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The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study

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ABSTRACT

Aims To estimate the prevalence and burden of disease attributable to opioid dependence globally, regionally and at country level. **Methods** Multiple search strategies: (i) peer-reviewed literature searches; (ii) systematic searches of online databases; (iii) internet searches; (iv) consultation and feedback from experts. Culling and data extraction followed protocols. DisMod-MR, the latest version of the generic disease modelling system, a Bayesian meta-regression tool, imputed prevalence by age, year and sex for 187 countries and 21 regions. Disability weight for opioid dependence was estimated through population surveys and multiplied by prevalence data to calculate the years of life lived with disability (YLDs). Opioid dependence premature mortality was computed as years of life lost (YLLs) and summed with YLDs to calculate disability-adjusted life years (DALYs). **Results** There were 15.5 million opioid-dependent people globally in 2010 [0.22%, 95% uncertainty interval (UI) = 0.20–0.25%]. Age-standardized prevalence was higher in males (0.30%, 95% UI = 0.27–0.35%) than females (0.14%, 95% UI = 0.12–0.16%), and peaked at 25–29 years. Prevalence was higher than the global pooled prevalence in Australasia (0.46%, 95% UI = 0.41–0.53%), western Europe (0.35%, 95% UI = 0.32–0.39) and North America (0.30%, 95% UI = 0.25–0.36). Opioid dependence was estimated to account for 9.2 million DALYs globally (0.37% of global DALYs) in 2010, a 73% increase on DALYs estimated in 1990. Regions with the highest opioid dependence DALY rates were North America (292.1 per 100 000), eastern Europe (288.4 per 100 000), Australasia (278.6 per 100 000) and southern sub-Saharan Africa (263.5 per 100 000). The contribution of YLLs to opioid dependence burden was particularly high in North America, eastern Europe and southern sub-Saharan Africa. **Conclusion** Opioid dependence is a substantial contributor to the global disease burden; its contribution to premature mortality (relative to prevalence) varies geographically, with North America, eastern Europe and southern sub-Saharan Africa most strongly affected.

Keywords Burden, DALYs, dependence, epidemiology, heroin, mortality, opioids, years of life lived with disability, years of life lost.

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INTRODUCTION

Opioid dependence is a chronic condition. Studies in high-income countries have suggested that dependent opioid users continue to use opioids despite the significant social and health problems that it causes them, such as being arrested and imprisoned for drug or property crimes, exposure to blood-borne viruses and infectious diseases and fatal and non-fatal opioid overdose. Research in Europe and the United States indicates that dependent heroin users, who seek treatment or come to attention through the legal system, may continue to use heroin for decades [1–4]. In this population, daily heroin use is punctuated by periods of abstinence, drug treat-

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ment and imprisonment [5]. In the year after completing a given episode of drug treatment, many users relapse to heroin use [6].

There has never been a systematic review of global-, regional- and country-level patterns of opioid dependence and associated disease burden. Such information is crucial to inform policy and programming efforts to prevent and treat this disorder.

The global burden of disease (GBD) framework was initiated by the World Bank World Development Report of 1993 [7], and uses information on mortality and disability associated with a given disease to estimate the years of life lost due to premature mortality (YLLs) and the years of life lived with disability (YLDs). YLLs and YLDs can be summed to produce disability-adjusted life years (DALYs), a summary measure of overall disease burden. Previous GBD studies (GBD 1990 and updates between 2000 and 2005) significantly enhanced the global awareness of mental and drug use disorders [8–10]. However, previous GBD estimates produced an overall estimate of burden for drug use disorders without separate estimates for specific drug types. For GBD 1990, drug use disorder was defined as 'dysfunctional and harmful drug use' [8] and in 2000 as 'opioid dependence and harmful use and cocaine dependence' [9]. Opioid dependence was never estimated separately.

