Characterising Cocaine and Opioid poly drug use trends and drug related harms in Scotland 2015-2022

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Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Taught Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, this work is my own work. Work done in collaboration with, or with the assistance of others, is indicated as such. I have identified all material in this dissertation which is not my own work through appropriate referencing and acknowledgement. Where I have quoted or otherwise incorporated material which is the work of others, I have included the source in the references. Any views expressed in the dissertation, other than referenced material, are those of the author.

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Plain Language Summary

Scotland has one of the highest drug-related death rates in Europe. Many individuals who use opioids also use other drugs at the same time. One combination of concern is cocaine and opioid (C&O), because it can increase health risks. Cocaine can place strain on the heart and blood vessels, while opioids also can affect heart function. Cocaine, as a stimulant, can mask the sedative effect of opioids. When used together, they can lead individuals to take higher doses, increasing the risk of overdose or other serious problems.

This study looked at the trends over time of C&O dependence and related health harms in individuals in Scotland who were receiving opioid agonist therapy (OAT), a substitution therapy for opioid dependence. We used data from national health records collected between 2015 and 2022. We included 37,409 individuals aged 15–64 with at least one OAT prescription in the past two years. We compared individuals who used opioid with those who also used cocaine. We focus on four health outcomes: drug-related deaths, all-cause mortality, non-fatal overdoses (where someone is taken to hospital but survives), and cardiovascular mortality.

We found that about 1 in 5 individuals (21.6%) receiving OAT also used cocaine. This group was more likely to experience a non-fatal overdose than individuals who used opioid, even after accounting for differences in age, sex, region, and accommodation status. The highest overdose risk was in young men aged 15–34. However, individuals with C&O dependence had a lower rate of cardiovascular mortality compared with those with opioid dependence.

Across all groups, older age, homelessness, and living in certain areas (such as Tayside) were linked to higher risks of death. Men generally had higher risks of cardiovascular death than women, especially in the middle-aged and older groups. This study found that individuals with combined C&O dependence had higher risks of non-fatal overdose compared with those with opioid dependence, but not consistently higher risks of other drug-related, all-cause or cardiovascular mortality.

Abstract

Background

Scotland has one of the highest drug-related mortality rates in Europe, with opioid dependence affecting over 1% of the adult population. Polydrug use, particularly concurrent cocaine and opioid (C&O) dependence, is increasingly prevalent, potentially exacerbating risks of overdose, cardiovascular harm, and premature mortality.

Methods

We conducted a retrospective cohort study using linked national datasets (2015–2022) to examine the trends over time of C&O dependence and associated harms among individuals aged 15–64 receiving opioid agonist therapy (OAT). Outcomes included drug-related deaths (DRD), all-cause mortality (ACM), non-fatal overdose (NFOD), and cardiovascular mortality (CVD). Poisson regression estimated incidence rate ratios (IRR) with confidence interval (CI), adjusting for age, sex, calendar year, region, and accommodation status.

Results

Among 37,409 individuals receiving OAT between 2015 and 2022, 8,074 (21.6%) had concurrent cocaine and opioid (C&O) dependence. In adjusted Poisson regression models, C&O dependence was associated with substantially higher non-fatal overdose (NFOD) rates compared with opioid dependence (adjusted IRR = 1.74, 95% CI 1.67–1.82). Drug-related deaths (DRD) showed no clear difference (adjusted IRR = 0.93, 95% CI 0.85–1.01), nor did all-cause mortality (ACM; adjusted IRR = 0.86, 95% CI 0.80–0.92) or cardiovascular deaths (CVD; adjusted IRR = 0.71, 95% CI 0.66–0.77). Other independent predictors of adverse outcomes included older age, male sex, residence in Tayside, and homelessness. Event rates for DRD, ACM, and NFOD generally increased over the study period, whereas CVD rates declined.

Conclusion

C&O dependence in OAT individuals is strongly linked to elevated NFOD risk, especially among younger men, but to lower CVD mortality compared with opioid.

Background

Scotland has consistently reported one of the highest drug-related mortality rates in Europe (1). In 2022/23, approximately 1.23% of the Scottish population aged 15–64 was estimated to be opioid dependence (2). In 2020, Scotland had the highest per capita drug-related deaths rate in the European Union, with 245 deaths per million people, which was more than 3.7 times higher than the overall deaths rate of 67.1 deaths per million people in the United Kingdom and surpassed most international regions (3). Polydrug use, particularly among people receiving OAT, is thought to contribute to persistently high rates of drug-related deaths in Scotland, with approximately 90% involving opioid, which are often used in combination with benzodiazepines, gabapentinoids, cocaine and alcohol. The drug related deaths have increased in Scotland and constitute a public health emergency (1).

The increase in reliance on C&O appears to be more acute among socially vulnerable groups, including individuals who are homeless, unemployed, or incarcerated. The drug crisis is fundamentally driven by economic and social unrest (4). The HIV outbreak in Glasgow from 2015 to 2019 was associated with public injections of cocaine and opioid dependence, highlighting social marginalization, especially homelessness and street drug use. This shows that the accommodation status and the region interact with the evolving drug market to drive infectious disease clusters (5,6).

The demographic structure of the affected population has changed significantly. Among individuals who received OAT treatment in Scotland over the past five years, the opioid dependent population is aging. Between 2014/15 and 2019/20, the number of individuals aged 15-34 is estimated to have decreased by 5,100, while the number of individuals aged 50-64 has increased by 2,800 (7). In Scotland, the prevalence of opioid dependence has risen significantly among those aged 50–64, while rates have declined among younger groups (7). Older individuals on OAT are at greater risk of methadone-specific mortality (methadone is a long-acting synthetic opioid used in maintenance therapy), likely due to age-related physiological changes (8).

