FACTORS ASSOCIATED WITH CO-PRESCRIPTION OF OPIOIDS AND GABAPENTINOIDS

MSc by Research

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Contents

List of tables and figures

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Declaration

I hereby declare that I am the author of this thesis, it is a record of the work that has been done by me, and it has not previously been accepted for a higher degree. I also state that all references cited have been consulted by me and the conditions of the relevant ordinance and regulations have been fulfilled.

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Abstract

Background: gabapentin and pregabalin are commonly used for relieving neuropathic pain, but also could lead to diversion, dependence and tolerance, with adverse effects on the central nervous system, especially when co-prescribed with opioids. The rates of prescribing gabapentinoids have significantly increased over the last decade. However, limited research has investigated the impact of excessive prescribing, and the factors associated with the co-prescribing of opioids and gabapentinoids are unknown.

Objectives: (1) to review existing evidence of the misuse of gabapentin and pregabalin systematically; (2) to examine the association between health outcomes/service use and co-prescribed opioids and gabapentinoids, after controlling for the potential confounders of socio-demographic factors and cancer.

Methods: (1) published literature on gabapentinoids misuse was searched systematically in key medical and pharmacy databases, and papers were selected based on inclusion/exclusion criteria (studies of adolescents and children, case studies and animal studies and irrelevant studies were excluded). After data abstraction and quality assessment, included citations were synthesised and summarised. (2) An existing dataset of 65,000 individuals in Tayside and Fife who had received at least one prescription of an opioid, with corresponding prescribing, healthcare, clinical and socio-demographic information, was linked with routine data on healthcare outcomes. Factors associated with co-prescribing of opioids and gabapentinoids were examined by Chi-square testing and logistic regression, stratified by age, sex and socioeconomic class.

Results: (1) 268 citations were found from the initial search, and 15 studies were included after study selection. These studies showed a growing number of prescriptions of gabapentinoids and reports of misuse reports internationally. From the observational studies using large databases, among the patients prescribed the medicine, the misuse prevalence of pregabalin ranged from 1.0% to 9.6%, and the prevalence of gabapentin misuse was 4.8%. Patients with substance misuse disorder were more likely to experience an overdose and to have non-medical use of gabapentin and pregabalin. Other types of included studies were generally of poor quality. (2) The results from data analysis demonstrated Accident and Emergency (A&E) attendance (for any cause) and repeated hospital admission were associated with co-prescription of opioids and gabapentinoids, after controlling for the potential confounding factors such as cancer and age.

Conclusions: overall evidence implied rising prevalence of gabapentinoid prescribing, and a rising trend of gabapentinoid misuse internationally, especially among patients with a history of substance misuse. The co-prescription of opioids and gabapentinoids was found to be associated with important socio-demographic and clinical factors. These highlight the need and opportunities for research aimed at preventing gabapentinoid misuse.

Keywords: Opioid; Gabapentin; Pregabalin; Misuse; Co-prescription

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1 Thesis objectives

This study aimed to investigate the misuse of gabapentinoids and factors associated with co-prescribed opioids and gabapentinoids. The objectives were based on the evidence gap identified in this area, and the availability of the data. To achieve these aims, this study contained two projects that related to each other. One was to review existing the evidence around the misuse of gabapentin and pregabalin in the population systematically, and to determine the key needs and directions for further studies. The other was a data-linkage study in Tayside and Fife, to examine the health outcomes/service use associated with co-prescribed opioids and gabapentinoids, after controlling for potential confounders including socio-demographic factors.

2 Systematic review: the misuse of prescribed gabapentinoids in population

2.1 Introduction

Everyone experiences pain. As an important role in our lives, the feeling of pain is so common. Pain is defined by The International Association for the Study of Pain (IASP) as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (1). Pain is classified as acute pain and chronic pain by the duration and pathoanatomic characteristics. Acute pain has a short duration, and can be relieved by curing the damaged tissue. Acute pain can act as a protection of the body. By implying the damage or potential damage of the tissue, it can influence the behaviour to avoid further injury and improve healing. On the contrary, chronic pain is long-term (over three months) and not protective (2). As well as producing the physical symptoms, chronic pain can lead to anxiety and depression (3) and affect the health by causing sleep disturbance and substance-related disorder (4). Chronic pain has become a significant problem in developed and developing countries. Chronic pain affects around 20% of the European (EU) (5) and the United States population (2), and the prevalence was reported even higher in the United Kingdom (UK), between one-third and one-half of the population of the UK (6).

Chronic pain is categorised into nociceptive pain and neuropathic pain by different mechanisms. Nociceptive pain is caused by actual or threatened damage to non-neural tissue and the activation of nociceptors (7), while the definition of neuropathic pain given by IASP is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (8). Neuropathic pain results from the damage or dysfunction of neural tissue (9), and it is characterised by burning pain, hyperalgesia

and allodynia (10). Diabetes, excessive alcohol intake, HIV infection, spinal cord injury, and some complex causes could lead to the damage of the nervous system. With both physical and mental symptoms, pain with neuropathic features is often more severe and complex to manage and decreases the quality of life. The clear mechanisms of neuropathic pain are unknown and there could be multiple mechanisms (11). It is recommended to treat neuropathic pain with multiple medications if required, combined with patient education (12). Seven percent of UK and EU populations suffer from neuropathic pain (13).

Gabapentin and pregabalin are indicated as first-line prescribed drugs in national and international clinical guidelines and recommended for the treatment of neuropathic pain (14). These two medications, grouped together as gabapentinoids, act by α-2 delta subunit of presynaptic voltage-dependent calcium channels. They affect chemicals and nerves in the body that are involved in the cause of seizures and some types of pain (15). The Food and Drug Administration (FDA) in the US approved gabapentin and pregabalin in 1993 and 2004 under the brand name Neurontin and Lyrica for the drug manufacturer Pfizer, respectively (16, 17). Initially developed to treat epilepsy, gabapentinoids are now widely used in neurology, psychiatry and primary healthcare (18). Generally, a typical adult dose of gabapentin for neuropathic pain usually starts at 300 mg, and may be increased to up to 3,600 mg a day (19). The maximum dose of pregabalin is 600 mg daily in two divided doses (16).

However, there are some problems with the use of gabapentin and pregabalin. The treatment with gabapentinoids may involve side effects, like ataxia, dizziness, drowsiness, fatigue, fever, nystagmus, sedation, and viral infection (20). Beside these side effects, gabapentin can interact with other medications. Opioids like hydrocodone and morphine can change the amount of gabapentin in the body and oxycodone can interact with pregabalin (18). Moreover, gabapentinoid prescriptions have increased significantly in the past decade in Scotland, which cannot simply be explained by the growing number of neuropathic pain diagnoses. A rising trend of gabapentinoid use is

related to drug-related death records from prison and substance misuse services. Also, the use of gabapentin and pregabalin has expanded from chronic neuropathic pain to other chronic and later acute pain conditions (21), despite a lack of effectiveness in these conditions.

There is an ongoing debate on whether there is an abuse tendency of gabapentinoid prescription and an association with drug addiction, dependence and diversion internationally. Though increasing prescriptions were reported in Scotland, data from The Health Improvement Network (THIN) database indicate that an overwhelming majority of pregabalin prescribing in the UK is consistent with product licensing (22). In other countries the prescriptions for gabapentinoids do not necessarily have the same trend. However, the published evidence is quite limited, the prevalence and patterns of prescribing gabapentinoids, and magnitude of the misuse remains unknown. The controversial conclusions on drug safety issues with gabapentinoids need to be compared and the abuse patterns need to be summarised worldwide.

Gabapentinoids prescribed excessively can affect patient safety, and local and national prescribing costs (2). This systematic review aims to describe and summarise current published literature on the prevalence of the misuse of prescribed gabapentinoids in the population, and the potential factors associated with the misuse. The results will inform local and national strategies to rationalise the prescribing and safety of gabapentin and pregabalin, and will give us an idea of evidence gaps on the misuse of medicine in treating neuropathic pain and limitations of relevant studies.

2.2 Methods

2.2.1 Search strategy

Pre-search

Before the structured systematic search, a rough search of existing and ongoing reviews was conducted by searching the key words of free texts in the database of Cochrane Database of Systematic Reviews (CDSR). CDSR contains systematic reviews conducted by the Cochrane Collaboration. The search would give an indication of the previous and current studies of systematic review of the misuse of gabapentin and pregabalin.

After pre-search, literature searching with a compliment of internet search and reference checking were used to identify the published studies of the misuse of prescribed gabapentin and pregabalin.

Literature search

To select the key electronic database, I checked previous systematic review studies in Medicine (23-25) and found some commonly used biomedical and pharmacological databases: MEDLINE, Ovid Embase and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Additionally, the database in the Centre for Reviews and Dissemination (CDR) was searched for meta-analyses and systematic reviews, using the search strategy and terms. The CDR database is a resource of meta-analyses and systematic reviews in medicine, including Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) and National Health Service Economic Evaluation Database (NHS EED). In addition, The Knowledge Network, the national knowledge management platform for health and social care in Scotland, was searched, finding many results coming from PsycINFO, a database in psychology. So considering

the characteristics of each database and the accessibility of the resources, MEDLINE, Ovid Embase, CINAHL, CDR and PsycINFO were chosen as the searching databases.

The search was conducted in November 2016. As gabapentin and pregabalin have only recently been introduced, a check of the published years would be applied after getting the search results and the filter would be set when needed, but there was no restriction of published year during the search. Alerts of my search were set in MEDLINE, Ovid Embase and CINAHL (the other two are much smaller databases and not available for setting alerts) and I checked the new publishing results until March 2017. The information on new published papers would be added only if it was included in the study.

The team for the review (SW, NT and JW) agreed that the keywords should include the drug names, the disease neuropathic pain (neuralgia) and "misuse". The search was the "misuse" and gabapentin/pregabalin/neuropathic pain. It is clear for the drug names: the two drugs (gabapentin, pregabalin), their trade names (Neurontin, Lyrica) and the classification (gabapentinoids). To better summarise "misuse", I first discussed with the review team and listed some keywords: misuse, abuse, overdose, addiction, diversion, dependence. Then I searched Medical Subject Headings (MeSH) terms in MEDLINE, and used the phrases of "prescription drug misuse", "substance-related disorders", "prescription drug overuse", and "prescription drug diversion". Other descriptions of "misuse" related to these meanings would be automatically searched as well when I used MeSH terms. The search was a combination of free texts and MeSH terms. The search strategy for each database was almost the same with tiny adjustments to fit the different databases. The inclusion/exclusion Criteria were generated based on Population, Intervention, Comparators, Outcomes and Study Designs (PICOS) to express the research question more detailed and specifically.

Research question   How much misuse of prescribed gabapentin and pregabalin is there in the population?

Inclusion criteria

Population: Adults in the general population

Interventions: prescribed gabapentin or pregabalin

Outcomes: Misuse, addiction, abuse, drug diversion, dependence

Study designs: Observational studies of a large dataset, survey, cohort studies

Exclusion criteria

Population: Studies of children, adolescents, prisoners and post-mortem studies

Outcomes: Using gabapentinoids as a medication to treat dependence on other drugs

Study designs: Case studies, animal studies

Language: Non-English studies

All kinds of study types were included except for case studies, as single cases could not reflect the pattern of the whole population. There was a specific focus on human population data, so animal studies were excluded. Studies on special groups (e.g. prisoner studies, post-mortem studies) were excluded since this study was describing the prevalence in the general population. Due to the limited resources to conduct the study and being unable to employ a translator, the search was restricted to English language documents only, and non-English language papers were excluded. As gabapentinoids can also be used for treating substance disorders caused by other

drugs (e.g. Opioids) in some countries, some studies with the keywords of substance disorders were actually focused on the treatment rather than misuse, and these citations were excluded.

Internet resources and reference scanning

As there are limited research groups and institutes conducting study of this topic and some reports by the government or institute may not get published in peer-reviewed journals, I manually searched for publications from these research teams and checked their websites on the Internet. After the search and selection of the citations from key electronic medical databases, I scanned the reference lists of included papers to see if there were any additional citations that were missed in the search, to add complementary citations. This system could also check if the literature search was good quality capturing most studies.

2.2.2 Paper selection

Each database was searched separately and all the results were combined and imported to Endnote, a software package to manage references. Endnote can exclude duplications automatically, and a manual check for duplicates was also applied. The review team (SW, NT and JW) had a pre-selection of a few citations and discussed how to apply the inclusion/exclusion criteria in practice. The titles of remaining citations were screened by two reviewers (SW and NT) independently. The reviewers scanned the titles and chose to either exclude the paper (exclude) or have a look at the abstract of this paper (pass). Only if the paper was not selected by either reviewer, this citation would be excluded. Following the title review, the remaining papers were screened by reviewing the abstracts. Editorials without new data only commenting on other studies were excluded. Then the full text screening was identified by two reviewers (SW and NT). If they could not reach an agreement after discussion, a third reviewer (JW) would make the decision whether to include this citation or not. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart would be made to show the process of the selection.

2.2.3 Data abstraction

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (Appendix 1) (26) is widely used for checking items that should be included in observational studies. In this study the STROBE checklist was used as the data abstraction form, since most included studies were observational studies and the STROBE checklist is suitable for collecting the relevant information. STROBE was chosen rather than using other abstraction forms because it is connected to the quality assessment, and can make it easier to assess in the next step. According to the checklist, the title, abstract, introduction, methods (including the study design, setting, bias, study size etc.), results, discussions and other information would be summarised in the form.

2.2.4 Quality assessment

Quality assessment tools were used to ensure the results were more rigorous with critical evaluation. According to the characteristics of study types of included citations, the assessment tools were modified based on several widely used tools.

The form of Quality Assessment Tool for Observational Cohort and Cross-sectional Studies by National Heart, Lung and Blood Institute (NHLBI) (Appendix 2) was used as the basis for the modified checklists. The review studies would be assessed by CASP tool (Appendix 3). NHLBI checklist combined with checklist from Critical Appraisal Skills Programme (CASP) (Appendix 4) and Joanna Briggs Institute (JBI) (Appendix 5) was used for assessing the quality of cohort studies and analytical cross sectional studies. The assessment of the surveys was based on the Survey Assessment Framework from Circum Network (Appendix 6).

2.2.5 Data summary

The included papers were summarised in tables by different study types. The summary tables were designed based on the characteristics of the study type. The tables mainly described the information of the study (author, publishes year and study region), study population/sample/cohort and their characteristics/recruitment, study period, prevalence/rate of misuse and main findings (trend of the misuse and potential factors).

2.3 Results

2.3.1 Study characteristics

From the pre-search, there were no existing or ongoing reviews for the same research question with the same search strategy as this systematic review in CDSR. The literature search included 468 citations from the key medical databases. After the selection of titles, 115 citations remained for abstract screening. The published years of these 115 citations ranged from 2001 to 2016, so no filters were required to restrict the publication year in the selection.

The reference checking found four new studies, including one case study, one prisoner study, and one post-mortem study, which were against the inclusion criteria. The remaining one of the four studies was included. The very small number of newly identified studies also implied the search had a good quality. The internet search found one relevant study of systematic review by Canadian Agency for Drugs and Technologies in Health (CADTH) that were not published in a journal.

So overall two extra citations (one from the reference lists and one from the internet search) were added to full text scanning. The flow chart (Figure 1) shows the process of study selection and exclusion. And finally 15 citations (12 journal articles and 3 editorials) were identified. Among these, there were six observational studies of a large database analysis, four questionnaire-based surveys, two cohort studies and three related systematic reviews. There were three new studies published after the initial search but they are not relevant, so they were not shown in the overall search flow chart. The majority of the included studies were published after 2015 and the earliest study was published in 2012.

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│   Medline    │ │ Ovid Embase  │ │   CINAHL     │ │  PsycINFO    │ │     CRD      │
│ 268 Citations│ │ 295 Citations│ │ 89 Citations │ │ 68 Citations │ │  6 Citations │
└──────────────┘ └──────────────┘ └──────────────┘ └──────────────┘ └──────────────┘
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468 Non-duplicate citations

Exclusion criteria:
Animal study
Case report
Treatment

355 Articles excluded after title screening

96 Articles excluded after abstract screening

19 articles retrieved

2 article from reference lists and internet

Full text scanning

15 articles included

Figure 1. Flow chart of study selection

2.3.2 Main findings

The epidemiological studies of observational analysis of large databases were all from EU, and other studies were from the US, EU and UK. From the search, there were twenty-nine, nine and three studies of non-English languages from MEDLINE, Ovid Embase and CINAHL, respectively. But they were all excluded because of language limitation. This restriction might cause the bias on examining the pattern of global distribution of the epidemic. However, these non-English studies are mostly from the EU, so this would not influence the conclusion of that the misuse was reported mainly in the US, EU and UK.

Large database analysis

Five out of six observational studies with large databases investigated the misuse and abuse of pregabalin, the remaining one study described both gabapentin and pregabalin misuse. These studies regarded the study population as patients who were prescribed gabapentin or pregabalin, and calculated prevalence by identifying the cases and reports of misuse among those medicine users. The prevalence of misuse cases among prescribed pregabalin patients ranged from 1.0% to 9.6%, and the prevalence for gabapentin misuse cases was reported as 4.8% (Table 1).