In GBD 2010 the burden estimation methodology was completely revised. It estimated the burden of 291 diseases and 67 risk factors, by age, sex, 187 countries and 21 world regions, for 1990, 2005 and 2010. Rather than selecting a range of plausible epidemiological estimates to calculate disease burden, GBD 2010 conducted systematic reviews of the literature to capture all available data on opioid dependence from 1990 onwards. Other methodological improvements included a Bayesian meta-regression approach to modelling the epidemiological data, which assisted in propagating uncertainty around final burden estimates; the quantification of disability for a more comprehensive list of health states using more representative survey data; and adjusting burden estimates for comorbidity [11,12].

This paper follows our systematic reviews of the epidemiology of opioid dependence [13–16] and the top-line GBD 2010 project publications [11,12,17–19]. In this paper we expand upon our previous reports by conducting the first in-depth investigation into the global burden of opioid dependence specifically as follows.

1 Detail the methodology used to estimate disease burden for this disorder.
2 Assemble data on the incidence, prevalence, remission and excess mortality of opioid dependence into a comprehensive disease model which adjusts for known sources of variability between studies.
3 Estimate fatal and nonfatal health loss due to opioid dependence.
4 Investigate country-, region-, age-, sex- and year-specific trends in the burden of opioid dependence.

METHODS

Case definition

We used the definition of opioid dependence included in the Diagnostic and Statistical Manual of mental disorders (DSM) [20] and the International Classification of Diseases (ICD) [21] diagnostic criteria for opioid dependence (DSM: 304.00; ICD: F11.2).

Systematic reviews

Systematic searches were conducted to identify data sources for the prevalence and incidence, remission of opioid dependence and excess all-cause mortality of people who are opioid-dependent. The search strategy adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22] and used the methodology recommended by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group [23]. Further details on these searches can be found in [13–16].

All extraction and quality assurance procedures were as recommended by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [24]. Studies were excluded if they did not contain primary data (e.g. review papers) or contained only data collected before 1990. Estimates were extracted for annual incidence, current (including past-month) prevalence and period (past year, life-time) prevalence [7,15]. Remission from opioid dependence was defined as no longer fulfilling the diagnostic criteria for the disorder. Studies on remission and mortality were included only if a follow-up of 3 or more years was reported [13].

Data points for opioid use or dependence were available from 91 countries, which accounted for 83.0% of the world's population aged 15–64 years. Our systematic reviews identified 195 dependence prevalence data points from 31 studies in 29 countries covering nine GBD world regions (161 data points were from studies using indirect prevalence estimate methods (34 data points were from direct methods); 79 data points of dependence excess mortality from 49 studies in 18 countries and six GBD world regions; and 10 dependence remission data points from 10 studies from eight countries and six GBD world regions [13–16]. The geographic distribution of these data points is shown in the Supporting information, Fig. S1. Full details of the reviews generating these data have been published elsewhere [13–16].

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Disability weights

To calculate disability weights, a lay-person description for opioid dependence was formulated by the Expert Group for inclusion in the 2010 GBD Health Measurement Survey [19]. This survey included lay descriptions to reflect the 291 diseases in GBD 2010. The survey was completed by community samples in five countries (Bangladesh, Indonesia, Peru, the United Republic of Tanzania and the United States) and an open-access online survey. In both a pairwise comparison method was used to arrive at a level of disability for each GBD health state [25]. Full details have been reported elsewhere [12,19].

In keeping with GBD 2010, survey data were used to combine epidemiological information on disorder severity with disability weights to estimate the proportion of cases who did not have disability associated with their disorder. GBD 2010 made use of survey data to adjust each disability weight for severity. For opioid dependence, these data came from the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) [26], which used the Short Form 12-item survey (SF-12) [27] to capture disability attributable to 20 diseases. First, a convenience sample of 2202 participants from the GBD Health Measurement Survey were asked to fill in the SF-12 to match the lay descriptions of 62 health states of diverse severity.

These data were then used to derive a mathematical relationship between SF-12 scores from NESARC and a GBD 2010 disability weight from the GBD Health Measurement Survey [19]. NESARC participants were each allocated their corresponding GBD 2010 disability weight. Secondly, regression methods were used to calculate average disability weights for each NESARC condition, while adjusting for any other comorbid condition. Similar to other diseases in GBD 2010, a proportion of NESARC participants diagnosed with opioid dependence were rated as having no disability (i.e. a disability weight of 0) at the time of the survey, once the disability attributable to comorbidities had been portioned out. Full details of this process have been reported elsewhere [11,12].

