | No.  | %     |
| Male                      |      |       |      |       |      |       |      |       |
| Ever used cannabis or hashish |      |       |      |       |      |       |      |       |
| Yes                        | 43   | 47.3  | 395  | 57.3  | 88   | 61.5  | 336  | 56.6  |
| No                         | 48   | 52.7  | 295  | 42.8  | 55   | 38.5  | 258  | 43.4  |
| Crude OR (95% CI) a         | 0.67 (0.43–1.04)                  | 1.23 (0.85–1.79)                     | 0.76 (0.44–1.34)                   | 1.21 (0.77–1.92)                     |
| Adjusted OR (95% CI) ab     |      |       |      |       |      |       |      |       |
| Ever used illicit drug c    |      |       |      |       |      |       |      |       |
| Yes                        | 35   | 20.7  | 228  | 22.9  | 47   | 24.7  | 204  | 22.9  |
| No                         | 134  | 79.3  | 772  | 77.2  | 143  | 75.3  | 686  | 77.1  |
| Crude OR (95% CI) a         | 0.88 (0.59–1.32)                  | 1.11 (0.77–1.59)                     | 0.98 (0.62–1.54)                   | 0.90 (0.60–1.35)                     |
| Adjusted OR (95% CI) ab     |      |       |      |       |      |       |      |       |
| Female                     |      |       |      |       |      |       |      |       |
| Ever used cannabis or hashish |      |       |      |       |      |       |      |       |
| Yes                        | 21   | 31.8  | 386  | 48.7  | 83   | 52.9  | 303  | 48.1  |
| No                         | 45   | 68.2  | 314  | 51.3  | 74   | 47.1  | 327  | 51.9  |
| Crude OR (95% CI) a         | 0.49 ** (0.29–0.84)               | 1.21 (0.85–1.72)                     | 0.58 (0.28–1.20)                   | 0.74 (0.46–1.19)                     |
| Adjusted OR (95% CI) ab     |      |       |      |       |      |       |      |       |
| Ever used illicit drug c    |      |       |      |       |      |       |      |       |
| Yes                        | 11   | 8.7   | 176  | 15.2  | 36   | 16.7  | 141  | 14.9  |
| No                         | 115  | 91.3  | 981  | 84.8  | 179  | 83.3  | 807  | 85.1  |
| Crude OR (95% CI) a         | 0.53 (0.28–1.01)                  | 1.15 (0.77–1.72)                     | 0.69 (0.33–1.45)                   | 0.83 (0.52–1.33)                     |
| Adjusted OR (95% CI) ab     |      |       |      |       |      |       |      |       |

Note: CI = confidence interval; OR = odds ratio; a Logistic regression; b adjusted for age, gender, ethnicity, hypertension, diabetes mellitus, coronary heart disease, angina pectoris, heart attack, stroke, persistent cold/flu last 12 months, head injury/loss of consciousness, broke nose/serious injury to face/skull, two or more sinus infections, smoking status, heavy alcohol use, and overweight; c Study participants who ever used cocaine/heroin/methamphetamine. ** p ≤ 0.01.
Table 4. Association between cannabis/illicit drug use and smell/taste dysfunction among study participants according to age.