Two studies found little association between the exposure to pregabalin and drug misuse, with a small misuse prevalence of 1.0% and 1.5% among pregabalin users. Asomaning et al (22) found there was not misuse of pregabalin and a history of substance abuse was not a risk factor for the overdose. The authors of this study were employees of Pfizer, the commercial company producing gabapentin and pregabalin. They tried to find out the reason why their findings were not consistent with other studies, and compared their study population with the study population in a Swedish study (30). The demographic characteristics of the two studies were similar, but the prescription and diagnosis patterns were quite different. They discussed that this

might be due to the data used in the study. With the limited information of indication and doses of the prescriptions, the data was actually not suitable for analysing the prevalence of pregabalin misuse. Bossard et al (28) searched for the misuse reports of pregabalin in French Pharmacovigilance Database (FPVD). Though the database was large with 184,310 reports, only eight of them reported misuse of pregabalin, and the first case was reported quite late, 2010. This implied the potential pitfalls of spontaneous reporting systems.

Another four studies found the misuse trend in the population and identified the factors related to the drug misuse among the users. In summary, male gender, younger age, lower income and substance abuse history could be potentially associated with drug abuse. Chiappini et al (27) examined both gabapentin and pregabalin, which was the only observational study to examine both drugs. In comparison, they found a higher reporting ratio of misuse coming from pregabalin users. Most misuse reports from both gabapentin and pregabalin involved opioid prescribing and female patients. However, Schjerning et al (31) found male gender was a risk factor for the misuse of pregabalin, as well as prescription of anti-psychotics. The Swedish study also found males had a higher risk of misuse of pregabalin, and also low income groups and people with a history of substance abuse disorders (30). Gahr et al (29) analysed the dataset of BfArM and found male sex and a history of polydrug use were risk factors for pregabalin misuse.

Table 1. Summary of gabapentinoid misuse in observational studies analysing large databases

Study	Study population	Data source	Definition	Prevalence	Main findings
Chiappini 2016 EU (27)	n=115,616 for pregabalin n=90,166 for gabapentin Adverse drug reaction reports relating to pregabalin/gabapentin 03/2006-15/07/2015 for pregabalin 03/2004-15/07/2015 for gabapentin	EudraVigilance (EV) database from European Medicines Agency (EMA)	Intentional product misuse, drug dependence and drug abuse etc. in Medical Dictionary for Adverse Drug Reactions (ADR)	6.6% for pregabalin (7,639/115,616) 4.8% for gabapentin (4,301/90,166)	Rising trend; Female more; More reports of pregabalin
Asomaning 2016 UK (22)	n=18,951 Prescribed pregabalin, first prescribed over 12 years old 09/2004-07/2009	The Health Improvement Network (THIN) primary care database in UK	READ codes (diagnosis codes) as proxy; Overdose of 600 mg/day	1.0% (136/13,480)	The proportion of overdose was small; History of substance abuse had no effect
Schjerning 2016 Denmark (31)	n=80,868 Exposed to at least one prescription of pregabalin 2004-2013	Danish Nationwide Prescription Registry	Anatomical Therapeutic Chemical (ATC) Codes and Defined Daily Dose (DDD); ICD-10; Overdose of 600 mg/day	9.6% for 6 months (4,090/42,520) 6.5% for 12 months (2,765/42,520)	Male gender, prescription of antipsychotics and benzodiazepines were risk factors

Table 1. (Continued)

Study population	Data source	Define	Prevalence	Main findings	
Bossard 2016 France (28)	n=521 Exposure to pregabalin 01/01/2010-31/12/2015	French Pharmacovigilance Database (FPVD)	Medical Dictionary for Adverse Drug Reactions (ADR)	1.5% (8/521)	No significant association between exposure to pregabalin and drug abuse or dependence
Boden 2014 Sweden (30)	n=48,550 Dispensed ≥3 prescriptions of pregabalin 06/2006-12/2009	Swedish National Health and Population Registry	Overdose of 600 mg/day	8.5% (4,130/48,550)	Male gender, 18-29 years age, low income, diagnosed with epilepsy, substance use disorder and abuse history were risk factors
Gahr 2013 Germany (29)	n=1,552 ADR reports relating to pregabalin 04/2008-08/2012	German Federal Institute for Drugs and Medical Devices (BfArM)	standardised Medical Dictionary for Regulartory Activities (MeDRA) query (SMQ)	3.5% (55/1,552)	Marked increasing reports; Male gender and a history of polydrug use were risk factors

Surveys

The surveys identified were questionnaire-based and self-report undertaken in the US and UK (Table 2). Three of the four survey studies recruited the patients diagnosed with substance abuse disorders from related clinics and centres, and then to see how many of them had drug misuse of gabapentinoids. The sample size was around 100-200 in the three studies and the gabapentinoids misuse rate of patients with substance abuse disorders was around 10% to 20% (32-34). All three studies found the opioid addicted population were more likely to get gabapentin and pregabalin abuse. The last study recruited the sample from a panel with unclear information about whether this panel was a general population sample or consisted of patients with any specific disease(s) (35).

Generally the surveys included in the study were poor quality studies. The questionnaire in the study conducted by Baird et al (32) had only nine questions, and the design was not comprehensive enough. The questions were designed too briefly, and lacked the information of demographic characteristics, health conditions and disease history. The study sample selected by Bastiaens et al (33) was from the community correctional centre's treatment programme, which could be seriously biased because the sample is likely to have higher risk of substance abuse than the general population. The study by Wilens et al (34) was of relatively higher quality according to the quality assessment, but this study was not specifically designed to investigate gabapentin or pregabalin misuse. This study examined misuse of several medications among opioid dependent patients and did not focus on gabapentin or pregabalin. These surveys cannot show the prevalence of gabapentin or pregabalin misuse, but can give a clue as to the possible association of the misuse of gabapentin/pregabalin and opioid prescriptions. Kapil et al (35) were in collaboration with a global market research company. A sample size of 1500 was chosen from panel members of the research company. But more details of the panel, how the sample was chosen, and the definition of misuse were not given. The age of the sample did not

follow a normal distribution. There were 38 of 1500 participants reported to have lifetime misuse of GABA-analogue. As well as the prevalence of gabapentin and pregabalin, this study also identified the source of misuse. The supply was obtained mainly from health services, family or acquaintances, and also some were from the internet and outside UK.

Table 2. Summary of gabapentinoid misuse survey studies

Study	Sample	Recruitment	Rate	Main findings
Baird 2013 Scotland (32)	n=129 11/2011-01/2012	From six substance misuse clinics in Lothian region of Scotland	ever used non-prescribed gabapentinoids: 22% (29/129)	Gabapentinoid abuse alongside with methadone
Bastiaens 2016 US (33)	n=250	Patients with substance use disorder from community correctional centre	non-medical use of gabapentin: 16% (41/250)	Gabapentin abuse appears specific to an opioid addicted population
Wilens 2015 US (34)	n=196 05/2013-08/2013	Admissions to a public detoxification programme in Massachusetts, Bay Cove Human Services	22% for gabapentin 7% for pregabalin (of 162 opioid dependent patients)	High levels of medication misuse of both controlled and non-controlled agents
Kapil 2013 UK (35)	n=1,500	UK panel members of a global market research company, aged 16 - 59.	Lifetime prevalence of misuse of gabapentin: 1.1% (17/1,500); pregabalin: 0.5% (8/1,500)	Appreciable misuse of baclofen, gabapentin and pregabalin in the UK. The majority of misuse was from illegal sources

Cohort studies

The summary of the two cohort studies is shown in Table 3. One of the two cohort studies was editorial (36) and provided limited details of the methodology and results. A big increase of proportion of using gabapentin specifically to "get high" was reported from a cohort of 503 adults in Appalachian Kentucky. However, this study was not originally designed for examining the misuse of gabapentin. Thus, the recruitment of the study population and the indicators analysed in the study were not comprehensive for identifying the prevalence and factors of gabapentin misuse.

Paulozzi et al (37) investigated the opioid analgesics medication for patients with a diagnosis of substance abuse. In the study, a cohort of 1.85 million adults was examined and the follow-up period was divided to "Pre-abuse period", "Abuse period" and "Post-abuse period". The participants in pre-abuse period were prescribed an opioid without diagnosis of substance abuse. In the abuse period, 9,009 (0.49% of the total population) were patients diagnosed with substance abuse. Then the outcomes were compared between participants diagnosed with substance abuse and not diagnosed in post-abuse period. Each period was half a year. In the study, patients with substance abuse were more likely to be prescribed gabapentin during the abuse period, but the number of prescriptions decreased in the post-abuse period among the patients with substance abuse.

Table 3. Summary of gabapentinoid misuse in cohort studies

Study	Cohort	Recruitment	Odds Ratio	Main findings
Paulozzi 2016 US (37)	n=1,850,129 opioid users without abuse diagnoses aged 18-64 01/2010-06/2011	People with employer-sponsored insurance from a commercial claims and encounters database	1.32 (95% CI: 1.24-1.40) for abuse period; 0.84 (95% CI: 0.80-0.89) for post-abuse period	Gabapentin prescribing to patients dropped after diagnosed with abuse, while opioid prescribing changed little
Smith 2014 US (36)	n=503 patients of opioid misuse 11/2008-09/2010	Participants in a study of social networks and infectious disease risk in Appalachian Kentucky		Potential factors: female gender and co-prescription of gabapentin and opioid

*CI, confidence interval

Systematic review studies

A review of misuse potential of pregabalin was conducted by Canadian Agency for Drugs and Technologies in Health (CADTH) (38). This study was not published in a journal but was found in the website of CADTH. There were 216 citations identified from the initial search and finally 7 of them were included in the study, including three case reports and two cross-over randomised controlled trials with a small sample of 15 and 16. The lack of high quality studies in the review by CADTH might be due to a limited search strategy, as the review did not show the terms and details of the search. The review was conducted in 2012, whereas most good quality studies identified in my systematic review were quite new studies published in 2015 and 2016.

Schjerning et al (39) conducted a review in 2014 using only one word, "pregabalin", as the term used for the search, so a large number of citations were found from the initial search. But finally only 13 epidemiology studies were included. Compared with my study, my study searched more databases, and used more accurate the terms for searching. Fewer citations were identified from initial search, but my final included studies covered the results from this review. More irrelevant searching results meant more extra work for the study selection. This review identified not only epidemiology studies, but also preclinical, clinical studies and case reports. To summarise from all types of studies, there was a significant abuse potential of pregabalin, especially for substance abuse patients. Also, Smith et al (25) found gabapentin is being misused internationally, especially among patients with opioid abuse.

Table 4. Summary of gabapentinoid misuse in systematic review studies

Study	Research question	Searched databases	Study selection	Main findings
Smith 2016 US(25)	Misuse, abuse and diversion of gabapentin	PubMed, Web of Science, CINAHL, PsycINFO, Cochrane	31, including 11 epidemiology studies	Gabapentin is being misused internationally, with higher risk among patients who abuse opioid
Schjerning 2016 Denmark(39)	The abuse potential of pregabalin	PubMed, Embase, European Medicine Agency (EMA), the US Food and Drug Administration (FDA)	13 epidemiology studies	The preclinical, clinical and epidemiology evidence suggested the abuse potential of pregabalin, especially in people with substance abuse disorder
CADTH 2012 Canada(38)	Clinical evidence for abuse and misuse potential of pregabalin	PubMed, Ovid Embase, Ovid PshycINFO, Cochrane, CRD	7, including 3 case reports and 2 randomised controlled trials	Pregabalin was reported to have low potential of abuse, but a history of drug addiction might play a role in the reward effect of pregabalin

2.3.3 Quality assessment

The assessment of the quality of the four types of studies are shown in Tables 5-8. Only seven studies were relatively high quality studies and other studies had obvious limitations. None of the reviews assessed the quality of included citations. The questionnaires for the survey studies were designed too simply so that the data obtained had very limited information. The description of recruitment and the analysis of the sample size of the surveys were not given in detail, and the population for the recruitment were biased, so the sample was not very representative of the general population. Overall, the descriptive studies of large database analyses were of higher quality.

Table 5. Quality assessment of observational studies of a large database analysis

	Assessment questions	Chiappini	Asomaning	Schjerning	Bossard	Boden	Gahr
1	Was the **research question** or **objective** in this paper clearly stated?	Y	Y	Y	Y	Y	Y
2	Was the **study population** clearly specified and defined?	Y	Y	Y	Y	Y	Y
3	Were inclusion and exclusion criteria for **recruitment** described in detail?	Y	Y	Y	Y	Y	Y
4	Were objective, standard criteria used for **measurement of condition**?	Y	Y	Y	Y	Y	Y
5	For exposures that can vary in amount or level, did the study examine **different levels of the exposure** as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	N	N	NA	N	NA
6	Were the **exposure measures** (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y
7	Were the **outcome measures** (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y
8	Was appropriate **statistical analysis** used?	Y	Y	Y	Y	Y	Y
9	Were **confounding factors** identified?	NA	NA	NA	NA	NA	NA
10	Were strategies to **deal with confounding factors** stated?	NA	NA	NA	NA	NA	NA
	Overall quality rating	H	L	H	H	H	M

*Y, Yes; N, No; H, high; M, moderate; L, low; C, cannot determine; NA, not applicable; NR, not reported

Table 6. Quality assessment of survey studies

	Assessment questions	Kapil	Wilens	Bastiaens	Baird
1	Questionnaire	M	M	L	L
2	Sampling	M	M	L	M
3	Data collection	NR	H	M	M
4	Data management	M	H	L	M
5	Data analysis	M	H	L	L
6	Reporting	M	H	L	L
	Overall quality rating	L	M	L	L

*H, high; M, moderate; L, low; C, cannot determine; NA, not applicable; NR, not reported
The details of the assessment are shown in Appendix 6

Table 7. Quality assessment of observational studies of cohort studies

	Assessment questions	Smith	Paulozzi
1	Was the **research question** or objective in this paper clearly stated?	Y	Y
2	Was the **study population** clearly specified and defined?	Y	Y
3	Were the subjects selected or **recruited** in an acceptable way and from the same population?	Y	Y
4	Was a **sample size** justification, power description, or variance and effect estimates provided?	N	Y
5	Was the **timeframe** sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	Y
6	Were the exposure measures (independent variables) **clearly defined**, valid, reliable, and implemented consistently across all study participants?	Y	Y
7	Were the **outcome measures** (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	N	Y
8	Was the **follow up** of subjects complete enough? If not, were the reasons to loss to follow-up described and explored?	Y	Y
9	Was appropriate **statistical analysis** used?	Y	Y
10	Were key potential **confounding** variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	N	Y
	Overall quality rating	L	H

*Y, Yes; N, No; H, high; M, moderate; L, low; C, cannot determine; NA, not applicable; NR, not reported

Table 8. Quality assessment of observational studies of systematic review studies

	Assessment questions	Smith	Schjerning	CADTH
1	Did the review address a clearly focused question?	Y	Y	Y
2	Did the authors look for the right type of papers?	Y	Y	Y
3	Do you think all the important, relevant studies were included?	Y	Y	N
4	Did the review's authors do enough to assess the quality of the included studies?	N	N	N
5	If the results of the review have been combined, was it reasonable to do so?	NA	NA	NA
6	Were the overall results of the review reported and summarised properly?	Y	Y	Y
7	Were the results precise with confidence intervals?	NA	NA	NA
8	Can the results be applied to the local population?	Y	Y	Y
9	Were all important outcomes considered?	Y	Y	N
10	Are the benefits worth the harms and costs?	Y	Y	Y
	Overall quality rating	H	H	L

*Y, Yes; N, No; H, high; M, moderate; L, low; C, cannot determine; NA, not applicable; NR, not reported

2.4 Discussion

Gabapentin and pregabalin both have similar structure as the neurotransmitter gamma-aminobutyric acid (GABA) and interact with calcium channels in the central nervous system, and are commonly used to treat neuropathic pain. Taking a large amount of gabapentin or pregabalin in a short time may lead to side effects, including feeling dizzy or sleepy, seeing double, slurring your words, diarrhoea confused or agitated, seizures and passing out (40). Generally the medication for neuropathic pain is used long-term and the patients need take gabapentinoids for several months to years. Some patients were reported to get addicted to pregabalin or gabapentin after the long-time intake and have withdrawal symptoms after stopping taking the medicine (24, 41).

But there are some slight differences between the two drugs (42). Gabapentin is used for treating migraine occasionally, while pregabalin is used for treating anxiety. Pregabalin is considered to have a higher risk of getting abused than gabapentin. Pregabalin was considered to potentially cause addiction and all the included observational studies of a large database analysis examined the misuse of pregabalin. Only one of these six studies also examined the misuse of gabapentin and found the misuse reports of gabapentin were less (27). However, the included survey studies suggested gabapentin, the medicine considered to cause little addiction or abuse before, might be used excessively for non-medical purposes as well. The majority of previous studies investigated the gabapentin or pregabalin separately, while actually gabapentin and pregabalin were misused and prescribed together for some people. It is more comprehensive to examine both gabapentin and pregabalin.

