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Research Paper

The epidemiology of regular opioid use and its association with mortality: Prospective cohort study of 466 486 UK biobank participants

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ABSTRACT

Background: Opioids have, at most, small benefits for non-cancer pain in the medium and long-term but there is good evidence that they cause harm. The current study describes the characteristics and clinical status of people taking regular opioids in Great Britain and determines whether use is associated with mortality risk.
Methods: An analysis of participants in UK Biobank, a prospective population-based study. At recruitment (2006–10) participants reported medicines which they regularly used in addition to lifestyle and health-related factors. Information was available on deaths until October 2016.
Findings: There were 466 486 participants (54% women) aged 40–69 years and without a prior history of cancer of whom 5.5% were regularly using opioids. Use increased with age-group, was more common in females (6.3% v. 4.6%) and 87% of persons using them reported chronic pain. The highest rates of use (~1 in 9) were in people with low household income, who left school <16 years and lived in areas with high deprivation. Amongst 15,032 people who could not work because of ill-health, 1 in 3 were regularly taking opioids. Regular users reported insomnia (88.7%), a recent major recent life event (57.3%) and were much more likely than non-users to rate their health as poor (RR 5.5, 99% CI (4.9, 6.1)). Those taking weak (4.2% of participants) or strong (1.4%) opioids were more likely to die during follow-up (6.9% and 9.1% respectively v. 3.3% in non-users) an excess which remained after adjustment for demographic, socio-economic, health and lifestyle factors (MRR 1.18 99% CI (1.06, 1.32) and 1.20 99% CI (1.01, 1.43)) respectively.
Interpretation: Regular use of opioids is common in Great Britain, particularly in groups of low socio-economic status. Most users still report chronic pain, poor health generally and are at increased risk of premature death although it is not established that this relationship is causal.
Funding: There were no external sources of funding obtained for the current analyses.

1. Introduction

Chronic pain is an important public health problem – around 2 in 10 of the general population sample reported persistent and intense pain in one pan-European study [1] while a meta-analysis of epidemiological studies conducted world-wide found that 3 in 10 persons had chronic pain [2]. The aetiology of chronic pain is multifactorial and complex, with onset of pain often in early adulthood. Long-term prospective studies demonstrate an increased risk related to adverse social environment in early life, as well as physically and emotionally traumatic events [3–6]. A review of factors which predict an episode of pain becoming chronic, and causing long-term disability, found the strongest evidence in relation to clinical factors (disabling, persistent and multi-site pain), older age, and mood [7]. A consequence of chronic pain is an increased risk of death [8]. Data from UK Biobank has shown, specifically, that persons with chronic widespread pain (CWP) have a markedly increased risk of dying during follow-up (mortality risk ratio (MRR) 2.43, 99%CI 2.17 to 2.72), an excess risk that was partly explained by low levels of physical activity, high body mass index, poor quality diet and tobacco smoking [9].

In managing chronic pain, although there will be differences in relation to specific diagnoses, both non-pharmacologic and pharmacologic approaches are generally important. Supported self-management is a cornerstone of common pain conditions from early in the course of symptoms through to long-term management. Non-pharmacologic approaches include physical activity, physical, behavioural and relaxation therapies and for conditions such as low back pain and fibromyalgia, these will be the primary approaches to management [10,11]. A wide range of analgesics have been used in the management of chronic pain – however a key recommendation from guidelines of

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Research in context

Evidence before this study

We have taken advantage of this large and well-phenotyped UK cohort. Prior to undertaking the analysis, we conducted a review to determine the current state of evidence with respect to the prevalence of the use of opioids in Europe. The search terms used included "opioid" and "prevalence" or "prescribing" or "trends" or "mortality" or "epidemiology" What we found was the evidence was exclusively around the *use* of opioids (using routinely collected data, mainly from primary care). These provided data on patterns and trends of use (including geographical influences on such).

Added value of this study

This study provides detailed information on the characteristics and health of people regularly using prescribed opioids. The data show that use is very strongly related to socio-economic factors. Indeed a truly startling figure from the manuscript is that, amongst people who are not able to work because of ill-health, that 1 in 3 are regularly using opioids.

While use is primarily for chronic pain, the data in this manuscript emphasise the poor health of people taking regular opioids. Almost all still report chronic pain and almost all report insomnia and few report their health as good. This suggests that opioids are not effective in the medium and long-term for the conditions for which they are prescribed.

Finally a multivariable analysis suggests that after health, socio-economic and lifestyle factors are taken into account, the regular use of opioids is associated with premature mortality. This mortality is driven by disease related deaths.

Implications of all the available evidence

This study emphasises the poor health of persons who are taking opioids regularly. Combining this with other information on the widespread use of opioids, and the current information that such persons experience premature mortality, it demonstrates that this is a major public health issue. There is a need to develop evidence on effective ways to support people stopping using opioids and an alternative approach to the management of chronic pain.

management is regular review and stopping medications which are not effective [12].

The World Health Organisation (WHO) analgesic ladder has provided a framework for the use of analgesics in patients with cancer pain [13]. The approach recommends that analgesics used should initially be non-opioids, and then opioids, with the expectation that the strength and dose of opioids would increase as cancer progressed. Success in the use of this approach in cancer patients at the end-of-life has led to the same approach being used for patients with chronic non-cancer pain. The idea that increasing pain intensity necessitates stronger medicines in higher doses may hold well for cancer pain where disease burden is progressing. Using this approach more generally, for non-cancer pain, has had the consequence of a dramatic increase in the use of prescription opioids, most obviously in the United States [14]. It has also made evident the negative consequences of such widespread use. Reported pain intensity in chronic non-cancer pain has little to do with tissue damage and escalation of potent medicines is not justified [15]. There is good evidence of an increased risk for serious harm (including overdose, opioid misuse, fractures, myocardial infarction, and markers of sexual dysfunction). At most they are likely to have only small benefits (in terms of pain, function and quality of life) in the medium and long-term [16] - indeed a recent meta-analysis assessed their benefits as similar to non-opioid analgesics in the management of non-cancer chronic pain, although the evidence came primarily from low quality studies [16,17].