| Variables | Participants with Smell Dysfunction | Participants without Smell Dysfunction | Participants with Taste Dysfunction | Participants without Taste Dysfunction |
|-----------|-------------------------------------|----------------------------------------|-----------------------------------|---------------------------------------|
|           | No. | %      | No. | %      | No. | %      | No. | %      |
| 40–49 years | Ever used cannabis or hashish | | | | | | | |
| Yes | 19 | 29.7 | 378 | 49.2 | 86 | 53.4 | 295 | 47.5 |
| No | 45 | 70.3 | 391 | 50.9 | 75 | 46.6 | 326 | 52.5 |
| Crude OR (95% CI) | 0.44 ** (0.25–0.76) | 1.27 (0.90–1.79) |
| Adjusted OR (95% CI) | 0.66 (0.32–1.35) | 0.97 (0.63–1.52) |
| Ever used illicit drug | | | | | | | | |
| Yes | 7 | 10.9 | 145 | 18.9 | 33 | 20.5 | 115 | 18.5 |
| No | 57 | 89.1 | 624 | 81.1 | 128 | 79.5 | 506 | 81.5 |
| Crude OR (95% CI) | 0.53 (0.24–1.18) | 1.13 (0.74–1.75) |
| Adjusted OR (95% CI) | 0.72 (0.29–1.80) | 0.94 (0.57–1.55) |
| 50–59 years | Ever used cannabis or hashish | | | | | | | |
| Yes | 45 | 48.4 | 403 | 56.5 | 85 | 61.2 | 344 | 57.1 |
| No | 48 | 51.6 | 310 | 43.5 | 54 | 38.9 | 259 | 43.0 |
| Crude OR (95% CI) | 0.72 (0.49–1.11) | 1.19 (0.81–1.73) |
| Adjusted OR (95% CI) | 0.69 (0.37–1.20) | 1.04 (0.64–1.68) |
| Ever used illicit drug | | | | | | | | |
| Yes | 22 | 23.9 | 163 | 22.8 | 36 | 25.7 | 141 | 23.3 |
| No | 70 | 76.1 | 552 | 77.2 | 104 | 74.3 | 463 | 76.7 |
| Crude OR (95% CI) | 1.06 (0.64–1.77) | 1.14 (0.74–1.74) |
| Adjusted OR (95% CI) | 1.07 (0.59–1.97) | 0.89 (0.54–1.47) |
| 60–69 years | Ever used illicit drug | | | | | | | |
| Yes | 17 | 12.2 | 96 | 14.3 | 14 | 13.5 | 89 | 14.5 |
| No | 122 | 87.8 | 575 | 85.7 | 90 | 86.5 | 524 | 85.5 |
| Crude OR (95% CI) | 0.84 (0.48–1.45) | 0.92 (0.50–1.68) |
| Adjusted OR (95% CI) | 0.74 (0.40–1.39) | 0.68 (0.34–1.35) |

Note: CI = confidence interval; OR = odds ratio; * Logistic regression; ** adjusted for gender, ethnicity, hypertension, diabetes mellitus, coronary heart disease, angina pectoris, heart attack, stroke, persistent cold/flu last 12 months, head injury/loss of consciousness, broke nose/serious injury to face/skull, two or more sinus infections, smoking status, heavy alcohol use, and overweight; c Study participants who ever used cocaine/heroin/methamphetamine. ** p ≤ 0.01.

Furthermore, to consider the effect of the duration of drug use and the age of first drug use, we also investigated the association between cannabis/illicit drug use and smell/taste dysfunction among study participants after adjusting for age of first cannabis/illicit drug use, days used cannabis/illicit drug during the past 30 days, and other demographic characteristics and comorbidities (Supplemental Table S1). The findings remained unchanged after adjusting for relevant confounders.

4. Discussion

To date, many medications, such as antimicrobials, antihypertensives, antidepressants, antipsychotics, antineoplastics, agents in cigarette smoke, and ethanol use, have been associated with chemosensory disturbances [31,32]. The potential olfactory dysfunction mechanisms based on these substances may be due to olfactory epithelium damage or central nervous system damage. Based on clinical experiences, this study initially hypothesised that illicit drug use might be associated with smell and taste function changes. However, we observed no association between participants with smell or taste dysfunction and cannabis or illicit drug use history. Notably, the association did not remain statistically significant after adjustments for confounders, including age, race, gender, or other physical comorbidities in males, females, and participants with different age groups.

Previous studies have investigated the relationship between substance use and smell/taste function. However, most current research only examined the impact of smoking and alcohol on taste or smell functions. Therefore, potential impacts on olfactory function have remained controversial. For instance, a study enrolled 48 drug addicts between the ages of 16 and 48.
Although 52.1% of the participants showed disturbances in olfactory performance, 16.7% were diagnosed with ageusia. Additionally, olfactory problems were detected in those who took drugs intravenously and smoked or inhaled drugs [33]. Another study enrolled 21 smokers and 59 non-smokers. Although their results showed smaller olfactory bulb volumes in smokers than in non-smokers, no difference in olfactory function between the two groups was observed [18]. Moreover, though Schriever et al. suggested that smoking negatively affects the olfactory system before it becomes obvious in decreased olfactory function, Vennemann et al. noted that heavy smokers (20 or more cigarettes per day) had an increased risk for impairments in smell and taste senses [19]. Therefore, since the temporal lobe mediates olfactory processing, and a correlation between general olfactory function and olfactory bulb volumes has been proposed, factors that affect the optimal function of this system could result in issues [9].