This study systematically searched and selected the current citations of misuse of both gabapentin and pregabalin in population. The overall evidence shows a potential misuse of gabapentinoids, with a growing number of both prescription of gabapentinoids and misuse reports internationally. From the six observational

studies of large database analyses, the misuse prevalence ranges from 1.0% to 9.6% among pregabalin users and the prevalence for gabapentin misuse was 4.8% (27). More than 16% patients with substance abuse disorder had ever been prescribed gabapentin (33) and 7% had been prescribed pregabalin reported from survey studies (34).

The identification of drug misuse in these studies largely depended on the system used for each database and how the data were collected. So the definitions of misuse were quite different. The Medical Dictionary for Adverse Drug Reactions (ADR) was used for the dataset from European Medicines Agency (EMA) (27) and French Pharmacovigilance Database (FPVD) (28), and the Medical Dictionary for Regulatory Activities was used for German Federal Institute for Drugs and Medical Devices (BfArM) (29). Other studies identified overdose of over 600 mg per day based on the guidebook for pregabalin, and combined with codes: READ codes, Anatomical Therapeutic Chemical (ATC) codes, and the 10th version of International Classification of Diseases (ICD-10) (22, 30, 31). The different definitions of "misuse" made it hard to combine the prevalence from these studies directly, and made the comparison of these studies more difficult. And thus, the narrative review was used in this systematic review to summary the findings and prevalence of the misuse. Some studies also examined the factors associated with overdose and misuse of gabapentin and pregabalin. A history of substance abuse disorder was identified as a potential factor and gender was also found to have an effect on the misuse. The cohort in Appalachian Kentucky showed more reports of gabapentin misuse among females (36). Chiappaini et al (27) found more adverse drug reaction (ADR) reports of misuse, abuse and dependence from females in EV database as well. In this study, overall ADR reports from females were more than three times of the reports from males. On the contrary, the Danish (31), Swedish (30) and German (29) studies concluded that male gender was associated with higher risks of overdose. In the study from Sweden, it suggested there was a 40% (95% CI: 31% – 49%) (CI, confidence interval) higher risk of getting overdose of pregabalin among males than females (30).

Many studies suggested that the patients with a history of substance abuse disorder, especially opioid use disorder, were more likely to misuse gabapentin or pregabalin (33, 43). In the Swedish study, it was 41% (95% CI: 31% – 52%) more likely to get overdose of pregabalin of patients ever diagnosed with substance misuse (30). A history of polydrug use was identified as a potential factor for the misuse of pregabalin in the German study (29). Most adverse drug reaction reports of misuse, abuse and dependence of gabapentin and pregabalin were combined with opioids from EV database (27). Prescription of antipsychotic drugs and benzodiazepines was associated with overdose of pregabalin from the Danish study (31). Prescribed methadone was identified to be associated with gabapentinoid abuse in the survey conducted in Scotland (32). The surveys conducted by Bastiaens et al (33) and Wilens et al (34) found more than 20% patients with an opioid use disorder had ever used gabapentin for non-medical purpose or in overdose. In the previous 30-days use of some opioids in a cohort increased 18.4% (95% CI: 4.3% - 33.1%) and 21.0% (95% CI: 7.1% - 35.7%) among gabapentin users, respectively (36). It was reported that there has been a significant increase in the number of opioid prescriptions in the past few decades as well (44). With more patients receiving high doses of opioids for long-term use, the morbidity of chronic pain remain high.

Other factors associated with gabapentinoid misuse, like age and income, were examined in some studies. However, due to very limited factors taken into consideration, no confounding factors were controlled in these studies, and the findings arising from these studies might be biased. So it is not clear about the effect of these factors on the misuse and abuse of gabapentin and pregabalin.

In summary, we could not confirm a clear conclusion based on the review. As mentioned in the results, many of the studies had obvious limitations and were not very high quality studies. In spite of the limitations of the design, data and analysis of the studies, the conflicts of interest of some studies would also weaken the power the study.

These studies had some connection with commercial pharmaceutical companies like Pfizer, Lundbeck, Orexo, Shire, etc. It is unknown if the results from these studies are reliable enough. For example, all the authors of the study examining the THIN primary care database were employed by Pfizer, and the study was funded by Pfizer (22). It is suspicious that this study produced findings that were inconsistent with other studies, in that they found very small percentage of patients having pregabalin overdose and a history of substance abuse was not a potential factor for the misuse. In addition, the first author of the Danish study and the systematic review of pregabalin abuse received speakers honoraria from Lundbeck, and the corresponding author received research grants from Pfizer and Lundbeck (31). Also, the first author of the survey study in Massachusetts received research support from several pharmaceutical companies in the previous three years (34). Two authors of the letter of a cohort study reported to have some financial relationships with commercial companies (36). The authors of the systematic review of gabapentin misuse were involved with some pharmaceutical companies including Pfizer (25). Besides, the Swedish data linkage study was developed from another project with Pfizer as one of the funding sponsors, but they declared that this study was independent from the project and Pfizer did not affect the study (30).

In all, seven of the fifteen citations reported no conflict of interest and the rest had more or less relationships with commercial pharmaceutical companies. Among the seven studies without any conflict of interest, only three of them were marked as high quality studies in the quality assessment.

This study has some strengths and is more comprehensive than the previous related reviews. Unlike the previous review that missed the quality assessment of included studies, this study assessed the quality of each study, and analysed the pitfalls. The tools used for the quality assessment were not simply taken from any existing tools, but modified from several commonly used tools according to the characteristics of each study type. The quality assessment of current evidence

revealed the lack of high quality studies investigating the misuse of gabapentin and pregabalin.

As well as the quality assessment, the search process was well-controlled in the study. The initial search result was quite focused on the research question, so that less work for the study selection and thus fewer errors would be made. This resulted from the exploration of search terms before the search. MeSH terms in combination with free text were used to make the search more efficient. The checking of reference lists suggested the good quality of the search, in that only one citation meeting the inclusion criteria was missed from my search and selection.

However, this study also has some limitations. After the quality assessment, the low quality studies were not excluded, and also the studies having some relationships with commercial pharmaceutical companies remained. This might decrease the power of the conclusion summarised from these studies. But this is due to the very limited amount of existing studies of the misuse of gabapentinoids. Gabapentin and pregabalin were introduced to the market less than 25 years ago, and people realised the possibility of getting dependence and abuse of the medicine just a few years ago. So it is natural that limited studies investigating the misuse of gabapentinoid and more studies with a high quality are needed to examine the misuse of gabapentinoids in the population. All the studies identified from the search and included after study selection were presented, but the conclusions were drawn from the high quality ones. According to the limited research, the overall evidence showed a rising trend of misuse of gabapentin and pregabalin internationally.

3 Bridging from systematic view to data analysis: factors associated with co-prescription of gabapentinoids and opioids

The systematic review of the misuse of gabapentin and pregabalin in the population found a rising trend of misuse with a growing number of prescriptions, especially among patients with a history of substance abuse disorder. It also suggested that people who were opioid users were at a higher risk of being misusers of gabapentinoids. The quality assessment showed there were few studies of good quality, and that more high quality studies were needed in the future research. There is therefore an evidence gap regarding the misuse of gabapentin and pregabalin, with a focus on co-prescribed opioids.

Some previous studies had investigated the safety and effects of using gabapentinoids and opioids together. An interview study with heroin users suggested that the combination of heroin and pregabalin could increase the effects of heroin but also the risk of abuse (45). In the respiration study from the same research group, pregabalin was found to have a respiratory depression effect when combined with morphine, and could further increase the risk of heroin fatalities. In a survey study, over one quarter of patients addicted to opioids reported the misuse of gabapentin (33). A post-mortem study showed that pregabalin had a potential to be abused and lead to death, especially in combination with opioids (46). Grosshans et al found 12.1% of opioid addicted patients had urine specimen positive for pregabalin (47). However, a separate study found that the combination of pregabalin and oxycodone did not increase the euphoric effect of the opioid (48).

In all, the evidence on the combination gabapentinoids and opioids was limited, and the current research came from small study samples and case studies. No study analysed a large population dataset to examine co-prescription of opioids and gabapentinoids.

The study reported here will address this evidence gap by conducting a data linkage analysis of the population of opioid users in Tayside and Fife, to examine the factors associated with co-prescribed opioids and gabapentinoids. In this study, the demography profiles were linked with prescription data and other clinical data. The association between health outcomes/service use and co-prescribed opioids and gabapentinoids will be examined after controlling for the potential confounding effects of socioeconomic factors.

4 Methods

4.1 Data management

4.1.1 Data source

The datasets for this study were obtained from Health Information Centre (HIC) services, including the datasets of demography profile, prescription, cancer registration, deaths, Accident and Emergency (A&E) attendance, hospital admission and psychiatric admission. Death data was collected in both years of 2012 and 2013, and cancer registration data were collected to the end of 2013. All other data were collected in 2012. Opioid and gabapentinoid prescriptions could be issued at any time during 2012. So in this study, a cross-sectional study was conducted for health service use (A&E attendance, repeated hospital admission, psychiatric admissions) and a cohort study for mortality.

The datasets were linked by matching the Pro-CHI number. The Community Health Index (CHI) is a unique number for each patient used in Scotland for health care purposes. Pro-CHI is an anonymised CHI number created by the HIC Data Analyst before releasing the data with Pro-CHI numbers. This study is part of 2183 Opioid Project and was funded by Chief Scientist Office (CSO) (Reference number: CZH-4-429). It received formal approval from NHS Tayside Research and Development.

The original demography data were collected by HIC and included 68,120 cases of individual profiles of all patients who were prescribed an opioid by a General Practitioner (GP) in Tayside and Fife in 2012. The data included Pro-CHI number, age, sex, the Scottish Index of Multiple Deprivation (SIMD) of health board, GP registration date, and some other health related variables. The SIMD is an area-based measurement of deprivation reflecting the socioeconomic level in Scotland (49). In our study, it was presented in quintiles of five categories, from the most deprived (SIMD=1) to the least deprived (SIMD=5) (50). Data were stored on a

secure server, accessible only by the HIC Data Analyst and the System Administrator.

A total of 580,815 GP prescriptions of opioids and gabapentinoids from Tayside and Fife were obtained in 2012. The medicines were identified by the guidance of prescribing, the British National Formulary (BNF) code of 4.7.1 (Non-opioid and compound preparation), 4.7.2 (Opioid analgesics), 4.7.4.1 (Treatment of acute migraine), 4.8.1 (Anti-epilepsy & Neuropathic pain) and 4.10.3 (Opioid dependence).

Dataset reporting deaths, psychiatric admissions, cancer registrations, A&E attendances and hospital admission were mainly presented with the Pro-CHI and date of the event. The mortality data were shown by a list of Pro-CHI numbers for those who died in 2012 and 2013, with the cause of death coded using ICD-10. For psychiatric admission, the variable showed the Pro-CHIs of patients who were admitted to a psychiatric centre in 2012.   The data from cancer registration showed the diagnosis of cancer from 1980 until the end of 2013. The variables in the A&E attendance dataset showed the date patients attended A&E and the reasons for attending. The date patients were admitted to a hospital is recorded in the hospital admission data. Both the A&E attendance and hospital admission data were collected until the end of 2012. An overview of the datasets is shown in Figure 2.
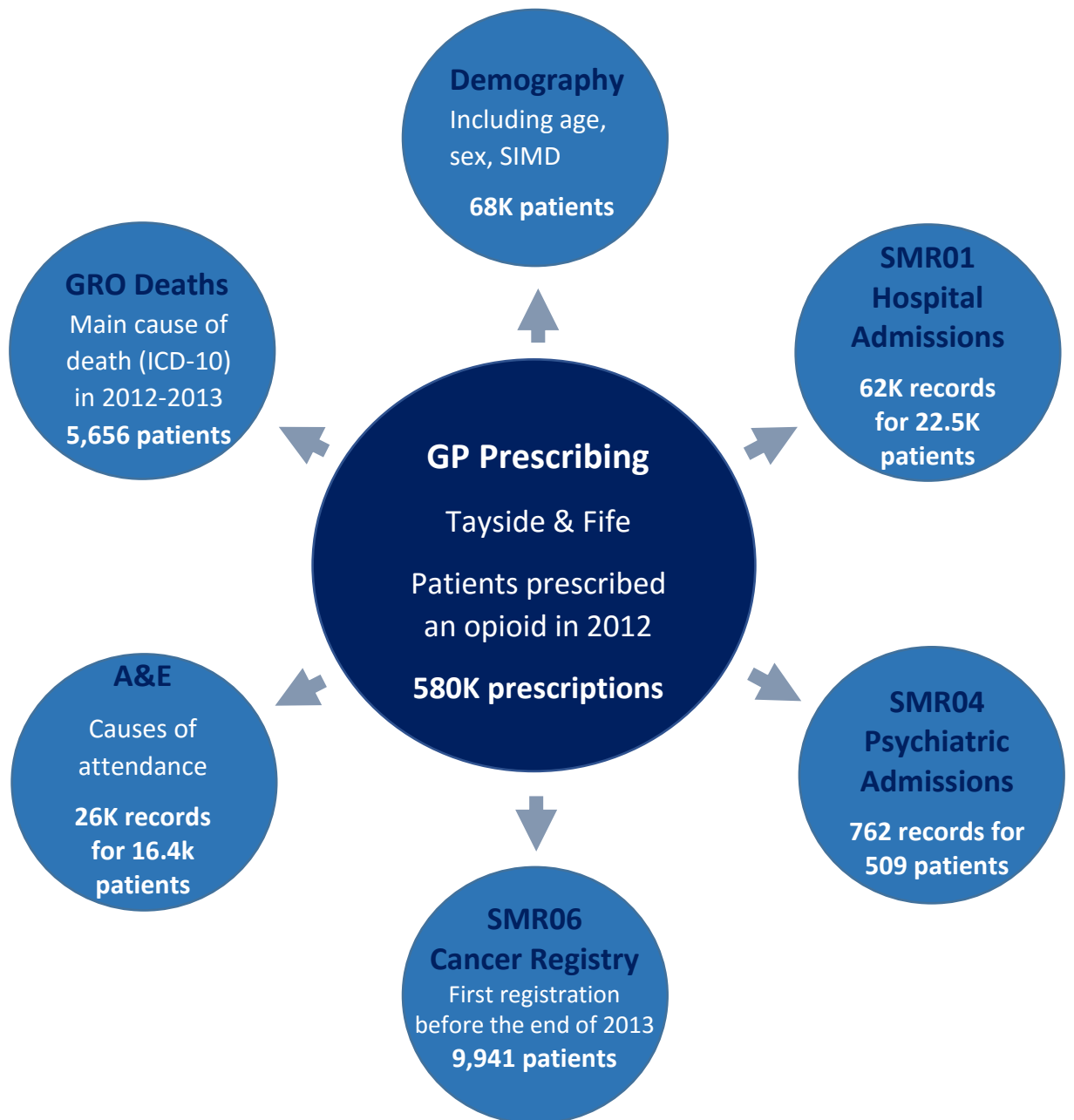
Figure 2. Overview of opioids prescribing data linkage for NHS Tayside & Fife (2012) for the study

4.1.2 Data cleaning and grouping

Within the demography data, age is a continuous variable and calculated until the end of 2012. A histogram of age with a normal curve was constructed to show the distribution of age. It was then categorised into age groups, the intervals of which were based on the histogram.

The prescriptions were recoded according to the effect intergradient, and drugs with the same ingredients were combined. For example, co-codamol (paracetamol and codeine), co-codaprin (aspirin and codeine) and co-codamol with bulizine (paracetamol, buclizine and codeine) were combined with codeine phosphate and all coded as codeine. The opioids were categorised into two groups based on the potency of the drug. Codeine, dihydrocodeine and meptazinol were categorised as WEAK opioid, and others were categorised as STRONG. The categorisation of Tramadol into the WEAK or STRONG potency groups and how it should be viewed in a clinical setting was discussed before undertaking any data analysis. Though other researchers have placed it in either category (30, 51), we thought it should go in the STRONG opioid group, as in the BNF it is recommended for moderate to severe pain, not mild pain like codeine, and it is now a controlled drug as all of the other strong opioids are.

The data relating to A&E attendance were extracted to present in two variables. One is, has the patient ever attended A&E for any reason in 2012, and the other is, has the patient ever attended A&E for specific causes potentially related to gabapentin and pregabalin (alcohol and/or substance misuse, collapse/fall/unresponsive, overdose and psychiatry). For the hospital admission data, the variable of repeated admission to hospital was created based on the frequency of being admitted; two admissions or more were recoded as repeated hospital admissions.