The purpose of this analysis is therefore to describe the epidemiology of opioid use in Great Britain, the health and quality of life of people using them and to examine whether their use is associated with excess mortality.

2. Methods

This study report adheres to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [18].

UK Biobank recruited around half a million persons aged 40–69 years who were registered with a general practitioner within the National Health Service (NHS) (see reference [19] for detailed methods). Approximately 9.2 million invitations were issued, between 2006–10, to people living within 25 miles of one of 22 assessment centres across Great Britain. At the assessment centre, participants responded to questions, including on demography, social, health and lifestyle factors, by using a touchscreen. Indices of multiple deprivation (at the small area level) were used for England, Scotland and Wales to determine the quintile of deprivation of their residential area (within the country of residence).

2.1. Pain and medications

In terms of pain, participants were asked "In the last month have you experienced any of the following that interfered with your usual activities?" If they answered positively, they were then provided with a list which included seven individual regional pain sites, or alternatively they could choose the response "pain all over the body". Respondents were asked whether the reported pain had lasted at least three months and those who reported this for at least one site (or pain all over the body) were categorised as having "chronic pain". Participants were asked if they were taking regular prescription medication and if so, in a nurse-led interview, were then asked what these were. Information was collected on regular treatments. It did not include short-term medications (such as a course of antibiotics) or prescribed medication that had not been taken. Interviewers chose the generic or trade name of the treatment from a list. Information on dose and formulation was not collected. For this analysis, the full list of treatments was searched for generic or trade names of opioids, including drugs listed in sub-paragraphs 4.7.1 (Non-Opioid Analgesics and Compound Preparations) and 4.7.2 (Opioid Analgesics) of the British National Formulary (BNF: https://www.bnf.org/products/bnf-online). Those that were not commonly prescribed for pain or did not appear in the BNF sub-paragraphs 4.7.1 and 4.7.2 were not coded as opioids. Treatments that contained an opioid listed in sub-paragraph 4.7.1 were classed as 'Combination' opioids. Other opioids were classed according to their chemical class (i.e. Codeine, Dihydrocodeine, etc.). Participants who took any opioid in the Tramadol, Morphine, Buprenorphine, Oxycodone, Fentanyl, or Hydromorphine categories were classed as taking a strong opioid.

2.2. Vital status and causes of death

For the purposes of collecting information on vital status, participants were identified on the Office for National Statistics (ONS) records. ONS collects information on cause of death from civil registration records. For registered deaths, the underlying cause of death is derived from the sequence of conditions leading directly to the death and is recorded on the death certificate. The analysis uses the UK Biobank dataset provided to us in April 2019, which contains death information (considered to be complete) up to 31 October 2016.

2.3. Statistical analysis

Descriptive analyses are reported for the use of prescription opioids by demography and social factors and in relation to pain status. In all

analyses, persons who reported a previous diagnosis of cancer (other than non-melanoma skin cancer) were removed, as opioids may have been prescribed because of cancer pain in such persons. Relationships with use are described using modified Poisson regression with robust error variances [20] and are expressed as crude risk ratios (RR) and adjusted for (as indicated in specific models) age, gender, ethnicity, region, primary employment status, university degree, deprivation, income and pain status, namely, the number of body sites in which pain was reported or pain all over the body and whether pain had lasted more than three months (i.e. chronic pain).

In examining the relationship between opioid use and subsequent mortality, the proportion of persons who died during follow-up according to their regular use of opioids at the time of recruitment, is described. Poisson regression models, with robust estimation of standard errors were used to quantify the relationship expressed as Mortality Risk Ratios (MRR) with adjustment for pain status, socio-economic factors, and lifestyle factors shown previously to be potential mediators of the relationship between chronic pain and mortality.

2.4. Role of the funding source

There were no external sources of funding for the conduct of this analysis.

3. Results

There were 466,486 persons who were recruited to UK Biobank who did not report a prior diagnosis of cancer (other than non-melanoma skin cancer) and these were eligible for the current analysis. Of these, 25,864 reported regular use of opioid medication, which represents 5.5% of participants. There were striking associations with socio-demographic factors and use of such medications (see Table 1). Use increased with age-group and was more common in females than males (6.3% v. 4.6%,

Table 1
Regular use of any opioid analgesics by social and demographic factors.