Briefly, a general comorbidity correction was applied to all estimates of YLD using microsimulation methods to create hypothetical populations for each age group, by gender, year and country. The probabilities of having no, one or more non-fatal health states simultaneously were based on the prevalence estimates for each health state. Analyses indicated that independent comorbidity (assuming no correlation) was far more decisive in predicting levels of comorbid disability than dependent comorbidity. For pragmatic reasons, i.e. the difficulty in finding information on all potential correlations and the large additional computational burden, we decided to take only independent comorbidity into account. For each hypothetical person in the microsimulation a combined disability weight was calculated between any comorbid health states using a multiplicative function and then re-apportioned to each health state proportional to the sum of comorbid disability weights. The average 'corrected' disability for each health state was calculated in each age, sex, year and country stratum and the decrement compared to the original disability weight taken as the comorbidity correction for YLD. Further details are reported in full elsewhere [11,12].

The disability weight for opioid dependence was estimated to be 0.50 (0.33–0.69) after adjusting for an estimated 16% (11–22%) of opioid dependence cases who had no disability, and accounting for disability attributable to comorbid disorders.

Statistical analyses

Prevalence models

We integrated these epidemiological estimates into a disease model capturing age and sex patterns for the disease, differences between regions and changes in disorder occurrence over time that was assessed by the GBD 2010 Expert Group and additional experts in the area of opioid dependence epidemiology. For this task we used DisMod-MR [12,28], the latest version of an incidence–prevalence–mortality (IPM) mathematical model [29], re-designed as a Bayesian meta-regression tool for GBD 2010. The IPM model was used together with a negative-binomial rate model to enforce internal consistency between estimates of prevalence, incidence, remission and excess-mortality.

We preferred 'indirect' estimates of the prevalence of opioid dependence to 'direct' estimates from surveys [30]. These methods use different sources of data to indirectly estimate the total number of drug users [31]. A simple example of one of these is the multiplier method. This involves multiplying, for example, (i) the number of opioid-dependent people who receive drug treatment in a year (an indicator) by (ii) an estimate of the proportion of opioid-dependent people who receive treatment in a year (the multiplier) to estimate the total size of the drug-using population. Examples of other indirect methods include capture–recapture and back-projection estimates [31].

In the absence of high-quality epidemiological estimates, we predicted estimates rather than excluding regions with no available data [12,28]. Covariates that were included in the model include method of estimation (indirect prevalence estimate versus household survey; a variable indicating whether the estimate was national or subnational; and sex. Values for incidence and prevalence were set to zero before age 15 to best fit the raw data. A

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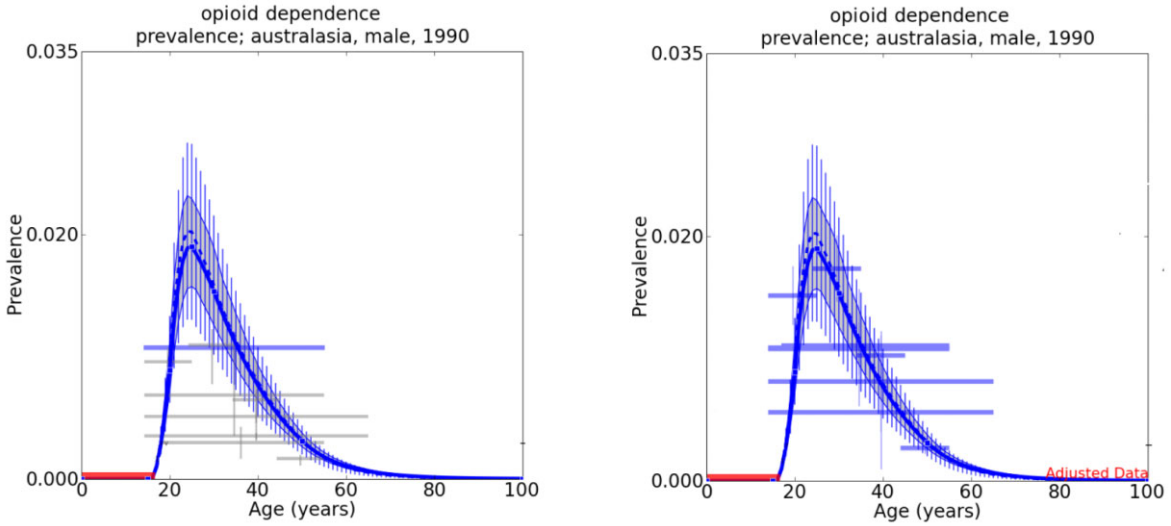