Considering that there could be a data extraction error from the original data obtained from HIC, the data was cleaned according to the requirements of

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recruitment of the study population. The demography data were cleaned by excluding duplicate cases first. As the population for this study were adults living in Tayside and Fife in 2012, patients not from Tayside or Fife, those who had died before 2012, were younger than 18 in 2012, and those who had registered out of the GP health boards in Tayside and Fife before 2012 would be excluded. For prescription data, all Pro-CHIs should have at least one opioid prescription; therefore the cases prescribed gabapentin or pregabalin ONLY would be excluded. For other datasets, the cases that did not meet the recruitment requirements would be automatically removed when merged with demography data by matching the Pro-CHIs.

4.1.3 Data linkage

In order to be linked with other datasets and convenient for data analysis, all the datasets were organised to present by each variable per column and one row per subject. While the GP description data were not presented in the expected way. It was originated in the form of cases of each prescription, with Pro-CHI, the drug name, prescribed date, and dose. So actually several rows may have referred to one subject. The data were organised to the form with single Pro-CHI as the cases and the drugs as variables with the count of prescriptions for each patient. The package of Reshape2 in R software was used to complete this conversion. The codes used in R software are shown below:

> library (reshape2)

> data1 <- melt (PrescriptionData, id.vars="Pro-CHI")

> data2 <- dcast (data1, Pro-CHI~PrescriptionData$DrugCode, length)

Then all the datasets were linked and merged together by matching the Pro-CHIs. Patients with incomplete information of demography or prescription were excluded.

4.2 Data analysis

4.2.1 Descriptive analysis

As the data was obtained for the 2183 Opioid Project, some variables in the whole data were irrelevant for this study, for example, the date when the person was diagnosed with diabetes. There were in total 22 variables in the original demography data, with only the age, sex and health board SIMD relevant for this study. The consistency of each gender and SIMD was analysed. While undertaking the steps of data linkage by merging all the datasets, some cases were lost. However, the frequency and corresponding percentage were calculated before and after merging the data with the difference of the percentages of a category analysed and reported.

The frequency of prescription was initially counted from prescription items. However, during the analysis of the prescribing data, a data collection problem was found, so I changed the way to count the frequency of prescriptions. The collection problem was, for one prescription, there might be more than one prescription item with different doses. For example, a prescription of 250 units of a drug was shown in two prescription items of 200 units and 50 units in one day. Thus, the dates of prescription were counted as the frequency; in one day, more than one prescription item of the same medicine were counted as one valid prescription, to avoid double counting of dates resulting from different doses of the medicine. The frequency of each drug prescribed by all the patients and the average frequency ($\bar{f}$) of each drug prescribed per patient was calculated:

$$\bar{f} = \frac{f}{n} \qquad (1)$$

In the equation, f is the total frequency of prescriptions for all patients of one drug; n is the number of patients who were prescribed this drug. Also, the

frequencies of different potency of drugs were calculated to see which were prescribed more, weak or strong opioids.

4.2.2 Chi-square test

The patients recruited in this study were prescribed at least one opioid in Tayside and Fife in 2012, and some were also prescribed gabapentin or pregabalin. The health outcomes/service use of patients prescribed opioid only and both opioids and gabapentinoids were compared. The health outcomes/service use included death, cancer, psychiatric admission, A&E attendance and hospital admission. The binary variable of death had two categories of being alive or dead from the beginning of 2012 till the end of 2013. The groups for hospital admissions were repeated admission to hospital (hospital admission frequency was twice or more times), or not repeated admission (hospital admission frequency was zero times or once). The variable of psychiatric admissions was categorised into yes and no. The A&E attendances were recoded into two variables: one was attended for any cause or not, the other one was attended for alcohol and/or substance misuse, collapse/fall/unresponsive, overdose and psychiatry or not. For example, if a patient only attended A&E because of an allergy, then the variables of this patient were yes for "attended for any cause" and no for "attended for drug related cause". All these health outcomes/service use were in 2012, except for the cancer and deaths. For cancer, it was a diagnosis of cancer before the end of 2013 or not.

Chi-square testing is a statistical method used to compare the proportions of categorical variables. In this study, it was used to investigate the differences between the patients prescribed opioid only, and who were prescribed both opioids and gabapentinoids. The null hypothesis (H_0) was defined that there is no association of health outcomes/service use with being prescribed both opioids and gabapentinoids. On the contrary, the alternative hypothesis (H_1) was that health outcomes/service use were related with co-prescribing of opioids and gabapentinoids.

The Chi-square test was used to see if the difference was statistically significant and if the null hypothesis could be rejected or not. The significance level was set as 5%, which means it is 5% likely that the null hypothesis is rejected but actually it is true. The Chi-square test in this study would show the relationships between the health outcomes/service use and the co-prescribing opioids and gabapentinoids. If the difference between patients prescribed both opioids and gabapentinoids and patients prescribed opioids only is significant, then the health outcomes/service use might be the factor for the co-prescription. But this association could be affected by confounding factors, so further regression analyses were required.

4.2.3 Logistic regression

Logistic regression is used to investigate the association between a dependent binary variable and one or more independent variables. In this study, the variables of health outcomes/service use are binary. Thus, logistic regression models were fitted to examine the association between the binary health outcomes/service use and demographic and prescriptive factors. The dependent variable was each health outcomes/service use, and the independent variables were all categorical. Demographic factors such as age group, sex and deprivation were fitted in the models. Cancer condition was fitted in the models as an independent binary variable. A reference category was chosen from each categorical variable. For SIMD and gender, the category with largest size would be considered as the normative group, and set as the reference category, to make other categories to compare with this group. For other variables, as the older age, diagnosed with cancer and co-prescribing opioids and gabapentinoids are factors for the health outcomes/health services that we want to examine, the youngest age group, no cancer and prescribed opioid only were defined as reference group. The fitted logistic regression model is shown below:

$$Hx \sim Age\ group + Sex + SIMD + Cancer + Gabapentinoid \quad (2)$$

where, Hx is each health outcomes/service use.

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The logistic regression models could be used for prediction, and this requires the model to be best fit. Some factors would be examined to see if the model fits better with or without this variable. However, because of the restriction of the data, the independent variables were very limited and the models were lacking in other potential confounding factors for which to be controlled. In addition, the logistic regression used in this study was not for prediction, but to examine the relationships between the variables. So we decided to keep all five available factors in. Even if some of the factors were insignificant, this would not influence the overall findings from the regression. The 95% confidence interval (CI) was calculated, which means it is 95% likely that the true value is within this interval.

All the analyses in the study were conducted in SPSS 22.0 and R.

4.3 Ethics and permission

This study was considered by the East of Scotland Research Ethics Service, who determined that ethical approval was not required as all data for this study were anonymised prior to being released to the researchers. The Data User Agreement for the Safe Haven was signed by the author and supervisors.

The server "Safe Haven" is used to protect data confidentiality. In the Safe Haven IT environment, the users can get secure access to statistics software to undertake the analysis. Data and any results from the analysis cannot be exported out of the server without approval by HIC administrators.
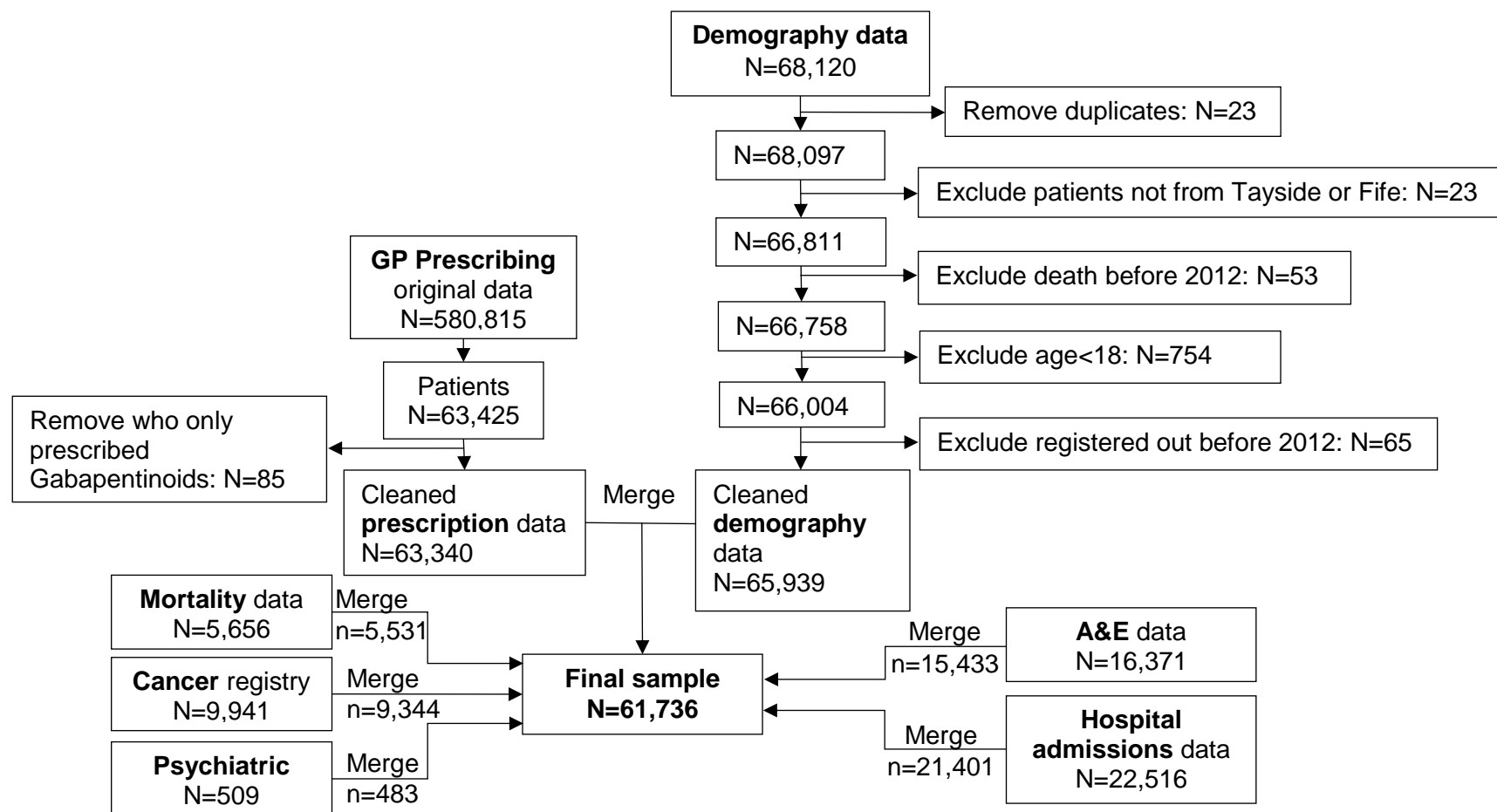
5 Results

5.1 Data cleaning

In the demography dataset, nineteen pairs of duplicate cases were identified in SPSS. Given that the duplicates were small in number, each duplication was checked manually. The duplicate pairs with paradoxical information were both excluded, for example the same Pro-CHI but different genders or SIMD. One pair of duplicate cases had the same information apart from one year difference of age. Considering the age would be classified into age groups in the further analysis, and this minor difference would not change the age category, only one of the cases were excluded. For other duplicate cases with the same main variables (Pro-CHI, age, gender, SIMD), the ones with the later date of GP registration and more complete information were retained. So, twenty-three cases were excluded because of duplication. There were 65,939 cases in the demography dataset after the cleaning.

The study population of prescription dataset was patients in Tayside and Fife ever prescribed at least one opioid in 2012. Thus, those who were prescribed gabapentin or pregabalin ONLY and no opioid, were excluded. After the reshaping in R, eighty-five Pro-CHIs were removed in the GP prescription data, and the cleaned data had 63,340 subjects.

The variables of health outcomes/service use were computed to be binary. There were five outcome variables after the data management: death in 2012-2013, psychiatric admission in 2012, repeated hospital admission in 2012, A&E attendance for drug related causes in 2012, A&E attendance for any cause in 2012.

5.2 Data linkage

The demography data (N=65,939) and prescription data (N=63,340) were merged in SPSS and the cases were matched by Pro-CHI. There were 61,736 cases left after merging. The health outcomes/service use data were linked into this merged dataset as dependent variables. The following flow chart shows the process of data cleaning and linking (Figure 3). The numbers on the arrows show how many subjects were merged into the final sample. The patients with Pro-CHIs in only one of the cleaned demography and GP prescription data were automatically excluded when using the function of "merge files" in SPSS.

Demography data
N=68,120

Remove duplicates: N=23

N=68,097

Exclude patients not from Tayside or Fife: N=23

N=66,811

Exclude death before 2012: N=53

N=66,758

Exclude age<18: N=754

N=66,004

Exclude registered out before 2012: N=65

GP Prescribing
original data
N=580,815

Patients
N=63,425

Remove who only prescribed Gabapentinoids: N=85

Cleaned **prescription** data
N=63,340

Merge

Cleaned **demography** data
N=65,939

Mortality data
N=5,656

Merge
n=5,531

Cancer registry
N=9,941

Merge
n=9,344

Psychiatric
N=509

Merge
n=483

Final sample
N=61,736

Merge
n=15,433

A&E data
N=16,371

Merge
n=21,401

Hospital admissions data
N=22,516

Figure 3. Flow chart of data cleaning and data linkage of demography and clinical data in Tayside and Fife (2012)

5.3 Descriptive analysis

The variable of age in the demography dataset was continuous, and the distribution of the age is shown in the histogram (Figure 4). The curve of the age distribution was bell-shaped. Given that patients younger than 18 years in 2012 were excluded in the data cleaning, the distribution was slightly skewed. Overall, age almost followed a normal distribution. The mean age was 58.28±0.07 years, which was close to the median age of 59 years. The oldest age was 106 years and the interquartile range (IQR) was 45 years to 75 years. The width of the interval of age groups was decided to be around 20 years, and the age was categorised into four groups (18-39, 40-59, 60-79, and 80-106 years).
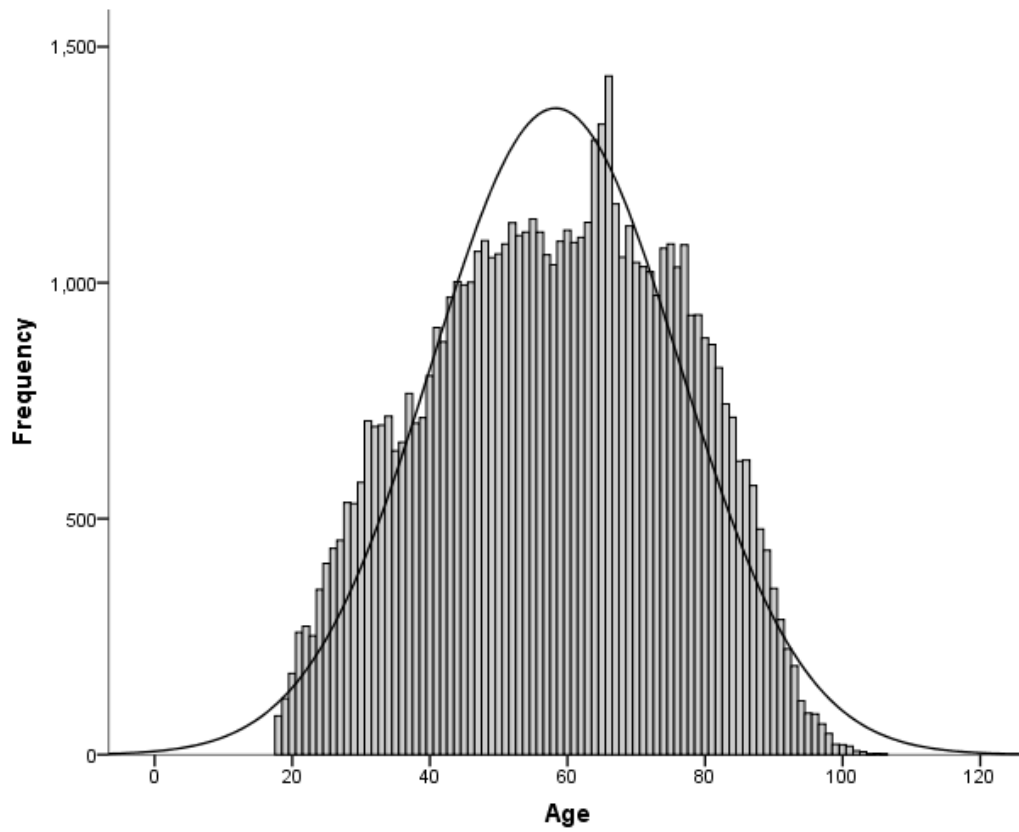
Figure 4. Histogram of age distribution of patients in Tayside and Fife prescribed at least one opioid in 2012

Table 9. Characteristics of demography of patients prescribed opioid in Tayside and Fife in 2012

| Characteristic	Before merging (n=65,939)		After merging (n=61,736)		Percentage changed (%)
	Frequency	Percentage (%)	Frequency	Percentage (%)	
Gender					
Female	39,581	60.0	37,043	60.0	<0.1
Male	26,358	40.0	24,693	40.0	<0.1
Age					
18-39 years	11,592	17.6	10,749	17.4	-0.2
40-59 years	21,723	32.9	20,662	33.5	0.5
60-79 years	23,816	36.1	22,041	35.7	-0.4
over 80 years	8,808	13.4	8,284	13.4	0.1
Health board SIMD					
1 - most deprived	16,734	26.1	15,927	26.5	0.4
2	14,367	22.4	13,609	22.7	0.3
3	12,346	19.3	11,598	19.3	0.1
4	11,053	17.2	10,161	16.9	-0.3
5 - least deprived	9,607	15.0	8,724	14.5	-0.5

After merging, there were over 8,000 patients categorised in the eldest age group (over 80 years), comprising 13.4% of the whole study sample, which was the smallest age group. The largest group was the second eldest group (60-79 years), which represented 35.7% with over 22,000 cases. The youngest group (18-39 years) had approximately half the number of the patients in age group of 60-79 years. And the group of 40-59 years had 2.2% less than the percentage of the largest age group among overall study sample. Females represented 60.0% of the whole study sample. There were 26.5% patients resident in areas categorised as most deprived (SIMD=1). In this study, fewer people lived in less deprived areas (Table 9).