		Opioid Use No: n (%)	Opioid Use Yes: n (%)	Adjusted RR[1,2] (99% CI)
Age (years)	40–45	48,522 (96.6)	1705 (3.4)	1 [Ref]
	45–49	61,043 (96.1)	2462 (3.9)	1.08 (1.00–1.17)
	50–54	68,858 (95.4)	3357 (4.7)	1.15 (1.07–1.24)
	55–59	79,942 (94.4)	4739 (5.6)	1.16 (1.08–1.24)
	60–64	103,711 (93.7)	7020 (6.3)	1.17 (1.08–1.26)
	65–70	78,546 (92.3)	6581 (7.7)	1.31 (1.20–1.42)
Gender	Male	206,841 (95.4)	10,057 (4.6)	1 [Ref]
	Female	233,781 (93.7)	15,807 (6.3)	1.43 (1.39–1.48)
Ethnicity	White	413,507 (94.4)	24,380 (5.6)	1 [Ref]
	Mixed	2632 (94.4)	155 (5.6)	1.07 (0.88–1.30)
	Asian or Asian British	9135 (95.3)	452 (4.7)	1.01 (0.89–1.13)
	Black or Black British	7275 (94.2)	448 (5.8)	1.17 (1.04–1.31)
	Chinese	1485 (98.3)	25 (1.7)	0.45 (0.27–0.74)
	Other ethnicity	4111 (94.3)	246 (5.7)	1.19 (1.01–1.39)
	Not known	2477 (94.0)	158 (6.0)	1.12 (0.92–1.37)
Area of residence	South East England	39,283 (92.2)	1149 (2.8)	1 [Ref]
	London	61,745 (96.9)	1975 (3.1)	0.83 (0.76–0.91)
	South West England	38,136 (95.5)	1803 (4.5)	1.38 (1.25–1.51)
	East Midlands	29,809 (94.8)	1634 (5.2)	1.30 (1.18–1.43)
	Yorkshire and Humberside	65,101 (94.1)	4056 (5.9)	1.46 (1.34–1.58)
	West Midlands	39,129 (93.9)	2564 (6.1)	1.43 (1.31–1.57)
	Scotland	31,321 (93.5)	2178 (6.5)	1.55 (1.42–1.70)
	North West England	68,346 (93.2)	4973 (6.8)	1.51 (1.39–1.64)
	Wales	17,784 (92.7)	1407 (7.3)	1.81 (1.64–2.00)
	North East England	49,968 (92.4)	4125 (7.6)	1.68 (1.55–1.83)
Age completed full time education (years)	<16	84,320 (89.4)	10,033 (10.6)	1.24 (1.19–1.29)
	16	92,270 (93.9)	6041 (6.1)	1 [Ref]
	17	33,972 (95.1)	1741 (4.9)	0.90 (0.84–0.96)
	18	35,749 (96.1)	1440 (3.9)	0.81 (0.75–0.87)
	>18	38,710 (96.0)	1619 (4.0)	0.80 (0.75–0.86)
	Not known	155,601 (96.9)	4990 (3.1)	0.71 (0.68–0.75)
Deprivation	Lowest quintile	90,127 (96.4)	3353 (3.6)	1 [Ref]
	2	88,996 (95.8)	3899 (4.2)	1.10 (1.04–1.16)
	3	88,556 (95.1)	4563 (4.9)	1.22 (1.16–1.29)
	4	87,765 (94.2)	5420 (5.8)	1.41 (1.34–1.49)
	Highest quintile	84,634 (90.8)	8597 (9.2)	1.75 (1.65–1.84)
	Not known	544 (94.4)	32 (95.6)	1.45 (0.93–2.25)
Average Household Income (£)	Less than 18,000	78,618 (88.9)	9820 (11.1)	1 [Ref]
	18,000 to 30,999	94,514 (94.7)	5322 (5.3)	0.81 (0.78–0.85)
	31,000 to 51,999	100,399 (96.7)	3447 (3.3)	0.69 (0.66–0.73)
	52,000 to 100,000	80,166 (98.0)	1616 (2.0)	0.53 (0.49–0.57)
	>100,000	21,481 (98.9)	240 (1.1)	0.34 (0.29–0.40)
	Not known	65,444 (92.4)	5419 (7.6)	0.89 (0.85–0.93)
Primary Employment	Employed	264,171 (97.1)	7952 (2.9)	1 [Ref]
	Retired	138,296 (92.4)	11,346 (7.6)	1.76 (1.67–1.85)
	Looking after home	12,331 (94.9)	666 (5.1)	1.43 (1.29–1.58)
	Not working due to health	9963 (66.3)	5069 (33.7)	6.62 (6.30–6.94)
	Unemployed	7475 (95.1)	383 (4.9)	1.23 (1.07–1.40)
	Unpaid work	2053 (95.5)	97 (4.5)	1.33 (1.03–1.72)
	Student	1241 (96.2)	49 (3.8)	1.11 (0.77–1.60)
	Not known	5092 (94.4)	302 (5.6)	1.53 (1.31–1.78)

[1] Risk Ratio.
[2] Adjusted for age, gender, ethnicity, region, age completed education, primary employment status, deprivation, and income.

Table 2
Specific opioids reported by participants as being taking regularly?

	Opioid drug/preparation-	N	%
Weak opioids	Combined[1]	17,065	3.7
	Codeine	2304	0.5
	Dihydrocodeine	1617	0.4
	Meptazinol	67	0.0
	Pethidine	24	0.0
	Dextropropoxyphene	1	0.0
Strong opioids	Tramadol	5346	1.2
	Morphine	508	0.1
	Buprenorphine	349	0.1
	Oxycodone	220	0.0
	Fentanyl	233	0.0
	Hydromorphone	7	0.0

[1] Combined = preparations listed in the BNF Sub-paragraph 'Non-Opioid Analgesics and Compound Prep', e.g. co-codamol, co-codaprin, etc.

adjusted for demographic, employment status, education level and economic factors RR 1.43 99%CI (1.39–1.48)). There was little variation by ethnic group except that use of opioids was uncommon amongst persons of Chinese origin (1.7%, adjusted RR 0.45 99% CI (0.27–0.74) in comparison to persons identifying as "white"). There were marked differences between areas of residence, from 2.8% in South-East England to 7.6% in the North-East of England (adjusted RR 1.75 99% CI (1.61–1.91)). The highest rates of reported use were found in persons with low household income (11.1% in those reporting annual household income of less than £18,000), those who left school before 16 years (10.6%) and who lived in areas with the highest levels of deprivation (9.2%). Amongst the 15,032 people who reported that they could not work because of ill-health 33.7% were regularly taking opioids. A total of 6419 persons (1.3%) reported regular use of strong opioids. Use of strong opioids also showed a strong relationship with area of residence, high levels of deprivation, low income and not working due to ill-health (supplementary table).