Moreover, cocaine use is associated with substantial cardiovascular harm, affecting both vascular and myocardial integrity. Acute exposure can trigger coronary vasoconstriction,

arrhythmias, myocardial ischemia and infarction, while chronic use has been linked to structural myocardial changes such as hypertrophy, dilated cardiomyopathy and myocarditis (9). These pathophysiological effects may be further compounded in individuals with concurrent opioid dependence. Stimulants such as cocaine can mask the sedative effect of opioid, which may lead individuals to increase the dosage of opioid to achieve the desired effect, thereby significantly increasing the risk of overdose and cardiovascular risks (10). Opioids themselves may interfere with cardiovascular function and pharmacological management, with potential interactions affecting medications commonly prescribed for cardiovascular disease (11).

In conclusion, the persistently high drug-related mortality rate in Scotland reflects the complex interaction among the changing patterns of substance use, social vulnerability and demographic changes among opioid dependent populations. Increasingly dependent on C&O, especially in accept the OAT and marginalised in the elderly, poses a multifaceted challenge to public health. In this context, this study aimed to investigate the trends in C&O dependence compared to opioid dependence and whether it is associated with greater drug-related harm. Specifically, we investigated the risks of non-fatal overdose, drug-related deaths, all-cause mortality and cardiovascular mortality among different demographic and social groups.

Methods

Data Sources

This study utilised linked national datasets from Scotland to characterise patterns of C&O dependence and associated harms between 2015 and 2022. The data for this study were provided by Public Health Scotland (PHS) through Scottish Public Health Drug Linkage Programme (SPHLDP). The primary source of treatment exposure data was the Prescribing Information System (PIS), which records prescriptions issued by clinicians and dispensed by pharmacies. For this analysis, OAT prescriptions were extracted for the period 2009–2023, with the study period restricted to 1 January 2015–31 December 2022. Key variables from PIS included the prescription payment date, a unique patient identifier, date of birth, and the

individual's NHS health board of residence. The board of residence is derived from the most recent OAT prescription.

Data on drug misuse history were obtained from the Scottish Drug Misuse Database (SDMD) for 2015–2021 and its successor, the Drug and Alcohol Information System (DAISy), for 2021–2022. These systems record data about individuals coming to drug services for help, including personal information and the drugs used. When the recorded substances include cocaine, crack cocaine or cocaine powder, we will determine that this person used cocaine. The accommodation status based on the most recent record in the SDMD or DAISy.

Drug-related hospital admissions were identified from the Scottish Morbidity Records Acute hospital inpatient and daycase database (SMR01), restricted to admissions where drug poisoning was recorded as the cause of admission. Non-fatal overdose events were defined as admissions with International Classification of Diseases, 10th Revision (ICD-10) codes T40.0, T40.1, or T40.3, corresponding to opioid, heroin and methadone drug-related poisoning. The NFOD analyzed was limited to inpatient cases, while the majority of NFOD cases were actually not admitted to the hospital.

Mortality data were sourced from the Scottish Morbidity Records death registration database (SMR99) - a subset of National Records of Scotland's death registration database, held by PHS. All-cause mortality encompassed all deaths occurring during the study period, regardless of cause. We used confirmed DRD via the supplementary NRS datafile. Full definitions of ICD-10 codes used to define causes of death (including drug-related and cardiovascular mortality) are provided in Supplementary Table 3.

Study Design and Population

A retrospective cohort design was employed. The cohort comprised individuals aged 15–64 years who were resident in Scotland and received at least one OAT prescription and one SDMD/DAISy record between 1 January 2015 and 31 December 2022. This cohort was created and provided by the supervisor team. Follow-up began at the start of the study period for anyone who received OAT during the two years prior and ended at the earliest of: (i) date of death, (ii) two years after the final OAT prescription (to capture ongoing risk after treatment cessation), or (iii) the end of the study period (31 December 2022).

Individuals who had received at least one OAT prescription between 2009 and 2023 were initially considered. Exclusions were applied sequentially to remove those without SDMD or DAISy records, those outside the target age range (15-64), those without any OAT prescriptions in 2013-2022, and individuals not residing in Scotland or lacking regional health board information. After applying these criteria, a final cohort was established, comprising 37,409 individuals aged 15–64 with at least one OAT prescription in the past two years.

The participants were divided into two exposure groups. The first one is C&O dependence, individuals who have a history of cocaine use in the any record in SDMD or DAISy. The dependence of cocaine was determined based on the any records of substances reported during the research period, including cocaine, crack cocaine or cocaine powder. The second group consists of opioid dependence with no recorded cocaine use in SDMD or DAISy records.

Covariates included year, age group (15–34, 35–49, and 50–64 years), sex (male/female), NHS health board of residence (Greater Glasgow and Clyde (GGC), Tayside, or Other), and accommodation status (Homeless and Other). The accommodation situation in prison was classified under "Others" because we have no way to determine that this person remained in prison throughout the study cohort, and the relevant data may be incomplete.

Statistical Analysis

Descriptive analyses were first conducted to summarise demographic, clinical, and exposure characteristics of the cohort, stratified by drug dependence category (opioid vs. cocaine and opioid). Categorical variables were presented as counts and percentages.

Crude rates of drug-related deaths, all-cause mortality, non-fatal overdose, and cardiovascular mortality were calculated per 1,000 person-years (PY) for each exposure group across calendar years from 2015 to 2022. Person-time at risk was calculated for each individual from the date of cohort entry to the earliest of death, two years after the last OAT prescription, or study end. Rates were accompanied by 95% CI and plotted to illustrate temporal trends.

To evaluate the association between the exposure group and each outcome, a Poisson regression model with a logarithmic link function was fitted, using the natural logarithm of PY as the offset term. The unadjusted model only includes exposure variables (drug type). Then adjust the model to incorporate all potential confounding factors: age, sex, year, residential board and accommodation status. The model results were expressed as an IRR with a 95% CI.