The merging of the cleaned demography dataset and the GP prescription dataset made the size of the combined dataset decrease from 65,939 to 61,736. There were 4,203 profiles lost after the merging. The differences of the percentages of each category before and after the merging were calculated to see if the loss of cases changed the distribution of the demographic characteristics. It shows that the percentages of each group of age, sex and SIMD had only very tiny changes after merging. There was no evidence to suggest that the lost 4,203 subjects came from a specific population; instead, these were random patients. The influence of the merging on changing the distribution of demography of the population was little.
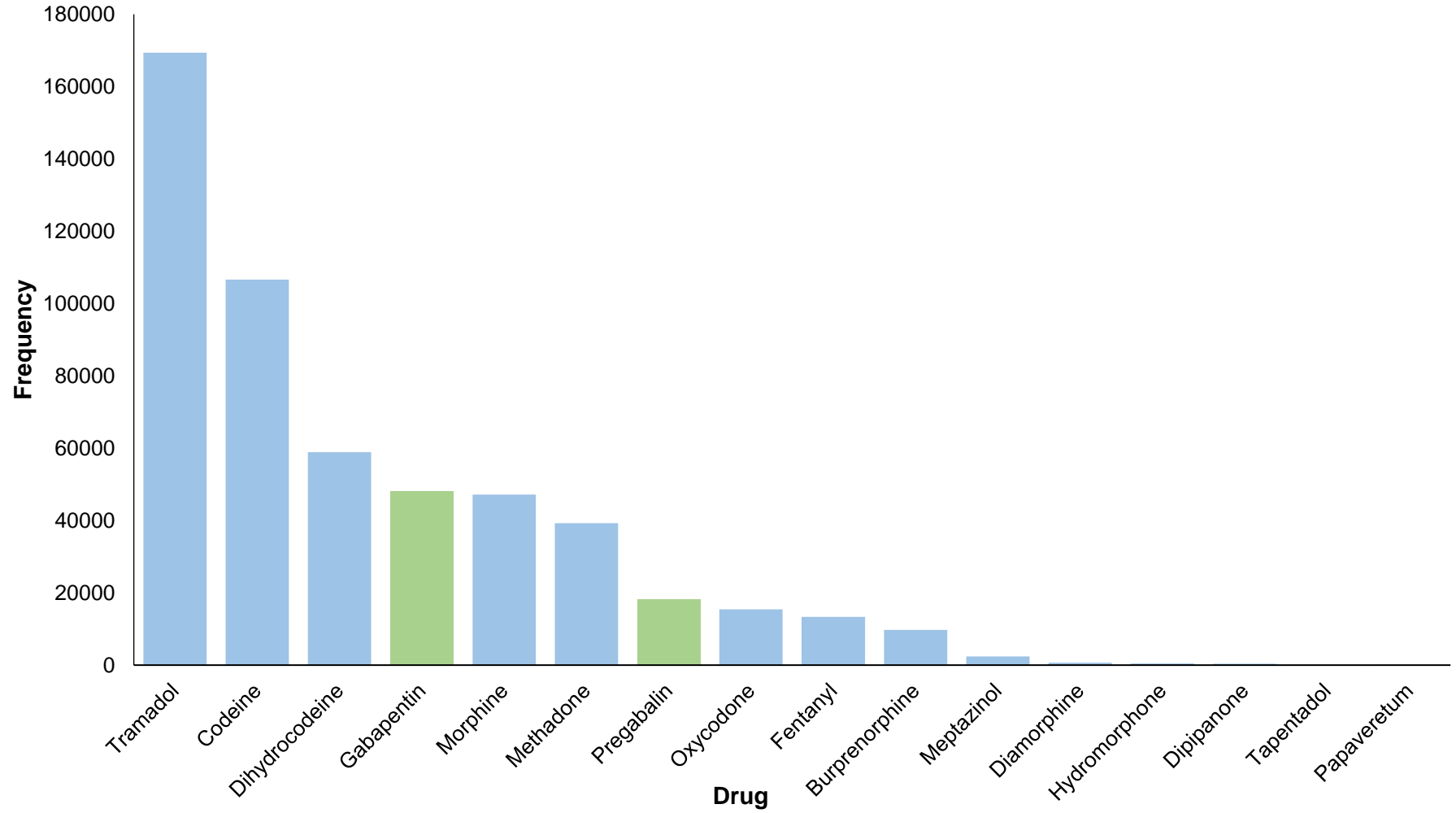
Figure 5. Bar Chart of total frequency of each opioids and gabapentinoids prescribed to all patients in Tayside and Fife (2012)

Among all the opioids, tramadol was prescribed the most to all patients, with over 169,000 prescriptions in 2012 (Figure 5). Two weak opioids, codeine and dihydrocodeine, were the second and third most prescribed. The total number of prescriptions of dihydrocodeine was about one third of the number of prescriptions of tramadol. There were around 168,000 prescriptions of weak opioids (codeine, dihydrocodeine and meptazinol), and almost 296,000 prescriptions of all strong opioids. The majority of opioid prescriptions were of strong opioids. Gabapentin was prescribed more than twice as much as pregabalin was. Both gabapentinoids were prescribed more than 66,000 times among all patients in Tayside and Fife who also received an opioid prescription during 2012.
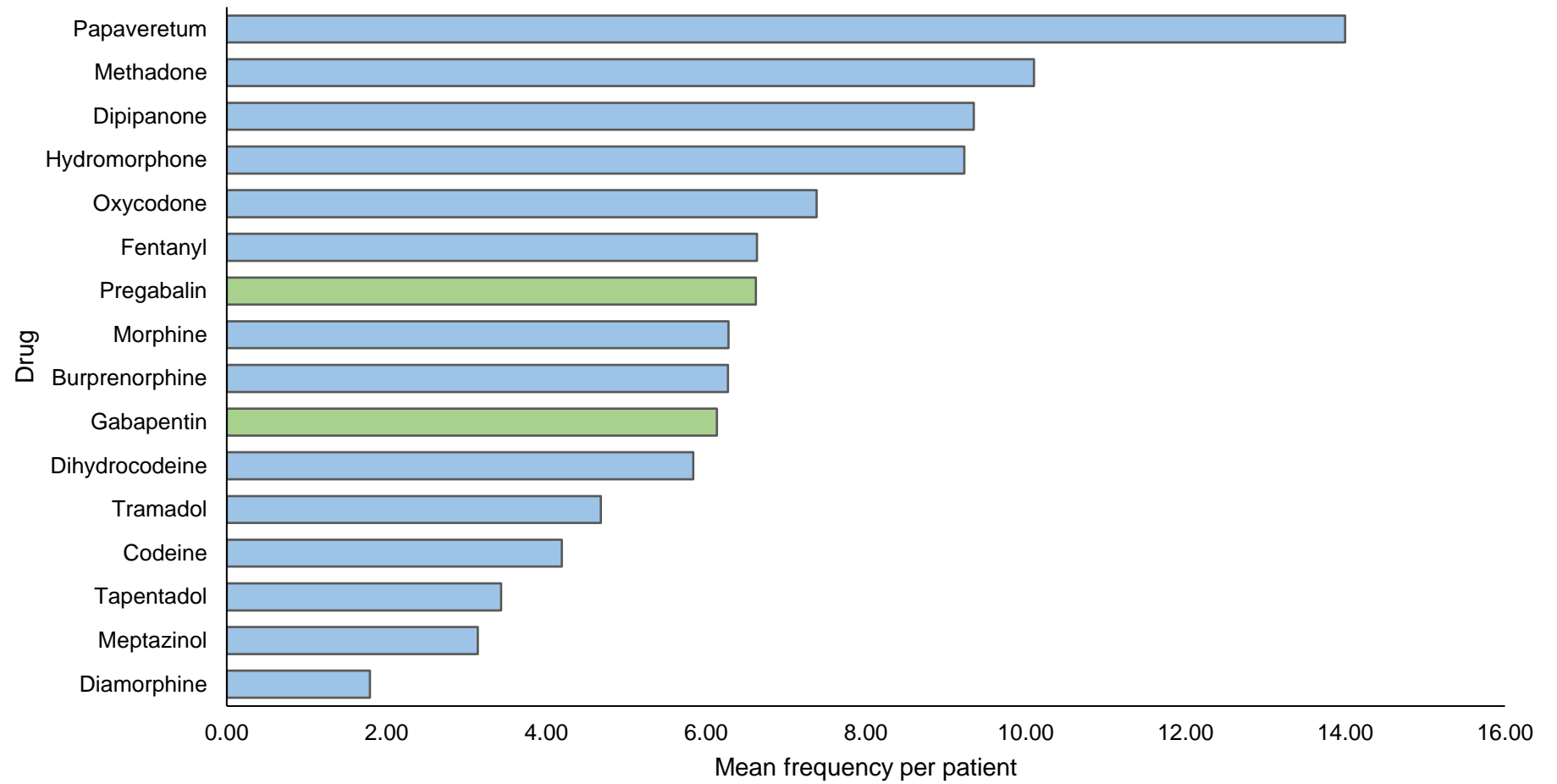
Figure 6. Average frequency of prescriptions per patient of each opioids and gabapentinoids in Tayside and Fife (2012)

Papaveretum was prescribed the least in total among all the patients (Figure 5), while the average frequency of papaveretum among the patients who were prescribed this drug was the most (Figure 6). Very few patients from Tayside and Fife were ever prescribed papaveretum in 2012, but each of them had 14 prescriptions on average. Tramadol and the weak opioids were prescribed on average less often than other opioids. The mean prescription of tramadol was 4.68 per patient who was ever prescribed tramadol in 2012. Almost 48,000 patients were prescribed at least one strong opioid, which composed 77.71% of the whole study sample. Among these 48,000 patients, they had 6.17 prescriptions of strong opioids on average. There were 9,841 patients prescribed both opioids and gabapentinoids. These patients had 6.72 prescriptions of gabapentin or pregabalin on average in 2012.

Table 10. Comparison of health outcomes/service use in patients prescribed opioids only and both opioids and gabapentinoids in Tayside and Fife

	Opioid only (n=51,895)		Opioid + GABA (n=9,841)		Total (n=61,736)	P-value*
Deaths$^\Delta$						
Live	47,119	90.80%	9086	92.33%	56,205	<0.001
Dead	4,776	9.20%	755	7.67%	5,531	
Psychiatric Admissions						
No	51,506	99.25%	9747	99.04%	61,253	0.037
Yes	389	0.75%	94	0.96%	483	
A&E						
Attended for drug related causes†	2,133	4.11%	432	4.39%	2,565	0.204
Not attended for drug related causes†	49,762	95.89%	9409	95.61%	59,171	
Attended for any cause	12,776	24.62%	2657	27.00%	15,433	<0.001
Not attended for any cause	39,119	75.38%	7184	73.00%	46,303	
Hospital Admissions						
Repeated (admitted twice or more)	9,439	18.19%	2280	23.17%	11,719	<0.001
Not repeated (admitted once or never)	42,456	81.81%	7561	76.83%	50,017	
Cancer$^\Delta$						
No	43,987	84.76%	8405	85.41%	52,392	0.104
Yes	7,908	15.24%	1436	14.59%	9,344	

*Significance of Chi-square test

†Drug related causes include alcohol and/or substance misuse, collapse/fall/unresponsive, overdose and psychiatry

$^\Delta$Deaths were in the year of 2012 and 2013; cancer was first registered before the end of 2013; other health outcomes/service use were during 2012
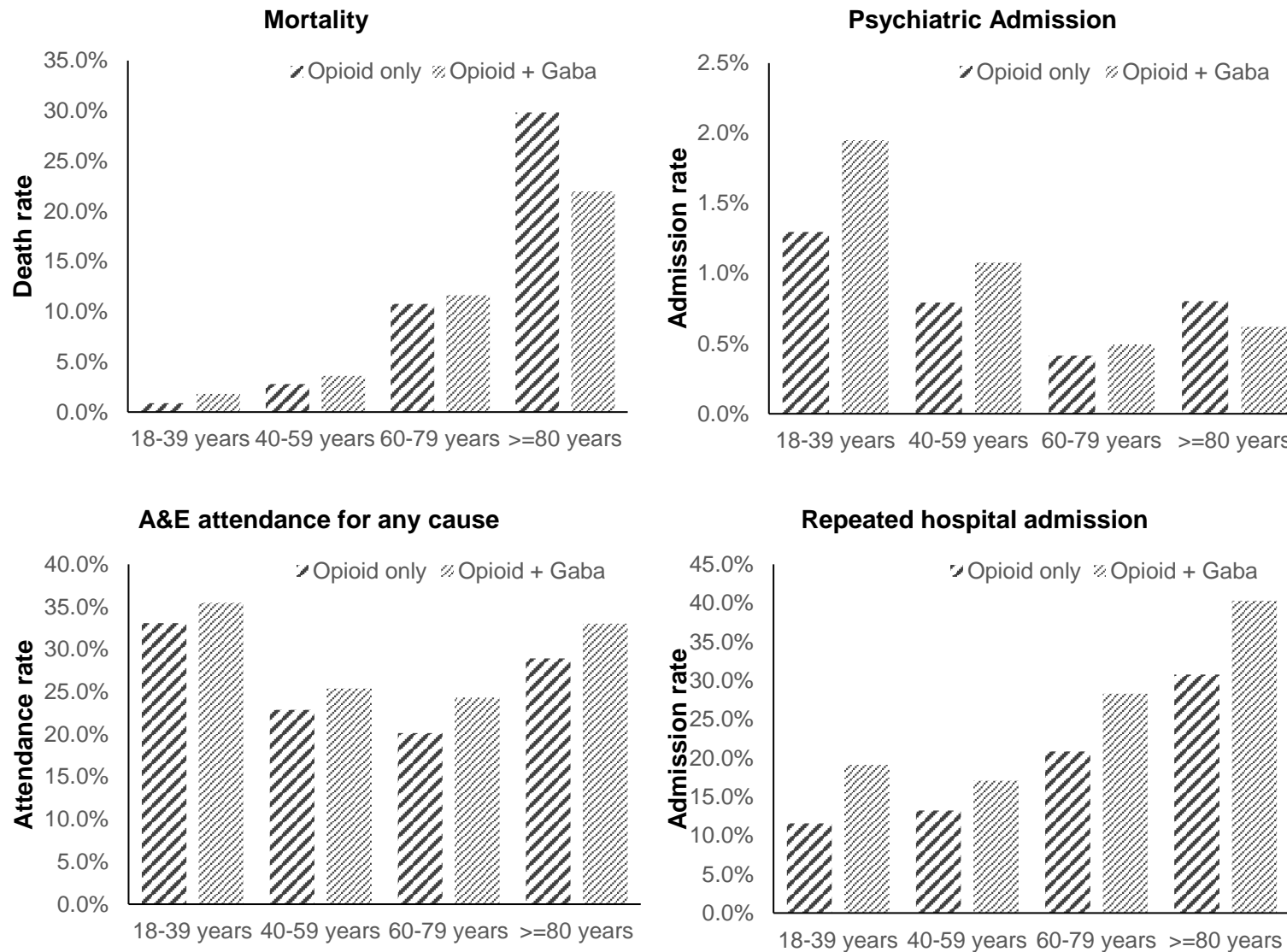
5.4 Chi-square test

The patients who were prescribed an opioid only and those who were prescribed both opioids and gabapentinoids were compared by their health outcomes/service use (Table 10). An unexpected result was that patients who were co-prescribed opioids and gabapentinoids had a lower mortality, and the difference was significant on Chi-square testing. However, the difference was not big and this result might be biased by other confounding factors. Further analysis by logistic regression was undertaken to test for possible confounders.