The most common opioid reported was combined preparations, and thereafter codeine and dihydrocodeine. The most common strong opioids were tramadol then morphine and buprenorphine (Table 2). Of persons reporting taking regular opioids, 23,731 (5.1%) reported using a single opioid, 1976 (0.4%) were taking two opioids and 157 (0.03%) were taking 3 or more.

The vast majority (87.3%) of persons regularly taking opioids reported chronic pain: the likelihood of taking opioids increased with greater number of reported pain sites from 3.8% in those reporting one site up to 30.7% in those who reported 7 sites or "pain all over the body" RR (16.66 99% CI (15.42–17.99)) adjusted for age, gender, demographic factors, socio-economic factors and primary employment (Table 3). When the relationship was examined by the reporting of pain at individual sites, with adjustment as above plus total number of pain sites reported, all individual pain sites, with the exception of facial pain, were associated with an excess risk of regular opioid use (data not shown). The associations shown in Table 1 were not explained when adjusted for pain status (chronic pain and number of pain sites) although some were attenuated, most noticeably female gender (RR 1.23 95% CI (1.19–1.26)) and amongst those living in areas with the highest level of deprivation (RR 1.50 95% CI (1.42–1.58)).

The relationship of opioid use with health, lifestyle factors and life events is detailed in Table 4. After adjustment for potential confounding factors, persons rating their health as "poor" were considerably more likely to regularly take opioids compared to those rating their health as "excellent" (RR 5.44 99% CI (4.89–6.05) as were those reporting only minimal physical activity. Those reporting poor quality sleep (both less and more than the average of 7–8 h, as well as usually suffering from insomnia (RR 1.56 99% CI (1.48–1.64)) and poorer mental health (i.e. reported having consulted a GP for "anxiety, nerves or depression" (RR 1.29 99% CI (1.25–1.34)) were also more likely to report regular opioid use. There was a "dose-risk" relationship between the number of adverse events in last two years and likelihood of using opioids such that those reporting at least four such events were over 50% more likely to be taking opioids regularly (RR 1.55 99% CI (1.36–1.76)).

3.1. The relationship between opioid consumption and mortality

16,432 persons died during follow-up. Of participants who at recruitment were not regularly taking opioids, 3.3% died during follow-up (428 per 100 000 person-years (py)); in comparison 6.9% of those taking weak opioids (892 per 100 000 py) and 9.1% of those taking strong opioids died (1194 per 100 000py) (age and sex adjusted Mortality Risk Ratio (MRR) 1.86, 99% CI (1.73, 2.00) and 2.59 99% CI (2.34, 2.88) respectively) (Table 5). Chronic pain was also related to excess mortality; for example, of persons who at recruitment reported "pain all over their body" or pain at all seven regional sites 6.8% died during follow-up in comparison to 3.2% of persons with no pain (MRR 2.29, 99% CI 2.06, 2.56). In addition, lifestyle factors (physical activity, BMI, diet (including alcohol consumption and cigarette smoking), socio-economic factors (years of education, income and level of deprivation of area of residence) and morbidities were also importantly linked with risk of mortality. When adjustment was made for all these factors, there remained an association between regular opioid use at recruitment and risk of death over the following 6–10 years (MRR weak opioids 1.18 99% CI (1.06, 1.33)), strong opioids (MRR 1.20 99% CI (1.01, 1.43)). Of the deaths which occurred amongst persons using regular opioids 39% were cancer deaths (in comparison to 53% in non-opioid users), 28% were cardiovascular (v. 23%), 11% were respiratory (v. 6%), 18% were other diseases (v. 13%) and 3% were from external causes (v. 4%).

Table 3
Regular use of opioid analgesics in relation to pain reporting.

		Opioid Use No, n (%)	Opioid Use Yes, n (%)	Adjusted RR[1,2] (99% CI)
Chronic pain	*No*	259,318 (98.8)	3271 (1.2)	1 [Reference]
	Yes	179,367 (88.9)	22,460 (11.1)	6.69 (6.38–7.02)
Number of pain sites	*0*	181,619 (99.0)	1797 (1.0)	1 [Reference}
	1	123,042 (96.2)	4925 (3.8)	3.72 (3.47–4.00)
	2	71,910 (92.9)	5468 (7.1)	6.27 (5.85–6.72)
	3	35,369 (87.1)	5225 (12.9)	10.14 (9.46–10.87)
	4	14,521 (81.0)	3396 (19.0)	13.32 (12.38–14.33)
	5	5044 (74.3)	1748 (25.7)	15.84 (14.59–17.20)
	6	1387 (69.7)	604 (30.3)	17.60 (15.81–19.60)
	7 or all over	5793 (69.3)	2568 (30.7)	16.66 (15.42–17.99)

[1] Risk Ratio.
[2] Adjusted for age, gender, ethnicity, region, primary employment, age completed education, deprivation, and income.

Table 4
Regular use of any opioid analgesic in relation to health status.