Age and sex were included as covariates because they are strong determinants of drug-related outcomes and could confound the association between C&O dependence and health harms. To assess whether the effect of C&O dependence varied across subgroups, we tested for potential effect modification by sex, age group, and accommodation status. This is accomplished by including the interaction terms between exposure and these variables in the fully adjusted Poisson regression model. P-values from these tests are reported as indicators of the strength of evidence for interaction, rather than as strict cutoffs for statistical significance.

Results

Characteristics of the Study Cohort

The final study cohort comprised 37,409 unique individuals aged 15–64 years who were resident in Scotland and had received at least one opioid agonist therapy prescription in the past two year between 2015 and 2022. Table 1 summarises the baseline demographic, clinical and exposure characteristics. Most individuals were male (68.3%), with females accounting for 31.7% of the cohort. The age distribution was skewed towards older adults, with 49.8% aged 35–49 years, 44.4% aged 15–34 years, and only 5.8% aged 50–64 years at the time of inclusion. In terms of the drug dependence, 78.4% (n = 29,335) were classified as opioid dependence, while 21.6% (n = 8,074) met the definition for C&O dependence.

Accommodation status was dominated by the other (90.9%) and homeless (9.1%). Geographically, the largest part of the cohort resided in Other NHS regions in Scotland (65.0%), followed by Greater Glasgow and Clyde (26.7%) and Tayside (8.3%).

Indicators of drug-related harm showed that 14.9% of individuals experienced at least one non-fatal overdose during the observation period, while 8.7% died a drug-related death. All-cause mortality occurred in 14.7% of the cohort, and cardiovascular mortality accounted for 1.35% of deaths.

Table 1. Characteristics of the Study Cohort

Characteristic	N	%
Total participants	37,409	100.0
Drug		
Opioid	29,335	78.42
Opioid + Cocaine	8,074	21.58
Age group		
15–34 years	17,395	44.36
35–49 years	19,536	49.82
50–64 years	2,285	5.83
Sex		
Female	11,855	31.69
Male	25,554	68.31
Accommodation		
Other	34015	90.93
Homeless	3,394	9.07
Board		
Greater Glasgow and Clyde	9,987	26.7
Tayside	3,106	8.3
Other NHS regions in Scotland	24,316	65.0

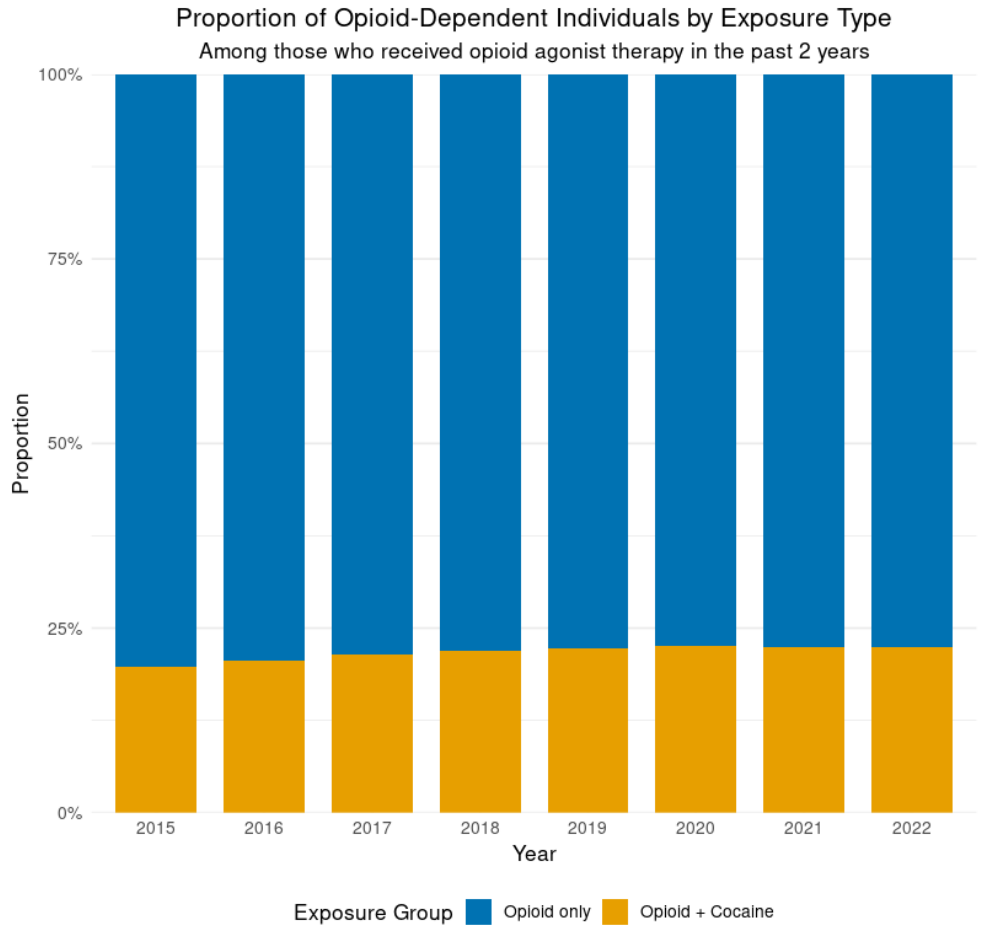
Table 2. Characteristics of Outcome

Outcome	No Event	Event Occurred	No Event (%)	Event (%)
Non-fatal overdose	31,838	5,571	85.1%	14.9%
All-cause mortality	31,918	5,491	85.3%	14.7%
Drug-related deaths	34,169	3,240	91.3%	8.66%

Cardiovascular mortality	36,905	504	98.7%	1.35%

Figure 1 shows the annual proportion changes of the opioid only and C&O dependence groups in the cohort during the years 2015/16 to 2021/22. Since 2015/16, the proportion of opioid and cocaine dependence has shown a slight upward trend.