The rate of patients being admitted to hospitals repeatedly (twice or more) in patients co-prescribed opioids and gabapentinoids (23.17%) was significantly higher than the rate of repeated hospital admissions in patients prescribed opioids only (18.19%). A similar significant difference was in the rates of A&E attendance for any cause in patients prescribed gabapentinoid (27.00%) or not (24.62%). But the difference in the rate of A&E attendance for drug related causes (alcohol and/or substance misuse, collapse/fall/unresponsive, overdose and psychiatry) was not significant on Chi-square testing. Psychiatric admission occurred in less than 1.00% of all the patients though the difference was significant (p=0.037).

A diagnosis of cancer might be a confounding factor for prescribing opioids and gabapentinoids, as patients with cancer frequently need the prescriptions to relief the pain. From the Chi-square test, the likelihood of a diagnosis of cancer was not significantly different between patients who were co-prescribed gabapentinoids and those who were not.
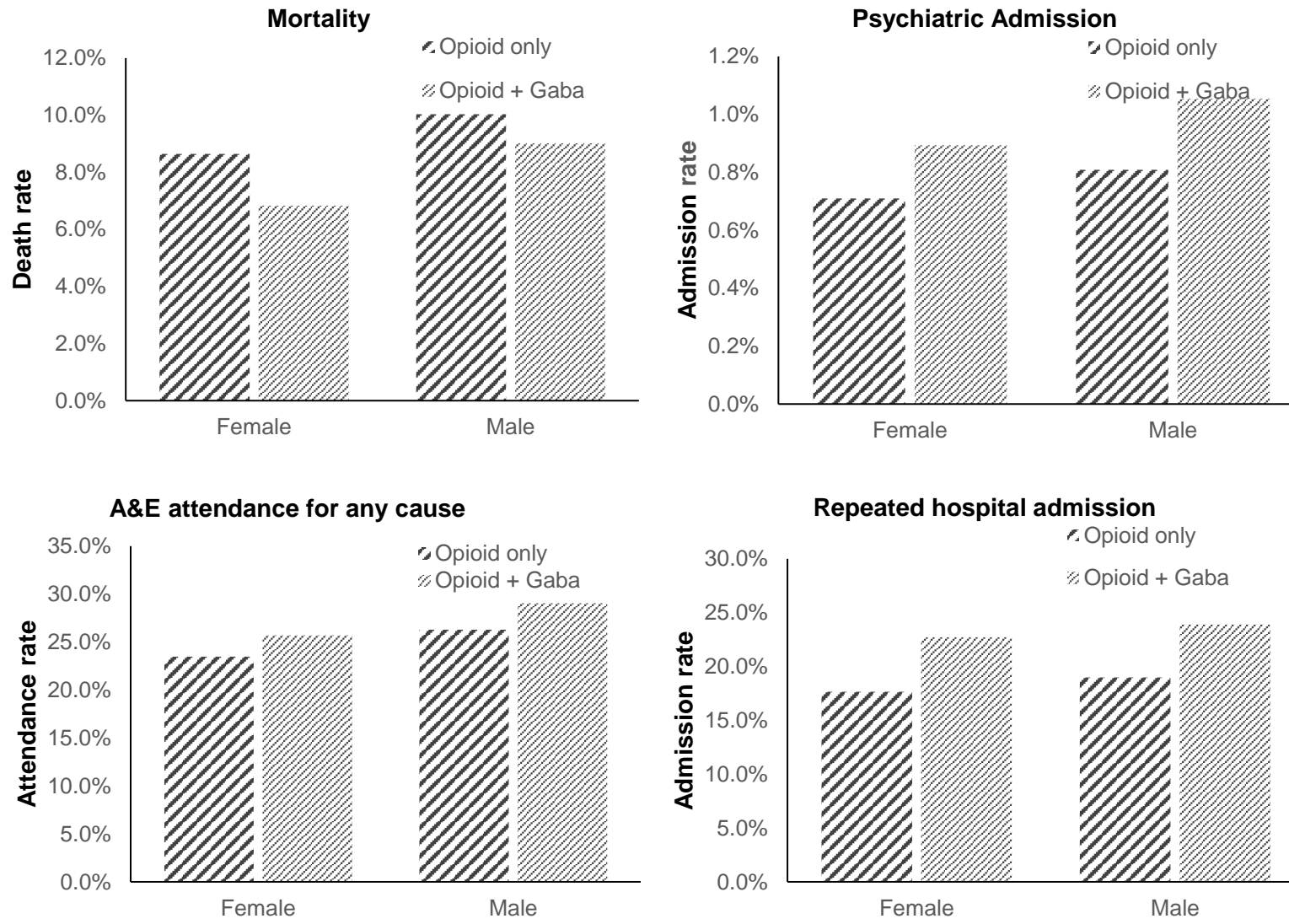
Figure 7. Health outcomes/service use rates in patients prescribed opioid only and both opioids and gabapentinoids stratified by sex in Tayside and Fife

Figure 8. Health outcomes/service use rates in patients prescribed opioid only and both opioids and gabapentinoids stratified by age in Tayside and Fife
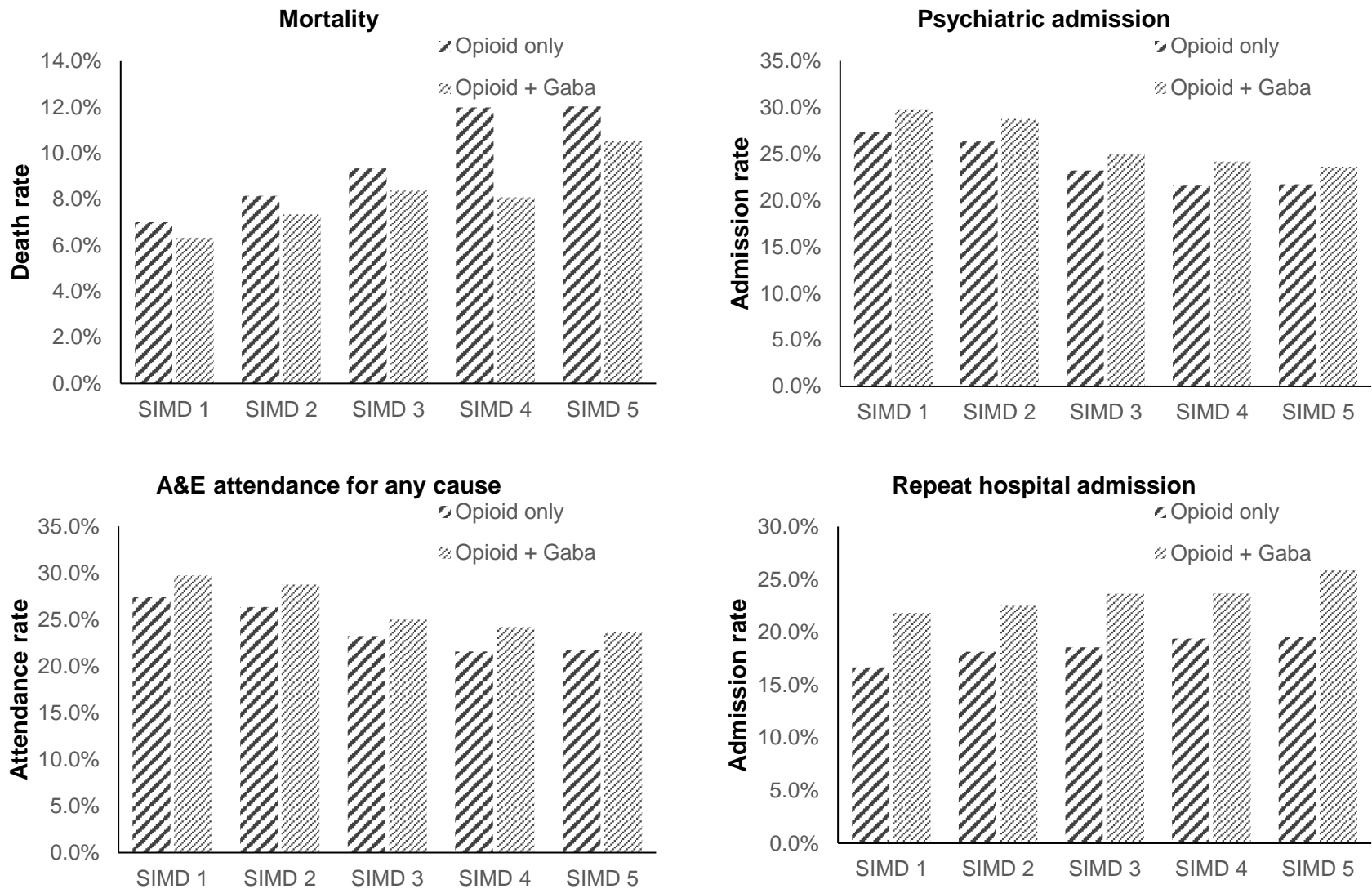
Figure 9. Health outcomes/service use rates in patients prescribed opioid only and both opioids and gabapentinoids stratified by SIMD of health board in Tayside and Fife

From the Chi-square testing, there were four health outcomes/service use factors that were significantly different between patients who were prescribed opioid and patients who were co-prescribed opioids and gabapentinoids: deaths, psychiatric admissions, repeated hospital admissions, and A&E attendance for any cause. The comparison of the rates of these four outcome variables between patients co-prescribed both opioids and gabapentinoids or not was stratified by sex, age and SIMD (Figure 7-9). When stratified by age groups, we can see that it was only among patients aged over 80 years that a lower death rate among patients with co-prescription was apparent (Figure 8), and this age group influenced the overall results of death rates (Table 10). As older people are more likely to die, age could be considered as a possible confounding factor for the relationship between co-prescription and death.

As age increased, the attendance rate at A&E for any cause was U-shaped, the middle age groups attending less. In every age category, patients with co-prescription all had higher A&E attendance rate. Similar to the trend with death rate, the likelihood of repeated admission increased with age. Furthermore, patients who were co-prescribed opioids and gabapentinoids were more likely to experience repeated admission to hospital in each age group. In contrast to the rising trend of death rate and repeated hospital admission rate, the psychiatric admission rates decreased with increasing age. Except for the oldest age group (more than 80 years), patients receiving co-prescription were repeatedly admitted to hospital more in all age groups, but these differences were very tiny.

Female patients represented 60% of the overall study sample, but males had a higher rate of health service use. For psychiatric admissions, A&E attendance for any cause and repeated hospital admissions, patients with co-prescription of an opioid and a gabapentinoid had higher use of these health service in both genders. The differences among the five deprivation groups were small.

Table 11. Logistic regression of co-prescription of opioids and gabapentinoids associated with health outcomes/service use* in Tayside and Fife

	Mortality			Psychiatric admissions			A&E attendance for any cause			Repeated hospital admissions		
	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P
Co-prescription												
Opioid only	*Reference group*			*Reference group*			*Reference group*			*Reference group*		
Both opioids & gabapentinoids	1.01	(0.92-1.10)	0.91	1.25	(0.99-1.58)	0.07	**1.19**	**(1.13-1.25)**	**<0.01**	**1.49**	**(1.41-1.57)**	**<0.01**
Age			<0.01			<0.01			<0.01			<0.01
18-39 years	*Reference group*			*Reference group*			*Reference group*			*Reference group*		
40-59 years	**2.70**	**(2.18-3.34)**	**<0.01**	**0.60**	**(0.48-0.76)**	**<0.01**	**0.61**	**(0.58-0.65)**	**<0.01**	1.04	(0.97-1.12)	0.31
60-79 years	**7.86**	**(6.41-9.64)**	**<0.01**	**0.32**	**(0.25-0.42)**	**<0.01**	**0.53**	**(0.50-0.56)**	**<0.01**	**1.56**	**(1.45-1.67)**	**<0.01**
over 80 years	**25.75**	**(20.97-31.65)**	**<0.01**	**0.62**	**(0.46-0.85)**	**<0.01**	**0.87**	**(0.82-0.93)**	**<0.01**	**2.44**	**(2.26-2.64)**	**<0.01**
Sex												
Female	*Reference group*			*Reference group*			*Reference group*			*Reference group*		
Male	**1.38**	**(1.29-1.46)**	**<0.01**	1.14	(0.94-1.37)	0.17	**1.18**	**(1.14-1.23)**	**<0.01**	**1.15**	**(1.10-1.20)**	**<0.01**
Health Board SIMD			<0.01			0.08			<0.01			0.68
1-most deprived	*Reference group*			*Reference group*			*Reference group*			*Reference group*		
2	0.93	(0.84-1.02)	0.11	1.13	(0.89-1.44)	0.32	0.97	(0.92-1.02)	0.21	1.01	(0.95-1.07)	0.84
3	0.99	(0.90-1.09)	0.87	0.83	(0.63-1.10)	0.20	**0.82**	**(0.78-0.87)**	**<0.01**	1.00	(0.94-1.07)	0.89
4	**1.12**	**(1.02-1.24)**	**0.02**	0.98	(0.74-1.30)	0.89	**0.76**	**(0.71-0.80)**	**<0.01**	0.99	(0.92-1.05)	0.67
5-least deprived	1.04	(0.94-1.15)	0.47	0.74	(0.53-1.03)	0.08	**0.76**	**(0.71-0.81)**	**<0.01**	0.96	(0.89-1.03)	0.24
Cancer[‡]												
No	*Reference group*			*Reference group*			*Reference group*			*Reference group*		
Yes	**5.78**	**(5.42-6.15)**	**<0.01**	0.88	(0.65-1.18)	0.39	**1.20**	**(1.14-1.27)**	**<0.01**	**3.20**	**(3.05-3.37)**	**<0.01**

*Deaths were in the year of 2012 and 2013; other health outcomes/service use were during 2012
[‡]Cancer was first registered before the end of 2013
CI, confidence interval

5.5 Logistic regression

The association of co-prescribing of opioids and gabapentinoids and health outcomes/service use was examined by logistic regression, to account for any confounding effects (Table 11). After controlling for confounding variables (age, sex, deprivation and cancer), co-prescription was no longer significantly associated with death. The findings from the Chi-square test (Table 10) that a lower mortality was observed in patients prescribed both opioids and gabapentinoids, could be explained from the logistic regression, that the apparent association was caused by the confounders. Among the variables fitted in the model, an older age and a diagnosis of cancer were the most important factors relating to death. Compared with that in the youngest age group (18-39 years), the odds of people in the oldest age group (over 80 years) increased to have died by about 25 times. Also, no significant association was found in the rates of psychiatric admissions between those co-prescribed opioids and gabapentinoids and those prescribed opioids only, after accounting for confounders.

Demographic factors, cancer and co-prescription of opioids and gabapentinoids had significant effects on the rate of attendance at A&E for any cause. A higher socioeconomic class and older age were protective factors for attending A&E, while the effect of growing age on A&E attendance was not monotonic. The odds of oldest age group (over 80 years) to attend A&E were higher than the odds of age groups between 40 to 79 years, but lower compared to the odds of youngest age group (18-39 years). The odds of being repeatedly admitted to hospital was increased by 49% (95% CI: 41%-57%) when the patients co-prescribed both opioids and gabapentinoids, compared with odds of those who were prescribed opioids only. Male gender was a marker of higher risk of death and more health service use.

In all, after controlling the confounders of demographic factors and cancer, the co-prescription of opioids and gabapentinoids was associated with A&E attendance (for any cause) and repeated hospital admissions.

6 Discussion

For this study, the clinical datasets and demography dataset in Tayside and Fife were linked by identifying the unique Pro-CHI number of each patient. There were 61,736 adults prescribed at least one opioid in Tayside and Fife during 2012 recorded by the NHS, after cleaning and merging the datasets.

From the descriptive analysis of the demography data, there were 26.5% classified as being registered in the most deprived health board, and there were more people living in the more deprived areas. In our study, females represented 60% of the study sample, and the overall mean age of the study sample was 58.28 years. In an observational drug utilisation study of patients prescribed pregabalin in UK (N=13,480), the median age of patients was 58 years, and female composed 59.4% of the study sample (22). In a Swedish population study, 61.4% of the patients prescribed pregabalin were females (n =48,550) (30). The distribution pattern of demography is similar to that in our study.

Among the 61,736 patients, there were 9,841 people prescribed more than 66,000 prescriptions of gabapentinoids. A total of around 168,000 prescriptions of weak opioids (codeine, dihydrocodeine and meptazinol), and almost 296,000 prescriptions of all strong opioids were prescribed in Tayside and Fife during 2012, and tramadol was prescribed the most often, with over 169,000 prescriptions. With the analgesic effects, opioids are commonly used for treating different types of pain, including acute pain, cancer pain and chronic non-cancer pain (52). Tramadol is considered to be safer and has a lower abuse potential than other strong opioids do, so it serves as an important alternative to other opioids (53).

In some countries, there have been studies using gabapentinoids to treat the dependence on, and withdrawal from opioids (54, 55), and a combination of opioids

and gabapentinoids for treating neuropathic pain has also been investigated (56). However, opioids and gabapentinoids are not recommended to be prescribed together in the UK. Both opioids and gabapentinoids are dangerous and have a potential for abuse (44, 57). The misuse of gabapentin and pregabalin is related to opioid addiction (33, 43). In the cohort study in Appalachian Kentucky, participants who were gabapentin users were more likely than non-users to be abusing opioids (36). Lyndon et al found that co-prescription of opioids with gabapentinoids could increase the risk of acute overdose death (45).