Figure 1 Prevalence before and after covariate adjustment for males from Australasia, 1990

lower and upper limit of 0.05 to 0.3, respectively, was placed on remission consistent with limits in the data set [13].

An example of the estimated distribution of prevalence before and after adjustments made by covariates in DisMod-MR modelling is shown in Fig. 1. Figure 1 compares the DisMod-MR input prevalence estimates to the final DisMod MR output for males in 1990 from Australasia, a region for which we had a considerable amount of data available. The solid red line indicates the specified minimum age of onset of 15 years; the blue crosses represent the individual prevalence data points; the solid blue line shows the final pooled prevalence output. In Fig. S2 (Supporting information), the data points (blue crosses) are shown in the left plots before they were adjusted by covariates. Note that the grey crosses represent 'persons' estimates (i.e. estimates that were not gender-specific). Figure S2 (Supporting information) on the right plots them after they were adjusted, i.e. the difference between the two figures represents the adjustment made by the covariate.

Calculation of YLDs, YLLs and DALYs

GBD 2010 estimated 'prevalent' YLDs by multiplying prevalence estimates (i.e. DisMod-MR prevalence output) by the disability weight. DisMod-MR prevalence estimates and burden estimates were stratified by sex, age, 187 countries, 21 regions (see http://www.globalburden.com.au/docs/Regions.pdf and Supporting information for details) and years 1990, 2005 and 2010.

Premature mortality due to opioid dependence was computed as years of life lost (YLLs) based on cause of death estimates from 1980 to 2010 for 20 age groups, both sexes and 187 countries (for full details see [18]). Mortality was modelled explicitly for opioid dependence using the package CODEm [32]. Because opioid death is a relatively rare event and many death reporting systems do not report opioid-specific drug-related deaths, the parent cause of drug use disorders was first modelled using the package CODEm [32]. Where data were sparse or missing, the model of drug use disorder deaths was informed by indicators of use or production, such as opium production, and by risk factors that would make death due to overdose more likely, such as high blood pressure. Deaths were then allocated to specific drug use categories using fixed proportions. The proportion of all drug use deaths that were due to opioid use was computed everywhere where information on death due to a range of specific drugs was available. These proportions were fixed over age and sex but allowed to vary by region and time; 1628 years of data from 113 countries covering 17 regions were used to compute these proportions.

Burden time trends were explored by breaking down the change in DALYs between 1990 and 2010 into changes attributable to population growth, changing population age and sex structure, and changing opioid dependence prevalence. We calculated opioid dependence DALYs in 2010 based on two scenarios: if population growth increased to where it was in 2010 while the population age/sex structure and YLD rates remained at the 1990 levels; and if the age/sex-population structure was as in 2010 while the YLD rates were kept at the 1990 levels.

Where we report comparisons of prevalence and DALYs by country or region, we use age-standardized values using direct standardization to the global standard population proposed by the World Health Organization (WHO) in 2001 (http://www.who.int/healthinfo/paper31.pdf).

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RESULTS

Prevalence of opioid dependence

Globally, there were an estimated 10.4 million people who were opioid-dependent aged 15 years and older in 1990 (pooled point prevalence of 0.20% [95% uncertainty interval (UI) = 0.18–0.23%] and 15.5 million people in 2010 (0.22%, 95% UI = 0.20–0.25%; Table 1). The largest absolute numbers of opioid-dependent people in 2010 were estimated to be in South Asia (4.3 million people), East Asia (2.2 million), North Africa and the Middle East (1.37 million) and western Europe (1.32 million).