		Opioid Use No, n (%)	Opioid Use Yes, n(%)	Adjusted RR[1]
Hours of sleep	*4 or less*	4010 (77.5)	1163 (22.5)	1.55 (1.45–1.67)
	5 or 6	101,161 (92.7)	8024 (7.4)	1.23 (1.19–1.27)
	7 or 8	300,512 (95.9)	12,923 (4.1)	1 [Reference]
	9 or 10	30,068 (91.5)	2794 (8.5)	1.21 (1.16–1.28)
	11 or more	1492 (77.7)	428 (22.3)	1.41 (1.27–1.57)
Insomnia	*Never/rarely*	110,911 (97.4)	2926 (2.6)	1 [Reference]
	Sometimes	212,122 (95.5)	10,105 (4.5)	1.21 (1.15–1.27)
	Usually	116,227 (90.1)	12,749 (9.9)	1.56 (1.48–1.64)
Overall activity	*Minimal*	84,354 (91.9)	7407 (8.1)	1 [Reference]
	Low	74,214 (95.7)	3368 (4.3)	0.74 (0.70–0.77)
	Adequate	120,525 (95.3)	5929 (4.7)	0.74 (0.71–0.77)
	High	125,585 (96.3)	4803 (3.7)	0.67 (0.64–0.70)
Overall health rating	*Excellent*	77,541 (99.1)	732 (0.9)	1 [Reference]
	Good	261,428 (96.9)	8327 (3.1)	1.98 (1.80–2.19)
	Fair	84,888 (88.9)	10,598 (11.1)	3.92 (3.54–4.33)
	Poor	13,908 (70.2)	5908 (29.8)	5.44 (4.89–6.05)
Seen doctor for anxiety/ nerves/ depression	*No*	293,787 (96.1)	11,907 (3.9)	1 [Reference]
	Yes	142,478 (91.3)	13,598 (8.7)	1.29 (1.25–1.34)
Adverse events in last 2 years (illness, injury, assault, bereavement, divorce, financial difficulty)	*0*	245,686 (95.8)	10,801 (4.2)	1 [Reference]
	1	139,738 (93.8)	9301 (6.2)	1.16 (1.12–1.20)
	2	39,180 (91.4)	3693 (8.6)	1.26 (1.20–1.31)
	3	7710 (87.0)	1147 (13.0)	1.37 (1.27–1.47)
	4 or more	1201 (80.3)	295 (19.7)	1.55 (1.36–1.76)

[1] Adjusted for age, gender, ethnicity, region, primary employment, age completed education, deprivation, income, any chronic pain, and number of pain sites.

Table 5
Predictors of death during follow-up period.

Recruitment characteristic		Death during follow-up		MRR[1] (99% CI)	MRR[2] (99% CI)
		No: N (%)	*Yes: N (%)*		
Regular Opioid use	*None*	426,534 (96.7%)	14,513 (3.3%)	1 [Reference]	1 [Reference]
	Weak	18,136 (93.1%)	1336 (6.9%)	1.86 (1.73, 2.00)	1.18 (1.06, 1.33)
	Strong	5853 (90.9%)	583 (9.1%)	2.59 (2.34, 2.88)	1.20 (1.01, 1.43)
Chronic Pain	*No*	254,379 (96.8%)	8417 (3.2%)	1 [Reference]	1 [Reference]
	Yes	194,172 (96.1%)	7900 (3.9%)	1.22 (1.17, 1.27)	0.85 (0.78, 0.93)
Number of pain sites	*0*	179,617 (96.8%)	6004 (3.2%)	1 [Reference]	1 [Reference]
	1	123,741 (96.6%)	4334 (3.4%)	1.06 (1.01, 1.11)	1.07 (0.97, 1.17)
	2	74,684 (96.4%)	2794 (3.6%)	1.17 (1.11, 1.24)	1.05 (0.94, 1.17)
	3	38,990 (95.9%)	1665 (4.1%)	1.36 (1.27, 1.46)	1.09 (0.96, 1.25)