However, in our study, from the Chi-square test, the mortality of patients prescribed opioid only was significantly higher than the mortality of patients who were co-prescribed both opioids and gabapentinoids (percentage differences=1.53%). The result that co-prescription of gabapentinoids and opioids was related to lower mortality is not consistent with previous studies. This could be biased by other factors. For example, age is very closely related to death. Thus, logistic regression was conducted to control for potential confounding variables in the association between co-prescribed opioids and gabapentinoids and health outcomes/service. The relationship between co-prescribed opioids and gabapentinoids and death was no longer significant after controlling for the demographic variables and cancer. From the model, it was mainly older age and a diagnosis of cancer that were associated with higher mortality (Table 11).

The drug use was reported to be associated with certain health service use (58). As well as death, the association of co-prescription of opioids and gabapentinoids and health service use was also examined. The Chi-square testing showed that the patients prescribed both opioids and gabapentinoids had significantly higher rates of psychiatric admissions, A&E attendance for any cause and repeated hospital admissions. After controlling for the potential confounders of demography factors and cancer, A&E attendance for any cause and repeated hospital admissions were still associated with co-prescription.

A&E attendance could be seen as an indicator of adverse health condition. Patients with drug misuse commonly attend A&E for drug related causes. It has been found that patients attending A&E with drug related morbidity were more likely to have a subsequent drug related death (59). In our study, the relationship between co-prescribed opioids and gabapentinoids and A&E attendance for drug related causes was not found to be significant, while the A&E attendance for any cause was observed to be associated with co-prescription. This may result from inaccurate records, in that some drug-related attendances might have been miscoded. In this study, the alcohol and/or substance misuse, collapse/fall/unresponsive, overdose and psychiatry were defined as drug related causes. But there could be other reasons not listed here also drug-related, in an indirect way. Comparing the two outcomes of A&E attendance, the A&E attendance for any cause is less specific, but a much more objective and measurable outcome than the attendance for these specific reasons.

One of the main methods used for this study was data linkage. Different datasets were linked together at an individual level by the unique Pro-CHI number. By merging the data, the information available for each patient was richer, which allowed us to examine the different factors. However, the merging could cause a loss of cases too. In this study, it was mainly the demography data and GP prescribing data which determined the final sample size, and other datasets were merged to add variables but would not influence the number of cases. The demography dataset was cleaned first, with the removal of cases which did not meet the requirements of the recruitment and duplications.

The cleaned demography dataset contains the profiles of adults in Tayside and Fife who were prescribed at least one opioid in 2012. Ideally, the demography data could be perfectly connected with the prescription data. However, there were 4,203 subjects in the cleaned demography dataset whose Pro-CHIs were not part of the GP prescribing dataset. This might result from a data extraction error from HIC. Some subjects were not prescribed any opioid in Tayside and Fife during 2012, but they were

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mistakenly included in the raw demography dataset. By removing these subjects the quality of the data was improved.

However, it was possible that some patients were prescribed opioids that had been recorded in GP prescription data, but somehow were not included in the original demography data. The distribution of the demography data might be biased by missing these cases. For this study, the changes in percentages of each group of demographic variables were calculated, to see if after merging the pattern of the demography distribution changed. It turned out that the changes were very small and there was no evidence to show the data were biased after merging. So the loss of cases in the data linking process was not observed to change the demography distribution (Table 9).

There are some strengths to the study. First, the data linkage was used to combine the demographic profiles with prescription and clinical datasets, and this enlarged the data and had more information available. Also the influence of data merging was examined to make sure the linkage did not bias the data distribution, as discussed above.

Secondly, the datasets were well cleaned and managed before doing further data analysis (Figure 3). Given that many variables were already binary variables, death, cancer, psychiatric admissions, other variables of health outcomes/service use were all recoded to be binary variables, in order to allow the logistic regression modelling. The hospital admission data were provided as the dates and Pro-CHI numbers relating to admissions to hospitals. Originally this was a continuous variable of the number of times the patients were admitted to hospital, but it was computed to a binary variable with the groups of repeated hospital admissions in 2012 and fewer than two admissions. The indicator of repeated hospital admissions has been commonly used in studies of chronic diseases (60, 61), where it implies the poor health condition of the person, and also a burden on medical resources. Age was classified into four age groups based on the distribution of age shown in the histogram (Figure 4).

Thirdly, the demographic variables (age, sex and SIMD) and cancer were fitted in the logistic regression model as potential confounders and explained the biased results from Chi-square test. The demography is important for investigating the factors of diseases and health. Some diseases may occur more in a particular age group, and morbidities of chronic diseases tend to increase with the age growing, and also more medication (62). The health problems related to opioids and gabapentinoids are not reproductive, but males and females have different behaviours and habits. Socioeconomic status is also an important factor and people from different social class are exposed to different environments and social relationships. In this study, socioeconomic status was measured by the health board SIMD.

Cancer is another important potential confounding factor for the association between health outcomes/service use and co-prescription of opioids and gabapentinoids. These medicines are also commonly prescribed for cancer patients, as moderate to severe pain is common in cancer, and difficult to treat (63, 64). By fitting the factor of cancer in the logistic regression model, the potential effect of cancer on the prescription and health outcomes/service use was controlled.

However, there are also some weaknesses to the study. The data analyses in the study were restricted by the available data, and this is the main limitation of the study. The datasets were restricted to patients prescribed opioids in Tayside and Fife in 2012, and some datasets were also from 2013. Tayside and Fife are two small regions in Scotland, so compared with other national studies (27, 30, 37) using gabapentinoids and opioid prescription data, the sample size of this study was relatively small. Also, in this study, prescription data on gabapentinoids were only available on opioid prescribed patients (n=9,841). The prescription data on gabapentinoids for all the population in Tayside and Fife were not available.

Apart from the limitation of study sample size, the variables of the factors and confounders of the co-prescribed opioids and gabapentinoids in the study were also

limited. There were 22 variables in the original demography dataset. However, some variables in the demography dataset were repeated. For example, the anonymised date of birth and calculated age actually conveyed the same information. For SIMD, there were postcode SIMD based on the address of the patient, and health board SIMD based on the GP practice with which the patient was registered, and SIMD with 5 categories and 10 categories. Among these variables reflecting socioeconomic class, health board SIMD with 5 categories was chosen. Also there were some variables that were considered irrelevant for answering the research question, such as care home type, date of diagnosis of diabetes.

After excluding the repeated and irrelevant variables, only three demographic variables (age, sex, SIMD of health board) could be analysed as factors or potential confounders in the analysis. All these three demographic variables were fitted in the model, as they are important factors in disease and health related studies. As well as these three demographic variables, only the cancer registration could be included in the analysis as a potentially confounding variable. A lack of more information on the health condition and history of diseases made the fitting of logistic regression modelling more difficult. There could be some other potential confounders (e.g. chronic diseases, smoking status, previous medical history, and family history) that biased the measured association between the health outcomes/service use and co-prescribed opioids and gabapentinoids, and these variable would have been included in the analysis if they had been available.

In summary, A&E attendance for any cause and repeated hospital admissions were associated with co-prescribed opioids and gabapentinoids, after controlling for demographic factors and cancer. This implies that the co-prescription of gabapentinoids and opioids is associated with an increased overall risk of injury and/or acute ill health. Although further work of population-based studies with larger sample size and more comprehensive variables is needed to examine this in more detail, health service providers, prescribers and patients need to be aware of this risk,

avoiding co-prescription where possible and taking preventive steps to avoid these outcomes. Consideration is currently being given to introducing restrictions to prescribing gabapentinoids (making it a controlled drug). Until or unless these are in place, there should be education and awareness raising about this potential problem nationally.

7 Conclusions

Overall evidence from published papers on the use and misuse of gabapentinoid prescribing found the rising trend of misuse internationally. Patients with a history of substance abuse disorder were potentially more likely to misuse gabapentinoids, especially those patients with a history of opioid abuse. It suggested the key needs and directions for further studies that population studies are needed to examine factors of gabapentinoid misuse, with a focus on opioid users.

Followed by the systematic review, the database analysis study is so far the first study to examine the factors associated with co-prescribed opioids and gabapentinoids, to our knowledge. A&E attendance for any cause and repeated hospital admissions were associated with co-prescribed opioids and gabapentinoids in logistic regression models, after controlling for demographic factors and cancer. This implied that co-prescribed opioids and gabapentinoids could be potentially harmful, as a higher rate of the health service use suggested a worse health condition and greater burdens of medical resource use. For future studies, prescription data relating to gabapentin and pregabalin from the whole population are needed. Data from a larger and more representative population with more potential confounding variables would have more power in examining the harm and factors of the use and misuse of gabapentinoids.

8 References

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9 Appendices

Appendix 1: the STROBE checklist

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (e.g. average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Appendix 2: NHLBI checklist

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			
Quality Rating (Good, Fair, or Poor) (see guidance)			
Rater #1 initials:			
Rater #2 initials:			
Additional Comments (If POOR, please state why):			

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for Assessing the Quality of Observational Cohort and Cross-Sectional Studies

The guidance document below is organized by question number from the tool for quality assessment of observational cohort and cross-sectional studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.

Questions 2 and 3. Study population

Did the authors describe the group of people from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcomes of interest at the time they were recruited?

An example would be men over 40 years old with type 2 diabetes who began seeking medical care at Phoenix Good Samaritan Hospital between January 1, 1990 and December 31, 1994. In this example, the population is clearly described as: (1) who (men over 40 years old with type 2 diabetes); (2) where (Phoenix Good Samaritan Hospital); and (3) when (between January 1, 1990 and December 31, 1994). Another example is women ages 34 to 59 years of age in 1980 who were in the nursing profession and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes, and were recruited from the 11 most populous States, with contact information obtained from State nursing boards.

In cohort studies, it is crucial that the population at baseline is free of the outcome of interest. For example, the nurses' population above would be an appropriate group in which to study incident coronary disease. This information is usually found either in descriptions of population recruitment, definitions of variables, or inclusion/exclusion criteria.

You may need to look at prior papers on methods in order to make the assessment for this question. Those papers are usually in the reference list.

If fewer than 50% of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population. This increases the risk of bias.

Question 4. Groups recruited from the same population and uniform eligibility criteria

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the subjects involved? This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper.

Most cohort studies begin with the selection of the cohort; participants in this cohort are then measured or evaluated to determine their exposure status. However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially retrospective cohort studies–which is when data are obtained from the past (retrospectively), but the analysis examines exposures prior to outcomes. For example, one research question could be whether diabetic men with clinical depression are at higher risk for cardiovascular disease than those without clinical depression. So, diabetic men with depression might be selected from a mental health clinic, while diabetic men without depression might be selected from an internal medicine or endocrinology clinic. This study recruits groups from different clinic populations, so this example would get a "no."

However, the women nurses described in the question above were selected based on the same inclusion/exclusion criteria, so that example would get a "yes."

Question 5. Sample size justification

Did the authors present their reasons for selecting or recruiting the number of people included or analyzed? Do they note or discuss the statistical power of the study? This question is about whether or not the study had enough participants to detect an association if one truly existed.

A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a 2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates of effect size are given, instead of sample size calculations. In any of these cases, the answer would be "yes."

However, observational cohort studies often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It just may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecified question–i.e., it may have been an exploratory, hypothesis-generating study.

Question 6. Exposure assessed prior to outcome measurement

This question is important because, in order to determine whether an exposure causes an outcome, the exposure must come before the outcome.

For some prospective cohort studies, the investigator enrolls the cohort and then determines the exposure status of various members of the cohort (large epidemiological studies like Framingham used this approach). However, for other cohort studies, the cohort is selected based on its exposure status, as in the example above of depressed diabetic men (the exposure being depression). Other examples include a cohort identified by its exposure to fluoridated drinking water and then compared to a cohort living in an area without fluoridated water, or a cohort of military personnel exposed to combat in the Gulf War compared to a cohort of military personnel not deployed in a combat zone.

With either of these types of cohort studies, the cohort is followed forward in time (i.e., prospectively) to assess the outcomes that occurred in the exposed members compared to nonexposed members of the cohort. Therefore, you begin the study in the present by looking at groups that were exposed (or not) to some biological or behavioral factor, intervention, etc., and then you follow them forward in time to examine outcomes. If a cohort study is conducted properly, the answer to this question should be "yes," since the exposure status of members of the cohort was determined at the beginning of the study before the outcomes occurred.

For retrospective cohort studies, the same principal applies. The difference is that, rather than identifying a cohort in the present and following them forward in time, the investigators go back in time (i.e., retrospectively) and select a cohort based on their exposure status in the past and then follow them forward to assess the outcomes that occurred in the exposed and nonexposed cohort members. Because in retrospective cohort studies the exposure and outcomes may have already occurred (it depends on how long they follow the cohort), it is important to make sure that the exposure preceded the outcome.

Sometimes cross-sectional studies are conducted (or cross-sectional analyses of cohort-study data), where the exposures and outcomes are measured during the same timeframe. As a result, cross-sectional analyses provide weaker evidence than regular cohort studies regarding a potential cauasl relationship between exposures and outcomes. For cross-sectional analyses, the answer to Question 6 should be "no."

Question 7. Sufficient timeframe to see an effect

Did the study allow enough time for a sufficient number of outcomes to occur or be observed, or enough time for an exposure to have a biological effect on an outcome? In the examples given above, if clinical depression has a biological effect on increasing risk for CVD, such an effect may take years. In the other example, if higher dietary sodium increases BP, a short

timeframe may be sufficient to assess its association with BP, but a longer timeframe would be needed to examine its association with heart attacks.

The issue of timeframe is important to enable meaningful analysis of the relationships between exposures and outcomes to be conducted. This often requires at least several years, especially when looking at health outcomes, but it depends on the research question and outcomes being examined.

Cross-sectional analyses allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.

Question 8. Different levels of the exposure of interest

If the exposure can be defined as a range (examples: drug dosage, amount of physical activity, amount of sodium consumed), were multiple categories of that exposure assessed? (for example, for drugs: not on the medication, on a low dose, medium dose, high dose; for dietary sodium, higher than average U.S. consumption, lower than recommended consumption, between the two). Sometimes discrete categories of exposure are not used, but instead exposures are measured as continuous variables (for example, mg/day of dietary sodium or BP values).

In any case, studying different levels of exposure (where possible) enables investigators to assess trends or dose-response relationships between exposures and outcomes–e.g., the higher the exposure, the greater the rate of the health outcome. The presence of trends or dose-response relationships lends credibility to the hypothesis of causality between exposure and outcome.

For some exposures, however, this question may not be applicable (e.g., the exposure may be a dichotomous variable like living in a rural setting versus an urban setting, or vaccinated/not vaccinated with a one-time vaccine). If there are only two possible exposures (yes/no), then this question should be given an "NA," and it should not count negatively towards the quality rating.

Question 9. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable–for example, have they been validated or are they objective? This issue is important as it influences confidence in the reported exposures. When exposures are measured with less accuracy or validity, it is harder to see an association between exposure and outcome even if one exists. Also as important is whether the exposures were assessed in the same manner within groups and between groups; if not, bias may result.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of BP, where there may be quite a difference between usual care, where clinicians measure BP however it is done in their practice setting (which can vary considerably), and use of trained BP assessors using standardized equipment (e.g., the same BP device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged). In each of these cases, the former would get a "no" and the latter a "yes."

Here is a final example that illustrates the point about why it is important to assess exposures consistently across all groups: If people with higher BP (exposed cohort) are seen by their providers more frequently than those without elevated BP (nonexposed group), it also increases the chances of detecting and documenting changes in health outcomes,

including CVD-related events. Therefore, it may lead to the conclusion that higher BP leads to more CVD events. This may be true, but it could also be due to the fact that the subjects with higher BP were seen more often; thus, more CVD-related events were detected and documented simply because they had more encounters with the health care system. Thus, it could bias the results and lead to an erroneous conclusion.

Question 10. Repeated exposure assessment

Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence that the exposure status was correctly classified. Also, multiple measurements enable investigators to look at changes in exposure over time, for example, people who ate high dietary sodium throughout the followup period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout. Once again, this may not be applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.

Question 11. Outcome measures

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable–for example, have they been validated or are they objective? This issue is important because it influences confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups.

An example of an outcome measure that is objective, accurate, and reliable is death–the outcome measured with more accuracy than any other. But even with a measure as objective as death, there can be differences in the accuracy and reliability of how death was assessed by the investigators. Did they base it on an autopsy report, death certificate, death registry, or report from a family member? Another example is a study of whether dietary fat intake is related to blood cholesterol level (cholesterol level being the outcome), and the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes." An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weigh (if body weight is the outcome of interest).

Similar to the example in Question 9, results may be biased if one group (e.g., people with high BP) is seen more frequently than another group (people with normal BP) because more frequent encounters with the health care system increases the chances of outcomes being detected and documented.