Figure 1. Proportion of Opioid Dependent Individuals by Exposure Type



Crude Rates of Outcomes

Crude event rates varied over time and between exposure groups (Figures 2). For drug-related deaths, individuals in the opioid group experienced a steady increase in rates from 2015, peaking in 2020 at just over 20 per 1,000 person-years, followed by a modest decline.

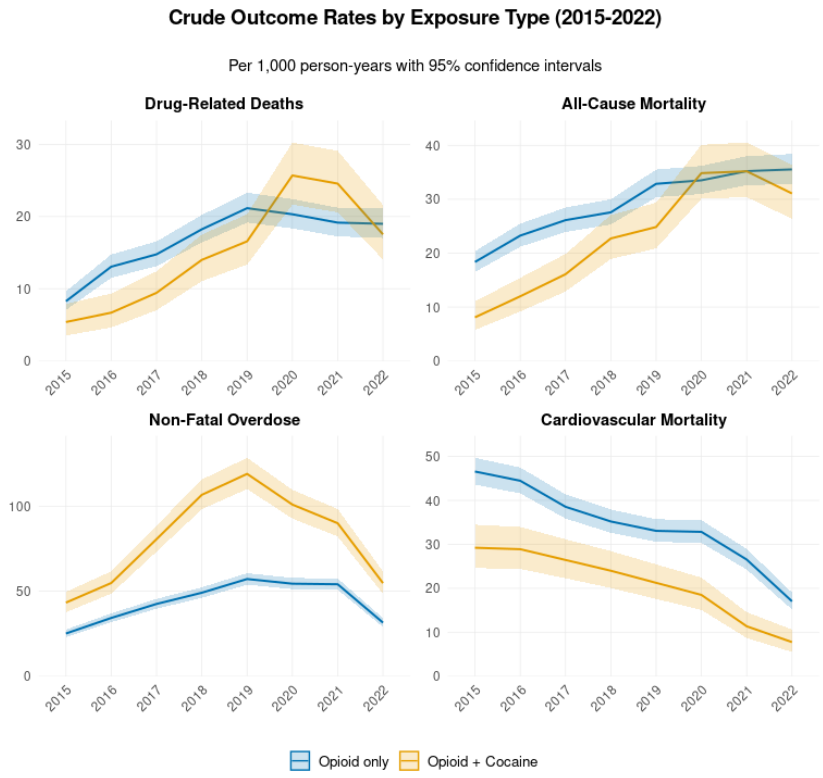
In contrast, the initial DRD rate of the cocaine exposure group was lower, but it rose sharply in 2020, surpassing that of the opioid group, and then declined in the following years.

For all-cause mortality, rates increased in both groups throughout the study period. Opioid dependence consistently showed slightly higher mortality rates until 2020, after which the gap between the two groups narrowed.

In terms of non-fatal overdose, rates peaked at over 125 per 1,000 person-years in 2019, before declining slightly but remaining elevated throughout the later years of follow-up. It is possible that the presence of cocaine dependence reflects broader patterns of illicit drug use and higher overdose risk, while its absence may indicate greater adherence to OAT and comparatively lower overdose risk.

Lastly, cardiovascular mortality showed a overall downward trend in both groups. However, compared with C&O dependence group, the mortality rate of cardiovascular diseases in the opioid only group has always been relatively high.

Figure 2. Crude Outcome Rates by Exposure Type (2015-2022)



Regression Analyses

In unadjusted models, individuals with C&O dependence experienced lower rates of drug-related deaths than those with opioid dependence (IRR = 0.91, 95% CI 0.84–0.99). After adjusting for age, sex, year, NHS board, and accommodation status, the association was attenuated and no longer statistically significant (adjusted IRR = 0.93, 95% CI 0.85–1.01). DRD risk was higher among participants aged 50–64 years (adjusted IRR = 1.53, 95% CI 1.35–1.73), males (adjusted IRR = 1.09, 95% CI 1.01–1.17), residents of Tayside (adjusted IRR = 1.19, 95% CI 1.05–1.36), and those experiencing homelessness (reference: other accommodation, adjusted IRR = 0.71, 95% CI 0.64–0.79). DRD rates also rose steadily across years, more than doubling by 2022 (adjusted IRR = 2.28, 95% CI 1.92–2.71; see Table 4 for full regression results).

For all-cause mortality, individuals with C&O dependence had lower rates compared with those with opioid dependence, both before (IRR = 0.81, 95% CI 0.75–0.87) and after adjustment (adjusted IRR = 0.86, 95% CI 0.80–0.92). ACM risk was strongly associated with older age (50–64 years: adjusted IRR = 2.39, 95% CI 2.18–2.63), male sex (adjusted IRR = 1.09, 95% CI 1.03–1.16), Tayside residence (adjusted IRR = 1.20, 95% CI 1.08–1.33), and homelessness (adjusted IRR = 0.72, 95% CI 0.66–0.78 for other accommodation). Mortality increased year-on-year, with a peak in 2021 (adjusted IRR = 1.91, 95% CI 1.70–2.16; see Table 5 for full regression results).

Non-fatal overdose rates were substantially higher among individuals with C&O dependence (unadjusted IRR = 1.89, 95% CI 1.82–1.97; adjusted IRR = 1.74, 95% CI 1.67–1.82). Younger individuals, males, residents of Tayside, and those experiencing homelessness were also at greater risk. NFOD rates peaked in 2019 (adjusted IRR = 2.55, 95% CI 2.34–2.79; see Table 6 for full regression results) before declining.