Our study focused on the relationship between cannabis, illicit drug use, and smell or taste function changes. Some prior studies have also investigated the relevant issue of cannabis. As reported, cannabinoids are involved in the neuromodulatory regulation of the sensory systems [34,35]. The active ingredient of cannabis, delta-9-tetrahydrocannabinol (THC), has also been reported to palliate symptoms in cancer patients [36–38]. Furthermore, it stimulates the orosensory reward pathway and enhances food enjoyment. Although cannabinoid type-1 receptors are located in different brain olfactory areas, including the olfactory epithelium and bulb [39,40], cannabinoid receptor agonists increase the hedonic reactions to sweet taste and reduce the aversive responses to quinine [24,35,36,41]. However, participants in that research were cancer patients who were explicitly administered THC. Case reports from students with an experience of marijuana intoxication also reported more vivid taste sensations and a richer sense of smell when intoxicated [42]. Similarly, a recent study showed that cannabidiol (CBD) protects against the psychoactive effects of THC [43]. Moreover, Woelfl et al. conducted a randomised controlled trial, which showed that CBD intake did not affect healthy volunteers, and a single dose of CBD before taking THC administration was insufficient to mitigate the impact of THC [44]. Nevertheless, cannabis contains over 400 chemical entities, with the ratios of each compound in recreational cannabis making it challenging to investigate the effect of drug users in real-world situations [45,46]. Our study did not notice a change in the smell or taste of individuals who ever used cannabis.

Additionally, our study did not find correlations between illicit drug use and dysfunction of taste or smell. Some previous research also investigated relevant issues. For instance, cocaine is usually administered illegally from the nasal route, and abusers often complain of decreased olfaction. Clinical pathology that contributes to reduced olfaction includes immune-mediated diseases and even nasal defects that require surgical reconstruction [47,48]. However, no olfactory or gustatory function tests were conducted on those users. Roebber et al. suggested that cocaine exposure did not change the taste sensitivity of animal models of mice [28]. Another study by Gordon et al. reported from three olfaction tests that most cocaine abusers did not develop permanent olfactory dysfunction [49]. Beidler and Smallman also proposed that nerves innervating the taste buds could regenerate after abrasion, making the taste buds retain function [50]. Therefore, there might be a restoration of chemosensory perception after quitting illicit drug use. Nevertheless, exploring the underlying mechanisms of individuals after using illicit drugs is needed.

Furthermore, Perl et al. noticed that heroin addicts estimated sweet tastes and savoury smells as more pleasant, and bitter, sour or putrid tastes and odours were considered less unpleasant by them than detoxified former addicts and healthy controls [26]. A randomised controlled trial with a small sample size measured sweet and salt taste perceptions of heroin users, recently detoxified subjects, and healthy volunteers. The results showed that heroin users and recently detoxified subjects had significantly greater measures of taste perception, and even this effect could be reversed by opiate antagonists [27]. These results suggest that heroin addicts might have altered taste and odour hedonic brain mechanisms. Findings in previous literature were similar to the trends found in our study. We observed that individuals with and without smell dysfunction included 2.4% and 3.2% of heroin users,
respectively. Even though the relationship did not reach statistical significance, heroin users were more sensitive to odours. With amphetamine, a scarce study investigated the association between smell or taste dysfunction and amphetamine use.

This study had some unique strengths. First, it included a large-scale sample size from a population with a history of illicit drug use and relatively accurate examination results on smell and taste function. Second, we used both self-reported questionnaires and examinations (including an 8-item odour identification test and 1-mM quinine whole-mouth taste identification test) to identify the smell and taste dysfunctions, eliminating recall bias from respondents. Finally, this study investigated the relationships between smell/taste dysfunction and illicit drugs, including cannabis or hashish, cocaine, heroin, and methamphetamine. Moreover, based on our extensive literature search, this research is the first to comprehensively study the relationship between different illicit drugs and smell/taste dysfunction. Notwithstanding, several limitations were encountered in this study. First, we could not explore the causal relationships because of the cross-sectional nature of this study. Second, this study did not consider certain medications that may affect smell and taste because the database lacked detailed information.