	4	17,245 (96.1%)	700 (3.9%)	1.35 (1.23, 1.50)	0.94 (0.79, 1.12)
	5	6517 (95.8%)	286 (4.2%)	1.58 (1.35, 1.83)	0.85 (0.66, 1.09)
	6	1913 (96.0%)	80 (4.0%)	1.65 (1.25, 2.19)	1.07 (0.73, 1.56)
	7 or all over	7803 (93.2%)	567 (6.8%)	2.29 (2.06, 2.56)	1.19 (0.98, 1.45)
Age Category (years)	*40–45*	49,892 (99.2%)	396 (0.8%)	1 [Reference]	1 [Reference]
	45–49	62,760 (98.7%)	796 (1.3%)	1.61 (1.37, 1.88)	1.71 (1.33, 2.20)
	50–54	70,924 (98.1%)	1361 (1.9%)	2.43 (2.10, 2.81)	2.33 (1.84, 2.95)
	55–59	82,301 (97.1%)	2464 (2.9%)	3.73 (3.25, 4.28)	3.41 (2.72, 4.28)
	60–64	105,927 (95.6%)	4905 (4.4%)	5.63 (4.92, 6.43)	4.64 (3.72, 5.80)
	65–69	78,706 (92.4%)	6508 (7.6%)	9.50 (8.32, 10.85)	6.89 (5.51, 8.62)
Gender	*Male*	206,662 (95.2%)	10,364 (4.8%)	1 [Reference]	1 [Reference]
	Female	243,848 (97.6%)	6066 (2.4%)	0.53 (0.51, 0.55)	0.51 (0.48, 0.55)
Body Mass Index (kgm^{-2})	*Underweight (< 18.5)*	2208 (93.0%)	166 (7.0%)	2.83 (2.34, 3.43)	1.76 (1.31, 2.38)
	Normal (18.5–24.9)	146,451 (97.1%)	4308 (2.9%)	1 [Reference]	1 [Reference]
	Overweight (25.0–29.9)	190,832 (96.6%)	6674 (3.4%)	0.96 (0.91, 1.01)	0.87 (0.81, 0.94)
	Obese (30.0–34.9)	77,950 (95.9%)	3302 (4.1%)	1.17 (1.10, 1.24)	0.94 (0.86, 1.02)
	Obese (35.0–39.9)	22,033 (95.2%)	1116 (4.8%)	1.55 (1.42, 1.68)	1.05 (0.93, 1.20)
	Obese (≥40)	11,036 (92.7%)	864 (7.3%)	2.56 (2.34, 2.81)	1.45 (1.24, 1.69)
Physical Activity (walking: mins/week)	0	9251 (93.7%)	622 (6.3%)	1.90 (1.71, 2.11)	1.22 (1.05, 1.40)
	1–100	101,757 (96.6%)	3594 (3.4%)	1 [Reference]	1 [Reference]
	101–210	115,233 (96.7%)	3939 (3.3%)	0.91 (0.86, 0.96)	0.97 (0.89, 1.05)
	211–420	90,340 (96.8%)	2983 (3.2%)	0.87 (0.82, 0.93)	0.92 (0.84, 1.01)
	>420	75,450 (96.8%)	2502 (3.2%)	0.90 (0.84, 0.96)	0.87 (0.79, 0.96)
Moderate Physical Activity (mins/week)	0	54,253 (95.3%)	2691 (4.7%)	1.58 (1.47, 1.69)	1.11 (1.005, 1.23)
	1–60	93,837 (97.1%)	2787 (2.9%)	1 [Reference]	1 [Reference]
	61–150	79,046 (97.0%)	2446 (3.0%)	0.98 (0.91, 1.05)	0.98 (0.89, 1.09)
	151–360	79,792 (96.9%)	2564 (3.1%)	0.95 (0.88, 1.01)	1.01 (0.91, 1.11)
	>360	79,205 (96.5%)	2908 (3.5%)	0.99 (0.93, 1.06)	1.06 (0.95, 1.17)
Vigorous Physical Activity (mins/week)	0	158,097 (95.6%)	7323 (4.4%)	1 [Reference]	1 [Reference]
	1–40	71,056 (91.2%)	2053 (2.8%)	0.65 (0.61, 0.69)	0.87 (0.79, 0.95)
	41–90	62,605 (97.4%)	1689 (2.6%)	0.64 (0.60, 0.69)	0.88 (0.79, 0.97)
	91–180	57,870 (97.5%)	1536 (2.5%)	0.63 (0.59, 0.68)	0.85 (0.76, 0.95)