There appears to be a lower risk of cardiovascular mortality among individuals with C&O dependence compared with opioid dependence (unadjusted IRR = 0.60, 95% CI 0.56–0.65; adjusted IRR = 0.71, 95% CI 0.66–0.77). CVD mortality was strongly associated with older age (50–64 years: adjusted IRR = 6.39, 95% CI 5.79–7.06), male sex (adjusted IRR = 1.22, 95% CI 1.15–1.29), and residence outside Greater Glasgow & Clyde and Tayside (adjusted IRR =

1.34, 95% CI 1.26–1.42). Mortality rates declined markedly across the study period (2022 vs 2015: adjusted IRR = 0.26, 95% CI 0.23–0.29; see Table 7 for full regression results).

Interaction Analyses

To further explore potential effect modification, we fitted Poisson regression models including interaction terms. When testing the interaction between age group and sex, the likelihood ratio test indicated no significant interaction for DRD (p=0.29), ACM (p=0.15), or CVD (p=0.076), but a highly significant interaction for NFOD (p<0.001). In the NFOD models, males aged 35–49 and 50–64 years had substantially l ower relative risks compared with females of the same age, after accounting for main effects (IRR=0.80, 95% CI: 0.73–0.88; IRR=0.67, 95% CI: 0.58–0.79, respectively). A weak positive interaction was also observed for CVD among older males (Age 50–64 × Male: IRR=1.27, 95% CI: 1.03–1.56, p=0.024).

We also examined the drug by accommodation interaction. The interaction term was not significant for DRD, ACM, or NFOD, indicating that the relative risks associated with combined cocaine and opioid use compared with opioid use alone were broadly similar across accommodation groups. However, a strong interaction effect was observed for CVD: individuals using both cocaine and opioid who were not homeless had a markedly lower relative risk compared with opioid-using homeless individuals (IRR=0.47, 95% CI: 0.38–0.57, p<0.001).

Conclusion

In this cohort, event rates for DRD, ACM, and NFOD generally increased over the study period, whereas CVD rates declined. Concurrent cocaine and opioid dependence was associated with a substantially higher risk of non-fatal overdose compared with opioid dependence, highlighting a burden of acute overdose risk. No clear differences were observed for drug-related deaths, all-cause mortality, or cardiovascular deaths between C&O and opioid groups, suggesting that the excess risk may be limited to acute events rather than long-term mortality. Interaction analysis revealed that young men (15-34 years old) dependent on C&O carried the highest risk of excessive NFOD, while elderly male (50-64

years old) had a relatively lower risk of excessive NFOD compared to female, but an increased mortality rate from cardiovascular diseases.

The limitation of this study lies in the fact that the classification relied upon by C&O is based on treatment records and may not be able to capture the correct use of cocaine. The interruption of OAT during homelessness or imprisonment may affect the outcome. For the cohort definition, this study defined that those who had one OAT record in the past two years were included without conducting a sensitivity analysis, which would lead to the incorrect inclusion of the cohort population.

Author Contributions

My supervisors provided academic guidance in defining the study cohort, variables, and outcomes, and assisted in developing the corresponding code. My supervisors created and provided the cohort data. My supervisors also offered suggestions on the selection of statistical models and the inclusion of interactions to ensure the rigor and efficiency of the methods. In addition, I received feedback on the presentation of results, including the choice and design of figures and tables. All data analysis, interpretation, and writing were conducted by the author.

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448 **Supplementary Material**

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450 **Table 3. ICD-10 Codes used to Define Outcomes**

Outcome	ICD-10 Codes	Definition
Non-fatal overdose (hospitalisation)	T40.0	Opium poisoning
	T40.1	Heroin poisoning
	T40.3	Methadone poisoning
Drug-related deaths (mental/behavioural)	F11–F16, F19	Mental and behavioural disorders due to opioids, cannabinoids, sedatives/hypnotics, cocaine, stimulants, hallucinogens, multiple/other substances
Drug-related deaths (accidental)	X40–X44	Accidental poisoning by drugs
Drug-related deaths (intentional)	X60–X64	Intentional self-poisoning by drugs
Drug-related deaths (homicide)	X85	Assault by drugs, medicaments and biological substances
Drug-related deaths (undetermined)	Y11–Y14	Poisoning by drugs, undetermined intent
Cardiovascular mortality	I00–I99	Diseases of the circulatory system (including ischemic heart disease, stroke, heart failure, etc.)

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455 **Table 4. Poisson Regression Results for Drug-related Deaths**

Category	Events	Person-years	Rate	95%CI	IRR	95% CI	P value	Adjusted IRR	95% CI	P value
Drug										
Opioid	2 595	155 496	16.7	16.1–17.3	1.00	—	—	1.00	ref	—
C&O	645	42 411	15.2	14.1–16.4	0.91	0.84–0.99	0.035	0.93	0.85–1.01	0.086
Age										
15–34	493	42 010	11.7	10.7–12.8	1.00	—	—	1.00	ref	—
35–49	2 137	126 035	17.0	16.2–17.7	1.44	1.31–1.60	<0.001	1.36	1.24–1.51	<0.001
50–64	610	29 863	20.4	18.8–22.1	1.74	1.55–1.96	<0.001	1.53	1.35–1.73	<0.001
Sex										
Female	974	64 562	15.1	14.2–16.1	1.00	—	—	1.00	ref	—
Male	2 266	133 345	17.0	16.3–17.7	1.13	1.05–1.21	0.002	1.09	1.01–1.17	0.034
Year										
2015	189	24 537	7.7	6.6–8.9	1.00	—	—	1.00	ref	—
2016	295	25 080	11.8	10.5–13.2	1.53	1.27–1.84	<0.001	1.51	1.26–1.81	<0.001
2017	346	25 384	13.6	12.2–15.1	1.77	1.48–2.12	<0.001	1.73	1.45–2.07	<0.001
2018	438	25 299	17.3	15.7–19.0	2.25	1.90–2.67	<0.001	2.18	1.84–2.59	<0.001
2019	506	25 117	20.1	18.4–22.0	2.62	2.22–3.10	<0.001	2.52	2.13–2.98	<0.001
2020	537	24 960	21.5	19.7–23.4	2.79	2.37–3.30	<0.001	2.67	2.26–3.16	<0.001
2021	500	24 559	20.4	18.6–22.2	2.64	2.24–3.13	<0.001	2.51	2.12–2.97	<0.001
2022	429	22 972	18.7	16.9–20.5	2.42	2.05–2.88	<0.001	2.28	1.92–2.71	<0.001
Board										
GGC	934	54 806	17.0	16.0–18.2	1.00	—	—	1.00	ref	—
Other	2 002	127 183	15.7	15.1–16.4	0.92	0.86–1.00	0.045	0.97	0.90–1.05	0.463
Tayside	304	15 919	19.1	17.0–21.4	1.12	0.98–1.27	0.085	1.19	1.05–1.36	0.008
Accommodation										
Homeless	359	16 580	21.7	19.5–24.0	1.00	—	—	1.00	ref	—
Other	2 881	181 327	15.9	15.3–16.5	0.73	0.66–0.82	<0.001	0.71	0.64–0.79	<0.001