5. Conclusions

In conclusion, our research provided insight into the relationship between illicit drug use and olfactory/gustatory functions, and this association did not remain statistically significant after adjustments for confounders, including age, race, gender, or other physical comorbidities in males, females and participants with different age groups. With the diversity and complexity of chemical compounds in each illicit drug, studies with multidisciplinary teamwork may be warranted to objectively assess the nature of chemosensory effects caused by each illicit drugs. Therefore, we recommend that future studies explore the mechanism and dose of illicit drug use that could have chemosensory impacts in humans.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/healthcare10050909/s1, Table S1. Association between cannabis/illicit drug use and smell/taste dysfunction among study participants after adjusting for age of first cannabis/ illicit drug use, days used cannabis/ illicit drug during the past 30 days and other demographic characteristics and comorbidities.

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Institutional Review Board Statement: Data from the National Health and Nutrition Examination Survey (NHANES) in the United States were used in this cross-sectional study. This study was exempted from a full review of the Institutional Review Board because the data used were de-identified secondary data from NHANES.

Informed Consent Statement: The research protocols for the NHANES received approval from the NCHS Research Ethics Review Board and written informed consent was obtained from each participant (https://www.cdc.gov/nchs/nhanes/irba98.htm, accessed 1 April 2022).

Data Availability Statement: Publicly available datasets were analyzed in this study. This data can be found here: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx, accessed 1 April 2022.
Conflicts of Interest: The authors declare that they have no competing interests.