Question 12. Blinding of outcome assessors

Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section.

As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is no, then blinding is adequate. An example of adequate blinding of the outcome assessors is to create a separate committee, whose members were not

involved in the care of the patient and had no information about the study participants' exposure status. The committee would then be provided with copies of participants' medical records, which had been stripped of any potential exposure information or personally identifiable information. The committee would then review the records for prespecified outcomes according to the study protocol. If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Question 13. Followup rate

Higher overall followup rates are always better than lower followup rates, even though higher rates are expected in shorter studies, whereas lower overall followup rates are often seen in studies of longer duration. Usually, an acceptable overall followup rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study examining the relationship between dietary sodium intake and BP level may have over 90 percent followup, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65 percent followup rate.

Question 14. Statistical analyses

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT, where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome–that are not of interest to the research question–should be controlled for in the analyses.

For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, BP, blood cholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.

Some general guidance for determining the overall quality rating of observational cohort and cross-sectional studies

The questions on the form are designed to help you focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity for cohort studies is the extent to which the results reported in the study can truly be attributed to the exposure being evaluated and not to flaws in the design or conduct of the study–in other words, the ability of the study to draw associative conclusions about the effects of the exposures being studied on outcomes. Any such flaws can increase the risk of bias.

Critical appraisal involves considering the risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. High risk of bias translates to a rating of poor quality. Low risk of bias translates to a rating of good quality. (Thus, the greater the risk of bias, the lower the quality rating of the study.)

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the exposure and outcome, the higher quality the study. These include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, sufficient timeframe to see an effect, and appropriate control for confounding–all concepts reflected in the tool.

Generally, when you evaluate a study, you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no" you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to doubt the results that are reported in the study or doubt the ability of the study to accurately assess an association between exposure and outcome?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on the details that are reported and consideration of the concepts for minimizing bias.

Last Updated March 2014

Appendix 3: CASP checklist for review studies
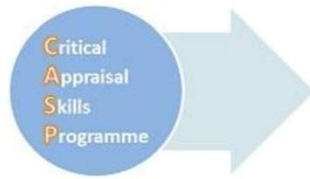
10 questions to help you make sense of a review

How to use this appraisal tool

Three broad issues need to be considered when appraising the report of a systematic review:

- **Are the results of the review valid?** (Section A)
- **What are the results?** (Section B)
- **Will the results help locally?** (Section C)

The 10 questions on the following pages are designed to help you think about these issues systematically.
The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.
These checklists were designed to be used as educational tools as part of a workshop setting
There will not be time in the small groups to answer them all in detail!

(A) Are the results of the review valid?

Screening Questions

1. Did the review address a clearly focused question?   ☐ Yes   ☐ Can't tell   ☐ No

HINT: An issue can be 'focused' In terms of
- The population studied
- The intervention given
- The outcome considered

---

2. Did the authors look for the right type of papers?   ☐ Yes   ☐ Can't tell   ☐ No

HINT: 'The best sort of studies' would
- Address the reviews question
- Have an appropriate study design (usually RCTs for papers evaluating interventions)

Is it worth continuing?

<u>Detailed questions</u>

3. Do you think all the important, relevant studies were included?

☐ Yes   ☐ Can't tell   ☐ No

HINT: Look for
- Which bibliographic databases were used
- Follow up from reference lists
- Personal contact with experts
- Search for unpublished as well as published studies
- Search for non-English language studies

---

4. Did the review's authors do enough to assess the quality of the included studies?

☐ Yes   ☐ Can't tell   ☐ No

HINT: The authors need to consider the rigour of the studies they have identified. Lack of rigour may affect the studies' results. ("All that glisters is not gold" Merchant of Venice – Act II Scene 7)

---

5. If the results of the review have been combined, was it reasonable to do so?

☐ Yes   ☐ Can't tell   ☐ No

HINT: Consider whether
- The results were similar from study to study
- The results of all the included studies are clearly displayed
- The results of the different studies are similar
- The reasons for any variations in results are discussed

(B) What are the results?

6. What are the overall results of the review?

HINT: Consider
- If you are clear about the review's 'bottom line' results
- What these are (numerically if appropriate)
- How were the results expressed (NNT, odds ratio etc)

---

7. How precise are the results?

HINT: Look at the confidence intervals, if given

(C) Will the results help locally?

8. Can the results be applied to the local population? ☐ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- The patients covered by the review could be
  sufficiently different to your population to cause concern
- Your local setting is likely to differ much from that of the review

9. Were all important outcomes considered? ☐ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- Is there other information you would like to have seen

10. Are the benefits worth the harms and costs? ☐ Yes ☐ Can't tell ☐ No

HINT: Consider

- Even if this is not addressed by the review,
  what do you think?

Appendix 4: CASP checklist for cohort studies

12 questions to help you make sense of cohort study

How to use this appraisal tool

Three broad issues need to be considered when appraising a cohort study:

Are the results of the study valid?   (Section A)
What are the results?   (Section B)
Will the results help locally?   (Section C)

The 12 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational pedagogic tools, as part of a workshop setting, therefore we do not suggest a scoring system. The core CASP checklists (randomised controlled trial & systematic review) were based on JAMA 'Users' guides to the medical literature 1994 (adapted from Guyatt GH, Sackett DL, and Cook DJ), and piloted with health care practitioners.

For each new checklist a group of experts were assembled to develop and pilot the checklist and the workshop format with which it would be used. Over the years overall adjustments have been made to the format, but a recent survey of checklist users reiterated that the basic format continues to be useful and appropriate.

Referencing: we recommend using the Harvard style citation, i.e.:

Critical Appraisal Skills Programme (2017). CASP (insert name of checklist i.e. Cohort Study) Checklist. [online] Available at: URL. Accessed: Date Accessed.

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(A) Are the results of the study valid?

1. Did the study address a clearly focused issue? ☐Yes ☐Can't tell ☐No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

---

2. Was the cohort recruited in an acceptable way? ☐Yes ☐Can't tell ☐No

HINT: Look for selection bias which might compromise
   the generalisability of the findings:
- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias? ☐Yes ☐Can't tell ☐No

HINT: Look for measurement or classification bias:
- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

4. Was the outcome accurately measured to ☐Yes ☐Can't tell ☐No

©**Critical Appraisal Skills Programme (CASP)** Cohort Study Checklist 13.03.17   2

minimise bias?

HINT: Look for measurement or classification bias:
- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

---

5. (a) Have the authors identified all important confounding factors?   ☐ Yes   ☐ Can't tell   ☐ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis?   ☐ Yes   ☐ Can't tell   ☐ No

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough?   ☐ Yes   ☐ Can't tell   ☐ No

(b) Was the follow up of subjects long enough?   ☐ Yes   ☐ Can't tell   ☐ No

HINT: Consider
- The good or bad effects should have had long enough

to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider
- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

9. Do you believe the results?   ☐ Yes   ☐ Can't tell   ☐ No

HINT: Consider
- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

(C) Will the results help locally?

10. Can the results be applied to the local population? ☐ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

---

11. Do the results of this study fit with other ☐ Yes ☐ Can't tell ☐ No

available evidence?

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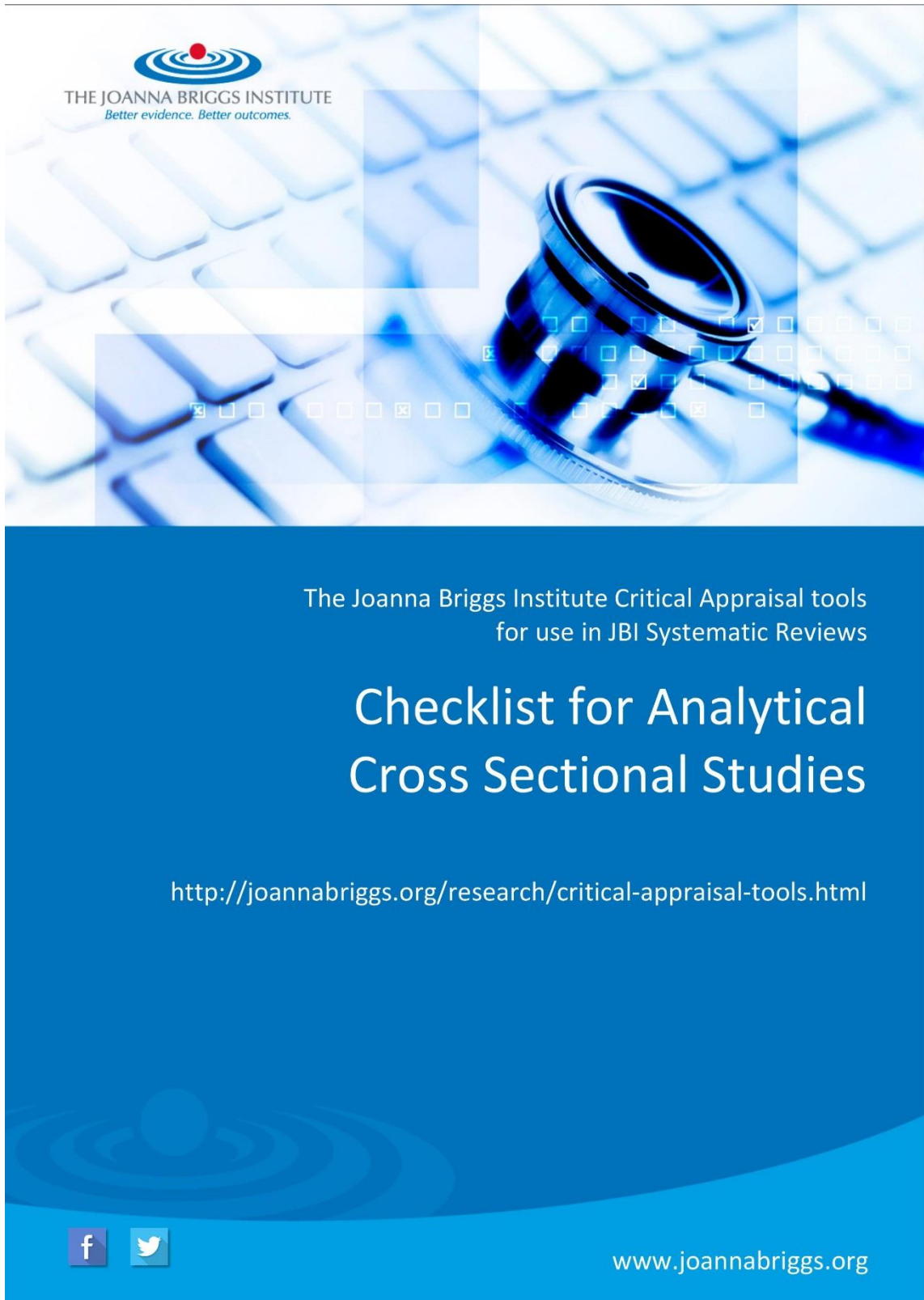
12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Appendix 5: the JBI checklist

THE JOANNA BRIGGS INSTITUTE
Better evidence. Better outcomes.

The Joanna Briggs Institute Critical Appraisal tools
for use in JBI Systematic Reviews

Checklist for Analytical Cross Sectional Studies

http://joannabriggs.org/research/critical-appraisal-tools.html

www.joannabriggs.org

The Joanna Briggs Institute

Introduction

The Joanna Briggs Institute (JBI) is an international, membership based research and development organization within the Faculty of Health Sciences at the University of Adelaide. The Institute specializes in promoting and supporting evidence-based healthcare by providing access to resources for professionals in nursing, midwifery, medicine, and allied health. With over 80 collaborating centres and entities, servicing over 90 countries, the Institute is a recognized global leader in evidence-based healthcare.

JBI Systematic Reviews

The core of evidence synthesis is the systematic review of literature of a particular intervention, condition or issue. The systematic review is essentially an analysis of the available literature (that is, evidence) and a judgment of the effectiveness or otherwise of a practice, involving a series of complex steps. The JBI takes a particular view on what counts as evidence and the methods utilized to synthesize those different types of evidence. In line with this broader view of evidence, the Institute has developed theories, methodologies and rigorous processes for the critical appraisal and synthesis of these diverse forms of evidence in order to aid in clinical decision-making in health care. There now exists JBI guidance for conducting reviews of effectiveness research, qualitative research, prevalence/incidence, etiology/risk, economic evaluations, text/opinion, diagnostic test accuracy, mixed-methods, umbrella reviews and scoping reviews. Further information regarding JBI systematic reviews can be found in the JBI Reviewer's Manual on our website.

JBI Critical Appraisal Tools

All systematic reviews incorporate a process of critique or appraisal of the research evidence. The purpose of this appraisal is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. All papers selected for inclusion in the systematic review (that is – those that meet the inclusion criteria described in the protocol) need to be subjected to rigorous appraisal by two critical appraisers. The results of this appraisal can then be used to inform synthesis and interpretation of the results of the study. JBI Critical appraisal tools have been developed by the JBI and collaborators and approved by the JBI Scientific Committee following extensive peer review. Although designed for use in systematic reviews, JBI critical appraisal tools can also be used when creating Critically Appraised Topics (CAT), in journal clubs and as an educational tool.

Critical Appraisal Checklist for | **2**
Analytical Cross Sectional Studies

JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

Reviewer_____Date_____

Author _____Year_____ Record Number _____

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
2. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were objective, standard criteria used for measurement of the condition?	☐	☐	☐	☐
5. Were confounding factors identified?	☐	☐	☐	☐
6. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐   Exclude ☐   Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

Explanation of analytical cross-sectional studies critical appraisal

How to cite: The Joanna Briggs Institute. Joanna Briggs Institute Reviewers' Manual: 2016 edition. Australia: The Joanna Briggs Institute; 2016.

Analytical cross-sectional studies Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. **Were the criteria for inclusion in the sample clearly defined?**

   The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants. The inclusion/exclusion criteria should be specified (e.g., risk, stage of disease progression) with sufficient detail and all the necessary information critical to the study.

2. **Were the study subjects and the setting described in detail?**

   The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them. The authors should provide a clear description of the population from which the study participants were selected or recruited, including demographics, location, and time period.

3. **Was the exposure measured in a valid and reliable way?**

   The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.
   Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

4. **Were objective, standard criteria used for measurement of the condition?**

   It is useful to determine if patients were included in the study based on either a specified diagnosis or definition. This is more likely to decrease the risk of bias. Characteristics are another useful approach to matching groups, and studies that did not use specified diagnostic methods or definitions should provide evidence on matching by key characteristics.

5. Were confounding factors identified?

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at the level of cohort design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

6. Were strategies to deal with confounding factors stated?

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured.

7. Were the outcomes measured in a valid and reliable way?

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

8. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section of cohort studies should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured.

For studies utilising regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

Appendix 6: Circum survey assessment framework

EXHIBIT 1 • Survey Assessment Framework

Building blocks	Principles			
	[R]igour the systematic application of best practices in the matter of survey research	**[N]eutrality** nature of what represents reality faithfully	**[B]alance** the sufficient yet parsimonious utilisation of resources toward the development of proof	**[T]ransparency** nature of what depicts reality completely and without alteration
[q]uestionnaire	• Content validity • Pretests • Response scales	• Reliability • Absence of bias	• Minimisation of response burden	• Research objective • Sponsor • Complete reproduction of the questionnaire
[s]ampling	• Adhesion to rules of random sampling • Justification of non random sampling	• Target population and population reached; filtering procedures • Sampling frame • Final dispositions; response rate; refusal rate; replacement procedures • Sampling margin of error	• Appropriateness of the nature of the sample considering the research purposes • Sample size	• Population definition • Sampling method • Sample size • Response rate
data [c]ollection	• Interviewer training • Quality controls, supervision • Call back schedule	• Criterion validity (corroboration) • Non-contamination • Double-blindedness	• Justification of the type of survey • Informed consent vs. hidden client • Avoidance of scarring effects • Confidentiality of data	• Data collection method • Identification of data collection agent • Dates, locations and periods of data collection • Notable social events during the data collection period
data [m]anagement	• Calculations and adjustments done correctly • Coding performed rigorously	• Weighting criteria used • Sources of population data • Assurance that adjustments do not unduly favour the researcher's hypotheses or interests	• Avoidance of excessive weighting • Effect of the adjustments made	• Mode of calculation of weights • Variance of the weighting scheme • Calculations and adjustments made
data [a]nalysis	• Technically correct use of statistical tools • For issues of causation, appropriate specification of the effect model	• Risk of disputes on results and interpretations • Coherence of conclusions with results	• Appropriateness of methods considering the research purposes • Appropriate of the research design considering the research purposes	• Raw and weighted sample sizes in tables • Description of analysis methods used
[r]eporting	• Disclosure of study weaknesses and possible bias	• Distinct presentation of objective results and of their interpretation • Selflessness of the researcher	• Level of support to conclusions offered by study results • Possible reservations on the internal and external validity of results	• Understandability of the presentation • Disclosure of all elements of information required by all 24 framework cells to assess the value of results