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Table 5. Poisson Regression Results for All-Cause Mortality

Category	Events	Person-years	Rate	95%CI	IRR	95% CI	P value	Adjusted IRR	95% CI	P value
Drug										
Opioid	4 499	155 496	28.9	28.1–29.8	1.00	—	—	1.00	ref	—
C&O	992	42 411	23.4	22.0–24.9	0.81	0.75–0.87	<0.001	0.86	0.80–0.92	<0.001
Age										
15–34	730	42 010	17.4	16.1–18.7	1.00	—	—	1.00	ref	—
35–49	3 373	126 035	26.8	25.9–27.7	1.54	1.42–1.67	<0.001	1.47	1.35–1.59	<0.001
50–64	1 388	29 863	46.5	44.1–49.0	2.67	2.45–2.93	<0.001	2.39	2.18–2.63	<0.001
Sex										
Female	1 605	64 562	24.9	23.7–26.1	1.00	—	—	1.00	ref	—
Male	3 886	133 345	29.1	28.2–30.1	1.17	1.11–1.24	<0.001	1.09	1.03–1.16	0.003
Year										
2015	401	24 537	16.3	14.8–18.0	1.00	—	—	1.00	ref	—
2016	526	25 080	21.0	19.2–22.8	1.28	1.13–1.46	<0.001	1.26	1.10–1.43	<0.001
2017	609	25 384	24.0	22.1–26.0	1.47	1.29–1.67	<0.001	1.41	1.24–1.60	<0.001
2018	671	25 299	26.5	24.6–28.6	1.62	1.43–1.84	<0.001	1.53	1.35–1.73	<0.001
2019	781	25 117	31.1	29.0–33.4	1.90	1.69–2.15	<0.001	1.76	1.56–1.98	<0.001
2020	844	24 960	33.8	31.6–36.2	2.07	1.84–2.33	<0.001	1.87	1.66–2.11	<0.001
2021	865	24 559	35.2	32.9–37.6	2.16	1.92–2.43	<0.001	1.91	1.70–2.16	<0.001
2022	794	22 972	34.6	32.2–37.1	2.11	1.88–2.39	<0.001	1.83	1.63–2.07	<0.001
Board										
GGC	1 569	54 806	28.6	27.2–30.1	1.00	—	—	1.00	ref	—
Other	3 429	127 183	27.0	26.1–27.9	0.94	0.89–1.00	0.049	1.03	0.97–1.10	0.292
Tayside	493	15 919	31.0	28.3–33.8	1.08	0.98–1.20	0.128	1.20	1.08–1.33	<0.001
Accommodation										
Homeless	580	16 580	35.0	32.2–37.9	1.00	—	—	1.00	ref	—
Other	4 911	181 327	27.1	26.3–27.9	0.77	0.71–0.85	<0.001	0.72	0.66–0.78	<0.001

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463 **Table 6. Poisson Regression Results for Non-fatal Overdose**

Category	Events	Person-years	Rate	95%CI	IRR	95% CI	P value	Adjusted IRR	95% CI	P value
Drug										
Opioid	6 780	155 496	43.6	42.6–44.7	1.00	—	—	1.00	ref	—
C&O	3 500	42 411	82.5	79.8–85.3	1.89	1.82–1.97	<0.001	1.74	1.67–1.82	<0.001
Age										
15–34	2 937	42 010	69.9	67.4–72.5	1.00	—	—	1.00	ref	—
35–49	6 127	126 035	48.6	47.4–49.8	0.70	0.67–0.73	<0.001	0.72	0.69–0.75	<0.001
50–64	1 216	29 863	40.7	38.5–43.1	0.58	0.55–0.62	<0.001	0.62	0.58–0.67	<0.001
Sex										
Female	3 024	64 562	46.8	45.2–48.5	1.00	—	—	1.00	ref	—
Male	7 256	133 345	54.4	53.2–55.7	1.16	1.11–1.21	<0.001	1.20	1.15–1.25	<0.001
Year										
2015	705	24 537	28.7	26.6–30.9	1.00	—	—	1.00	ref	—
2016	965	25 080	38.5	36.1–41.0	1.34	1.22–1.48	<0.001	1.36	1.23–1.50	<0.001
2017	1 286	25 384	50.7	47.9–53.5	1.76	1.61–1.93	<0.001	1.80	1.64–1.97	<0.001
2018	1 560	25 299	61.7	58.6–64.8	2.15	1.96–2.35	<0.001	2.21	2.02–2.41	<0.001
2019	1 780	25 117	70.9	67.6–74.2	2.47	2.26–2.69	<0.001	2.55	2.34–2.79	<0.001
2020	1 618	24 960	64.8	61.7–68.1	2.26	2.07–2.47	<0.001	2.34	2.15–2.56	<0.001
2021	1 525	24 559	62.1	59.0–65.3	2.16	1.98–2.36	<0.001	2.27	2.07–2.48	<0.001
2022	841	22 972	36.6	34.2–39.2	1.27	1.15–1.41	<0.001	1.36	1.23–1.50	<0.001
Board										
GGC	2 773	54 806	50.6	48.7–52.5	1.00	—	—	1.00	ref	—
Other	6 392	127 183	50.3	49.0–51.5	0.99	0.95–1.04	0.768	0.94	0.90–0.99	0.010
Tayside	1 115	15 919	70.0	66.0–74.3	1.38	1.29–1.48	<0.001	1.43	1.33–1.53	<0.001
Accommodation										
Homeless	1 603	16 580	96.7	92.0–101.5	1.00	—	—	1.00	ref	—
Other	8 677	181 327	47.9	46.9–48.9	0.50	0.47–0.52	<0.001	0.56	0.53–0.60	<0.001