References

1. Degenhardt, L.; Whiteford, H.; Hall, W.D. The Global Burden of Disease projects: What have we learned about illicit drug use and dependence and their contribution to the global burden of disease? Drug Alcohol Rev. 2014, 33, 4–12. [CrossRef] [PubMed]
2. United Nations Office on Drugs and Crime. United Nations Office on Drugs and Crime World Drug Report 2021; United Nations Publication, Sales No. E.21.XI.8; United Nations Office on Drugs and Crime: Vienna, Austria, 2021.
3. Peacock, A.; Leung, J.; Larney, S.; Collodge, S.; Hickman, M.; Rehm, J.; Giovino, G.A.; West, R.; Hall, W.; Griffiths, P.; et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction 2018, 113, 1905–1926. [CrossRef] [PubMed]
4. Hasin, D.S.; O’Brien, C.P.; Auricacome, M.; Borges, G.; Bucholz, K.; Budney, A.; Compton, W.M.; Crowley, T.; Lingen, W.; Petry, N.M.; et al. DSM-5 criteria for substance use disorders: Recommendations and rationale. Am. J. Psychiatry 2013, 170, 834–851. [CrossRef] [PubMed]
5. Baptiste-Roberts, K.; Hossain, M. Socioeconomic disparities and self-reported substance abuse-related problems. Addict. Health 2018, 10, 112–122. [CrossRef]
6. Blum, K.; Liu, Y.; Shriner, R.; Gold, M.S. Reward circuitry dopaminergic activation regulates food and drug craving behavior. Curr. Pharm. Des. 2011, 17, 1158–1167. [CrossRef]
7. Masterova, E.; Nevidimova, T.; Savochkina, D.; Nikitina, V.; Lobacheva, O.; Vetlugina, T.; Bokhan, N. Role of olfactory reactions, nociception, and immunoenodocrine shifts in addictive disorders. Am. J. Addict. 2017, 26, 640–648. [CrossRef]
8. Temmel, A.F.; Quint, C.; Schickinger-Fischer, B.; Klimek, L.; Stoller, E.; Hummel, T. Characteristics of olfactory disorders in relation to major causes of olfactory loss. Arch. Otolaryngol. Head Neck Surg. 2002, 128, 635–641. [CrossRef]
9. Mazal, P.P.; Haehner, A.; Hummel, T. Relation of the volume of the olfactory bulb to psychophysical measures of olfactory function. Eur. Arch. Otorhinolaryngol. 2016, 273, 1–7. [CrossRef]
10. Schäfer, L.; Schriever, V.A.; Croy, I. Human olfactory dysfunction: Causes and consequences. Cell Tissue Res. 2021, 383, 569–579. [CrossRef]
11. Papazian, E.J.; Pinto, J.M. Olfactory loss and aging: Connections with health and well-being. Chem. Senses 2021, 46, bjao045. [CrossRef]
12. Maheswaran, T.; Abikshyeet, P.; Sitra, G.; Gokulanathan, S.; Vaithiyanadane, V.; Jeelani, S. Gustatory dysfunction. Front. Med. 2014, 6, S30–S33. [CrossRef] [PubMed]
13. Welge-Lüssen, A. Re-establishment of olfactory and taste functions. GMS Curr. Top. Otorhinolaryngol. Head Neck Surg. 2005, 4, Doc06. [PubMed]
14. Dong, J.; Pinto, J.M.; Guo, X.; Alonso, A.; Tranah, G.; Cauley, J.A.; Garcia, M.; Satterfield, S.; Huang, X.; Harris, T.; et al. The prevalence of anosmia and associated factors among U.S. black and white older adults. J. Gerontol. Ser. A Biol. Sci. Med. Sci. 2017, 72, 1080–1086. [CrossRef] [PubMed]
15. Saltagi, A.K.; Saltagi, M.Z.; Nag, A.K.; Wu, A.W.; Higgins, T.S.; Knisely, A.; Ting, J.Y.; Illing, E.A. Diagnosis of anosmia and hyposmia: A systematic review. Allergy Rhinol. 2021, 12, 21526567211026568. [CrossRef] [PubMed]
16. Rebholz, H.; Braun, R.J.; Ladage, D.; Knoll, W.; Kleber, C.; Hassel, A.W. Loss of olfactory function—Early indicator for COVID-19, other viral infections and neurodegenerative disorders. Front. Neurol. 2020, 11, 1264. [CrossRef] [PubMed]
17. Olofsson, J.K.; Ekström, I.; Larsson, M.; Nordin, S. Olfaction and aging: A review of the current state of research and future directions. i-Perception 2012, 12, 2016695211020331. [CrossRef]
18. Schriever, V.A.; Reither, N.; Gerber, J.; Iannilli, E.; Hummel, T. Olfactory bulb volume in smokers. Exp. Brain Res. 2013, 225, 153–157. [CrossRef]
19. Vennemann, M.M.; Hummel, T.; Berger, K. The association between smoking and smell and taste impairment in the general population. J. Neurol. 2008, 255, 1121–1126. [CrossRef]
20. Fjaeldstad, A.W.; Ovesen, T.; Hummel, T. The association between smoking on olfactory dysfunction in 3900 patients with olfactory loss. Laryngoscope 2021, 131, E8–E13. [CrossRef]
21. Dinc, A.S.; O’Brien, C.P.; Auricacome, M.; Borges, G.; Bucholz, K.; Budney, A.; Compton, W.M.; Crowley, T.; Lingen, W.; Petry, N.M.; et al. DSM-5 criteria for substance use disorders: Recommendations and rationale. Am. J. Psychiatry 2013, 170, 834–851. [CrossRef] [PubMed]
22. Hasin, D.S.; O’Brien, C.P.; Auricacome, M.; Borges, G.; Bucholz, K.; Budney, A.; Compton, W.M.; Crowley, T.; Lingen, W.; Petry, N.M.; et al. DSM-5 criteria for substance use disorders: Recommendations and rationale. Am. J. Psychiatry 2013, 170, 834–851. [CrossRef] [PubMed]
23. Vennemann, M.M.; Hummel, T.; Berger, K. The association between smoking and smell and taste impairment in the general population. J. Neurol. 2008, 255, 1121–1126. [CrossRef]
24. Fjaeldstad, A.W.; Ovesen, T.; Hummel, T. The association between smoking on olfactory dysfunction in 3900 patients with olfactory loss. Laryngoscope 2021, 131, E8–E13. [CrossRef]
25. Dinc, A.S.; O’Brien, C.P.; Auricacome, M.; Borges, G.; Bucholz, K.; Budney, A.; Compton, W.M.; Crowley, T.; Lingen, W.; Petry, N.M.; et al. DSM-5 criteria for substance use disorders: Recommendations and rationale. Am. J. Psychiatry 2013, 170, 834–851. [CrossRef] [PubMed]
26. Perl, E.; Shufman, E.; Vas, A.; Luger, S.; Steiner, J.E. Taste- and odor-reactivity in heroin addicts. Isr. J. Psychiatry Relat. Sci. 1997, 34, 290–299. [PubMed]