(*continued*)

Table 5 (*Continued*)

Recruitment characteristic		Death during follow-up		MRR[1] (99% CI)	MRR[2] (99% CI)
	>180	51,434 (97.2%)	1486 (2.8%)	0.65 (0.60, 0.69)	0.84 (0.75, 0.93)
Physical activity (stairs times/day)	0	38,711 (94.1%)	2425 (5.9%)	1.12 (1.05, 1.20)	1.02 (0.93, 1.11)
	1–5	89,429 (95.7%)	3984 (4.3%)	1 [Reference]	1 [Reference]
	6–10	161,615 (96.9%)	5114 (3.1%)	0.71 (0.67, 0.75)	0.85 (0.79, 0.92)
	11–15	82,692 (97.3%)	2301 (2.7%)	0.63 (0.59, 0.68)	0.82 (0.75, 0.91)
	16–20	38,451 (97.3%)	1058 (2.7%)	0.63 (0.57, 0.68)	0.80 (0.70, 0.92)
	>20	31,363 (97.3%)	876 (2.7%)	0.68 (0.62, 0.75)	0.81 (0.69, 0.94)
Diet (Fruit and Vegetable Consumption)	*Lowest consumption*	101,510 (95.9%)	4393 (4.1%)	1 [Reference]	1 [Reference]
	Quintile 2	91,076 (96.7%)	3119 (3.3%)	0.77 (0.73, 0.82)	0.91 (0.84, 0.99)
	Quintile 3	40,106 (96.8%)	1343 (3.2%)	0.75 (0.69, 0.81)	0.92 (0.82, 1.02)
	Quintile 4	80,665 (96.8%)	2641 (3.2%)	0.73 (0.68, 0.77)	0.91 (0.83, 0.99)
Alcohol Consumption	*Highest Consumption*	64,907 (96.7%)	2205 (3.3%)	0.75 (0.70, 0.80)	0.90 (0.82, 0.99)
	(almost) daily	90,705 (95.9%)	3843 (4.1%)	1 [Reference]	1 [Reference]
	3–4 times/week	104,889 (97.1%)	3127 (2.9%)	0.82 (0.78, 0.88)	0.90 (0.82, 0.98)
	1–2 times/week	116,686 (96.9%)	3715 (3.1%)	0.94 (0.89, 0.99)	0.91 (0.83, 0.99)
	<1 time/week	101,408 (96.5%)	3698 (3.5%)	1.15 (1.08, 1.22)	0.95 (0.86, 1.04)
	Never	35,463 (94.7%)	1966 (5.3%)	1.59 (1.48, 1.70)	1.23 (1.10, 1.37)
Cigarette Smoking	*Current smoker*	45,818 (92.8%)	3546 (7.2%)	3.12 (2.96, 3.29)	2.44 (2.24, 2.65)
	Ex-regular	101,104 (95.1%)	5253 (4.9%)	1.59 (1.51, 1.66)	1.46 (1.35, 1.57)
	Ex-occasional	51,343 (97.1%)	1536 (2.9%)	1.09 (1.02, 1.17)	1.14 (1.02, 1.27)
	Never	249,750 (97.7%)	5942 (2.3%)	1 [Reference]	1 [Reference]
Morbidity count[3]	*0*	120,558 (98.0%)	2416 (2.0%)	1 [Reference]	1 [Reference]
	1	122,894 (97.4%)	3285 (2.6%)	1.15 (1.07, 1.23)	1.07 (0.97, 1.19)
	2	88,310 (96.4%)	3299 (3.6%)	1.40 (1.31, 1.50)	1.22 (1.10, 1.36)
	3	54,451 (95.2%)	2743 (4.8%)	1.72 (1.60, 1.85)	1.47 (1.32, 1.64)
	4	30,396 (94.4%)	1819 (5.4%)	1.93 (1.78, 2.09)	1.51 (1.34, 1.71)
	5	16,020 (93.2%)	1169 (6.8%)	2.27 (2.08, 2.49)	1.65 (1.43, 1.90)
	6	8481 (82.6%)	680 (7.4%)	2.49 (2.23, 2.78)	1.70 (1.43, 2.01)
	7	4437 (91.3%)	421 (8.7%)	2.91 (2.56, 3.32)	1.83 (1.49, 2.25)
	8	2257 (90.6%)	233 (9.4%)	3.15 (2.67, 3.73)	2.22 (1.74, 2.84)
	9	1259 (89.9%)	142 (10.1%)	3.63 (2.94, 4.48)	2.59 (1.92, 3.49)
	>=10	1147 (86.6%)	223 (13.4%)	4.77 (4.04, 5.63)	2.95 (2.27, 3.82)
Age completed full time education (years)	*<16*	88,210 (93.8%)	5824 (6.2%)	1 [Reference]	1 [Reference]
	16	95,204 (96.8%)	3202 (3.3%)	0.78 (0.74, 0.83)	0.93 (0.86, 0.999)
	17	34,717 (97.1%)	1030 (2.9%)	0.69 (0.63, 0.75)	0.88 (0.78, 0.98)
	18	36,264 (97.4%)	953 (2.6%)	0.67 (0.62, 0.74)	0.95 (0.84, 1.06)
	>18	39,102 (96.9%)	1264 (3.1%)	0.70 (0.65, 0.76)	1.02 (0.92, 1.13)
Average household income (£)	*Less than 18,000*	83,059 (93.8%)	5480 (6.2%)	1 [Reference]	1 [Reference]
	18,000 to 30,999	96,144 (96.2%)	3788 (3.8%)	0.66 (0.62, 0.69)	0.85 (0.79, 0.92)
	31,000 to 51,999	101,608 (97.8%)	2339 (2.3%)	0.47 (0.44, 0.51)	0.68 (0.61, 0.75)
	52,000 to 100,000	80,513 (98.4%)	1334 (1.6%)	0.39 (0.36, 0.43)	0.61 (0.53, 0.70)
	>100,000	21,443 (98.7%)	293 (1.4%)	0.33 (0.29, 0.39)	0.51 (0.37, 0.71)
	Do not know	18,475 (94.8%)	1011 (5.2%)	1.02 (0.94, 1.11)	1.03 (0.89, 1.19)
	Prefer not to answer	44,092 (96.2%)	1752 (3.8%)	0.69 (0.64, 0.74)	0.79 (0.70, 0.88)
Deprivation	*Lowest quintile*	90,849 (97.1%)	2727 (2.9%)	1 [Reference]	1 [Reference]
	2	90,161 (97.0%)	2826 (3.0%)	1.04 (0.97, 1.12)	0.93 (0.84, 1.03)
	3	90,242 (96.8%)	2962 (3.2%)	1.12 (1.05, 1.20)	1.00 (0.91, 1.11)
	4	89,972 (96.5%)	3302 (3.5%)	1.32 (1.24, 1.41)	1.08 (0.98, 1.19)
	Highest quintile	88,726 (95.1%)	4596 (4.9%)	1.92 (1.81, 2.04)	1.22 (1.11, 1.35)
Seen doctor for anxiety/ nerves/depression	*No*	295,416 (96.6%)	10,519 (3.4%)	1 [Reference]	1 [Reference]
	Yes	150,588 (96.4%)	5695 (3.6%)	1.26 (1.21, 1.31)	0.98 (0.92, 1.04)

[1] Mortality Risk Ratio adjusted for age and gender.
[2] Fully adjusted mortality risk ratio – i.e. adjusted for all factors in table.
[3] Self-reported illness (non-cancer) at baseline.

4. Discussion

Regular use of opioids in UK Biobank participants was very strongly related to socio-economic factors: around 1 in 10 people with the lowest level of incomes, those living in areas with the highest levels of deprivation and who left education at a young age, reported regular opioid use, while this rose to 1 in 3 of persons reporting that they were unable to work due to ill-health. After adjusting for pain status and socio-economic factors, regularly taking opioids was associated with poorer physical and mental health and quality of life (such as sleep quality) and was associated with increased risk of death, even after additionally taking into account lifestyle factors and other morbidities. The increased risk of death was not primarily as a result of non-disease deaths.