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Table 7. Poisson Regression Results for Cardiovascular Mortality

Category	Events	Person-years	Rate	95%CI	IRR	95% CI	P value	Adjusted IRR	95% CI	P value
Drug										
Opioid	5 371	155 496	34.5	33.6–35.5	1.00	—	—	1.00	ref	—
C&O	885	42 411	20.9	19.5–22.3	0.60	0.56–0.65	<0.001	0.71	0.66–0.77	<0.001
Age										
15–34	522	42 010	12.4	11.4–13.5	1.00	—	—	1.00	ref	—
35–49	3 714	126 035	29.5	28.5–30.4	2.37	2.17–2.60	<0.001	2.49	2.28–2.74	<0.001
50–64	2 020	29 863	67.6	64.7–70.7	5.44	4.95–6.00	<0.001	6.39	5.79–7.06	<0.001
Sex										
Female	1 612	64 562	25.0	23.8–26.2	1.00	—	—	1.00	ref	—
Male	4 644	133 345	34.8	33.8–35.8	1.39	1.32–1.48	<0.001	1.22	1.15–1.29	<0.001
Year										
2015	1 059	24 537	43.2	40.6–45.8	1.00	—	—	1.00	ref	—
2016	1 036	25 080	41.3	38.8–43.9	0.96	0.88–1.04	0.316	0.91	0.84–0.99	0.035
2017	913	25 384	36.0	33.7–38.4	0.83	0.76–0.91	<0.001	0.76	0.70–0.83	<0.001
2018	829	25 299	32.8	30.6–35.1	0.76	0.69–0.83	<0.001	0.66	0.61–0.73	<0.001
2019	765	25 117	30.5	28.3–32.7	0.71	0.64–0.77	<0.001	0.59	0.54–0.65	<0.001
2020	740	24 960	29.6	27.5–31.9	0.69	0.63–0.75	<0.001	0.56	0.51–0.61	<0.001
2021	569	24 559	23.2	21.3–25.2	0.54	0.49–0.59	<0.001	0.42	0.38–0.46	<0.001
2022	345	22 972	15.0	13.5–16.7	0.35	0.31–0.39	<0.001	0.26	0.23–0.29	<0.001
Board										
GGC	1 606	54 806	29.3	27.9–30.8	1.00	—	—	1.00	ref	—
Other	4 196	127 183	33.0	32.0–34.0	1.13	1.06–1.19	<0.001	1.34	1.26–1.42	<0.001
Tayside	454	15 919	28.5	26.0–31.3	0.97	0.88–1.08	0.610	1.18	1.06–1.31	0.002
Accommodation										
Homeless	481	16 580	29.0	26.5–31.7	1.00	—	—	1.00	ref	—
Other	5 775	181 327	31.8	31.0–32.7	1.10	1.00–1.21	0.049	0.91	0.83–1.00	0.044

Table 8. Age × Sex Interaction – Likelihood Ratio Tests

Outcome	ΔDeviance	p-value
Drug-related deaths	2.47	0.292
All-cause mortality	3.75	0.153
Non-fatal overdose	33.87	<0.001
Cardiovascular mortality	5.16	0.076

Table 9. Drug × Accommodation Interaction – Likelihood Ratio Tests

Outcome	ΔDeviance	p-value
Drug-related deaths	1.84	0.175
All-cause mortality	0.72	0.396
Non-fatal overdose	0.61	0.435
Cardiovascular mortality	53.42	<0.001

Table 10. Poisson Regression Results for Age × Sex Interaction

Category	DRD – IRR (95% CI), p	ACM – IRR (95% CI), p	NFOD – IRR (95% CI), p	CVD – IRR (95% CI), p
Drug				
Opioid	Ref.	Ref.	Ref.	Ref.
C&O	0.93 (0.85–1.01), 0.086	0.86 (0.80–0.92), <0.001	1.74 (1.67–1.82), <0.001	0.71 (0.66–0.77), <0.001
Age group				
15–34	Ref.	Ref.	Ref.	Ref.
35–49	1.48 (1.26–1.76), <0.001	1.63 (1.42–1.87), <0.001	0.84 (0.78–0.91), <0.001	2.23 (1.93–2.59), <0.001
50–64	1.75 (1.40–2.18), <0.001	2.63 (2.24–3.11), <0.001	0.83 (0.72–0.94), 0.004	5.48 (4.65–6.48), <0.001
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	1.23 (1.02–1.47), 0.029	1.25 (1.08–1.46), 0.003	1.42 (1.32–1.54), <0.001	1.02 (0.86–1.21), 0.83
Year				
2015	Ref.	Ref.	Ref.	Ref.
2016	1.51 (1.26–1.81), <0.001	1.26 (1.10–1.43), <0.001	1.36 (1.23–1.50), <0.001	0.91 (0.84–0.99), 0.034
2017	1.73 (1.45–2.07), <0.001	1.41 (1.24–1.60), <0.001	1.80 (1.64–1.97), <0.001	0.76 (0.70–0.83), <0.001
2018	2.18 (1.84–2.59), <0.001	1.53 (1.35–1.73), <0.001	2.20 (2.02–2.41), <0.001	0.66 (0.61–0.73), <0.001
2019	2.52 (2.13–2.98), <0.001	1.76 (1.56–1.98), <0.001	2.55 (2.33–2.78), <0.001	0.59 (0.54–0.65), <0.001
2020	2.67 (2.26–3.16), <0.001	1.87 (1.66–2.11), <0.001	2.34 (2.14–2.56), <0.001	0.56 (0.51–0.61), <0.001
2021	2.50 (2.12–2.97), <0.001	1.91 (1.70–2.16), <0.001	2.26 (2.07–2.47), <0.001	0.42 (0.38–0.46), <0.001
2022	2.28 (1.92–2.71), <0.001	1.83 (1.62–2.07), <0.001	1.36 (1.23–1.50), <0.001	0.26 (0.23–0.29), <0.001
Health Board				
Greater Glasgow & Clyde (GGC)	Ref.	Ref.	Ref.	Ref.
Other NHS regions in Scotland	0.97 (0.90–1.05), 0.47	1.03 (0.97–1.10), 0.29	0.94 (0.90–0.99), 0.011	1.34 (1.26–1.42), <0.001
Tayside	1.19 (1.05–1.36), 0.008	1.20 (1.08–1.33), <0.001	1.43 (1.33–1.54), <0.001	1.18 (1.06–1.31), 0.002
Accommodation				
Homeless	Ref.	Ref.	Ref.	Ref.
Other	0.71 (0.64–0.79), <0.001	0.72 (0.66–0.78), <0.001	0.56 (0.53–0.59), <0.001	0.91 (0.83–1.00), 0.044
Age × Sex interaction				
Age 15–34 ×Female	Ref.	Ref.	Ref.	Ref.
Age 35–49 × Male	0.87 (0.71–1.07), 0.197	0.85 (0.72–1.00), 0.057	0.80 (0.73–0.88), <0.001	1.20 (1.00–1.45), 0.053
Age 50–64 × Male	0.82 (0.63–1.06), 0.133	0.86 (0.71–1.04), 0.128	0.67 (0.58–0.79), <0.001	1.27 (1.03–1.56), 0.024

Table 11. Poisson Regression Results for Drug × Accommodation Interaction

Category	DRD – IRR (95% CI), p	ACM – IRR (95% CI), p	NFOD – IRR (95% CI), p	CVD – IRR (95% CI), p
Drug				
Opioid	Ref.	Ref.	Ref.	Ref.
C&O	1.06 (0.85–1.32), 0.575	0.92 (0.77–1.10), 0.366	1.68 (1.52–1.85), <0.001	1.38 (1.15–1.66), <0.001
Age group				
15–34	Ref.	Ref.	Ref.	Ref.
35–49	1.36 (1.24–1.51), <0.001	1.47 (1.35–1.59), <0.001	0.72 (0.69–0.76), <0.001	2.49 (2.27–2.74), <0.001
50–64	1.53 (1.35–1.73), <0.001	2.39 (2.18–2.63), <0.001	0.62 (0.58–0.67), <0.001	6.38 (5.79–7.05), <0.001
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	1.09 (1.01–1.17), 0.034	1.09 (1.03–1.16), 0.003	1.20 (1.15–1.25), <0.001	1.22 (1.15–1.29), <0.001
Year				
2015	Ref.	Ref.	Ref.	Ref.
2016	1.51 (1.26–1.81), <0.001	1.26 (1.10–1.43), <0.001	1.36 (1.23–1.49), <0.001	0.91 (0.84–0.99), 0.036
2017	1.73 (1.45–2.07), <0.001	1.41 (1.24–1.60), <0.001	1.80 (1.64–1.97), <0.001	0.76 (0.70–0.83), <0.001
2018	2.18 (1.84–2.59), <0.001	1.53 (1.35–1.73), <0.001	2.21 (2.02–2.41), <0.001	0.66 (0.61–0.73), <0.001
2019	2.52 (2.13–2.98), <0.001	1.76 (1.56–1.98), <0.001	2.55 (2.34–2.78), <0.001	0.59 (0.54–0.65), <0.001
2020	2.67 (2.26–3.16), <0.001	1.87 (1.66–2.11), <0.001	2.34 (2.15–2.56), <0.001	0.56 (0.51–0.61), <0.001
2021	2.51 (2.12–2.97), <0.001	1.91 (1.70–2.16), <0.001	2.27 (2.07–2.48), <0.001	0.42 (0.38–0.46), <0.001
2022	2.28 (1.92–2.71), <0.001	1.83 (1.63–2.07), <0.001	1.36 (1.23–1.50), <0.001	0.26 (0.23–0.29), <0.001
Health Board				
Greater Glasgow & Clyde (GGC)	Ref.	Ref.	Ref.	Ref.
Other NHS regions in Scotland	0.97 (0.90–1.05), 0.487	1.03 (0.97–1.10), 0.282	0.94 (0.90–0.99), 0.010	1.34 (1.27–1.42), <0.001
Tayside	1.20 (1.05–1.36), 0.007	1.20 (1.08–1.33), <0.001	1.43 (1.33–1.53), <0.001	1.19 (1.07–1.32), 0.001
Accommodation				
Homeless	Ref.	Ref.	Ref.	Ref.
Other	0.75 (0.65–0.85), <0.001	0.73 (0.66–0.81), <0.001	0.55 (0.51–0.59), <0.001	1.13 (1.01–1.27), 0.041
Drug × Accommodation interaction				
Opioid ×Homeless	Ref.	Ref.	Ref.	Ref.
C&O × Other	0.85 (0.67–1.08), 0.172	0.92 (0.76–1.12), 0.394	1.04 (0.94–1.16), 0.435	0.47 (0.38–0.57), <0.001