UK Biobank is a very large study, but the proportion of people invited, who agreed to take part was low (just over 5%). There is evidence that those taking part are healthier than the general population: specifically they are less likely to be obese, to smoke, and to drink alcohol on a daily basis and they have fewer self-reported health conditions. Rates of all-cause mortality have been shown at age 70–74 years to be 46% and 56% lower in men and women, respectively than the wider population [21]. The valid assessment, however, of an exposure outcome relationship does not rely on the population being representative of the underlying population aged 40–69 years who were eligible to take part. Thus our estimate of the use of opioids in Great Britain, although high, is likely to be an underestimate. We have, however, previously compared the prevalence of chronic pain in UK Biobank with other epidemiological studies which measured chronic pain, and shown, for example, that the estimates of prevalence of chronic pain and regional pain using UK Biobank were within 2% of the National Child Development Study [22]. The second methodological issue in examining factors associated with the use of opioids is the strong relationship with

their use in chronic pain. We do not think that regular opioid use is a cause of chronic pain and so we have adjusted for the presence of chronic pain and the number of pain sites. However, we do not have a measure of the severity of chronic pain and therefore there may be residual confounding e.g. if more severe pain was linked to greater interference with sleep and a greater likelihood of opioid use. There is also limited information on opioids in this study. We are not aware of the dose of opioids or for how long they have been used at the time of recruitment, nor of changes over follow-up; neither is information available on non-prescription ("over the counter") opioid use. Thus, for example, we cannot examine whether the relationship with poor physical and mental health, for example, is related to dose.

The factors associated with regular opioid use in this study (after adjustment for pain status) namely depression, anxiety and insomnia are recognised adverse effects of opioid use [23]. The results, in relation to mortality, do not necessarily mean that opioids themselves are leading to an increased risk of death. There could be unmeasured confounders of the relationship – if so, these factors need to be relatively common, be related to opioid use and be risk factors for premature death. Specifically, there could be confounding by indication, namely that persons are receiving opioids for unmeasured aspects of their clinical condition which are themselves related to an increased risk of death. Such a scenario may explain some or all of the association observed. The association of opioid use and misuse with premature death is well-documented, although that typically has been related to non-disease related deaths (e.g. Reference [24]). Non-disease related deaths were relatively uncommon in this analysis and not responsible for the excess mortality. Long term opioid use has been shown to relate to an increased risk of death by a number of potential mechanisms including the very common finding of disruption of nocturnal respiratory control leading to both respiratory and cardiovascular morbidity [25,26]. Studies of opioids and cancer have primarily focussed on the use of opioids during cancer surgery and subsequent survival. Two studies have reported a higher recurrence rate of breast and prostate cancers [27,28] although the only study of opioid use after surgery found no increased risk of recurrence in breast cancer patients [29]. A recent study of approximately 90 000 persons, using electronic records within UK general practice, has however linked the initial prescription of tramadol, in patients over 50 years with osteoarthritis, to higher mortality rates over the subsequent year (hazard ratio 1.71 95% CI (1.41,2.07) v. patients receiving nonsteroidal anti-inflammatory drugs) [30].

We have previously published data from Scotland, using record linkage, which demonstrated a sizeable increase in the prescriptions for opioids across the ten-year period from 2003 [31]. This study showed that 18% of the population in Scotland had been prescribed an opioid in the past year, much higher than the proportion reported in the current study (in which 6.5% persons from Scotland reported regular opioid use). There are likely to be at least three reasons for the discrepancy: the current study is based on "regular use of medication" while the previous study was based on a record of at least one prescription; the selection effects in participating; and that we have excluded persons with a cancer diagnosis in this analysis. The large variations in regular use of opioids across GB in this study, replicate a recent study from England [32] which found that high prescribing was related to deprivation, large primary care list size and rurality. A further study, from one area of Scotland, which analysed prescribing of analgesics between 1995–2010 also found that persons living in deprived areas (as well as those receiving large numbers of non- analgesic drugs) were most likely to be prescribed a strong opioid [33].

It is no surprise that users of opioids are likely to report chronic pain: we assume this is the reason for opioid use. However the data show high levels of continuing poor health among those using opioids including inability to work, poor physical and mental health, quality of life and poor sleep These findings accord with previous findings from a large epidemiological study in Denmark which noted that "*opioid treatment of long-term/chronic non-cancer pain does not seem to fulfil any of the key outcome opioid treatment goals*" [34].

Much evidence on the so-called "opioid epidemic" has come from the United States where the Center for Disease Control (CDC) has developed a guideline to improve the way opioids are prescribed to "ensure patients have access to safer, more effective chronic pain treatment while reducing the number of people who misuse or overdose from these drugs" [35] and the Scottish Intercollegiate Guidelines Network (SIGN) have recently revised their guideline on managing chronic pain in order to update recommendations on opioids [12]. The latter suggest early review of patients newly prescribed opioid medication and at least annual review thereafter. This manuscript has demonstrated high levels of regular opioid use amongst people in the UK, particularly those in lower socio-economic groups. Amongst users, chronic pain is still common, and a large proportion report poor physical and mental health, while the majority report sleep problems. This study adds to current evidence in showing that regular users also experience an increased risk of death (but not primarily as a result of non-disease deaths). It emphasises the need to take into account such potential harms and lack of benefit of regular opioid use in considering the long-term management of patients with pain.

5. Contributor and guarantor information

CS and GJM had the idea for the study which was planned by all authors. MB and GTJ undertook the analysis. GJM led the drafting of the manuscript to which all authors contributed and all critically reviewed drafts and revisions. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. GJM, GTJ and MB had access to all the data in the study and all authors made the decision to submit.

6. Data sharing agreement

On acceptance of a manuscript using UK Biobank data, the authors are required to submit the dataset (including any derived variables) and the analysis programs to UK Biobank. Data are available to researchers by application.

Declaration of Competing Interest

The authors have no relevant interests to declare.

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Supplementary materials

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