Figure 2 plots the point prevalence in 2010 by region (see also Table 1). Three high-income regions had a statistically significantly higher pooled prevalence than the global pooled prevalence: Australasia 0.46% (95% UI = 0.41–0.53%), western Europe 0.35% (95% UI = 0.32–0.39%) and North America 0.30% (95% UI = 0.25–0.36). In contrast, two sub-Saharan African (SSA) regions and South East (SE) Asia had statistically significantly lower pooled prevalence estimates: SSA East 0.15% (95% UI = 0.12–0.19%), SSA West 0.15% (95% UI = 0.11–0.20%) and SE Asia 0.15% (0.11–0.20%).

Countries with among the highest estimated prevalence included the United Kingdom (0.48%, 95% UI = 0.40–0.57%), Australia (0.46%, 95% UI = 0.42–0.49%), a number of western European countries such as Spain, Italy and Ireland and a number of countries in North Africa/Middle East (for country-level data see Supporting information, Table S2). The wide confidence intervals around many regional and country-level prevalence estimates indicates that there was considerable uncertainty around many of the estimates, and not all variation between regions was statistically significant.

The prevalence of opioid dependence was higher among males (0.30%, 95% UI = 0.27–0.35%) than among females (0.14%, 95% UI = 0.12–0.16%), with a male: female sex ratio of 2.5 (95% UI = 2.0–3.2). Prevalence peaked at age 25–29 years at between 0.5% (95% UI = 0.2–1.1%) and 1.9% (95% UI = 1.6–2.4%) among males across regions, and between 0.3% (95% UI = 0.2–0.4%) and 0.7% (95% UI = 0.6–0.9%) in females. The ratio of male to female prevalence was greatest in the high-income regions of western Europe (2.6), North America (2.5) and Australasia (2.5) and lowest in East Asia (1.8). Prevalence decreased steadily after the age of 30 years. The regional variation in prevalence is summarized further in Table 1.

Burden of opioid dependence

The estimated disease burden of opioid dependence increased by 73% from 0.21% (95% CI = 0.15–0.27) of global DALYs in 1990 to 0.37% (95% CI = 0.28–0.46) in 2010. An estimated 42% increase was due to increased global prevalence between 1990 and 2010 and to 4% due to population ageing and 28% to population growth).

The remainder of the Results section focuses on 2010 data. A total of 9.2 million DALYs were attributable to opioid dependence in 2010 (Table 2). Seven million of these DALYs occurred as a result of YLD, accounting for 43.7% of YLDs attributed to illicit drug use disorders overall and 0.94% of all YLDs globally. A further 2.0 million years of life were lost due to opioid dependence.

Figure 3 presents global DALYs attributable to opioid dependence by age and sex. The sex ratio and peak in the mid- to late 20s in DALYs paralleled trends in estimated prevalence. European regions were estimated to have comparatively higher rates among males (DALY rates approximately three times that of females) and East Asia the lowest (males 1.7 times that of females, Table 2). In all regions (with the exception of Asia East), a larger proportion of deaths due to opioid dependence occurred in males than females. Mortality rates were nearly five times higher among males than females in western Europe and SE Asia (data not shown in detail).

Table 3 presents regional age-standardized DALY estimates per 100 000 population; YLL and YLD rates are also presented in Table 3. The highest rates were in North America (292.1 per 100 000), eastern Europe (288.4 per 100 000), Australasia (278.6 per 100 000) and southern SSA (263.5 per 100 000). The latter was largely driven by higher DALY rates in South Africa (see Supporting information, Table S2 for country-level details). Among the countries with the highest estimated standardized DALY rates were Norway, Estonia, the United Kingdom, the United States, the Russian Federation and Australia. It should be noted that variations in age-standardized DALY rates should be interpreted with caution because of the considerable uncertainty in estimates, particularly at country-level (Supporting information, Table S2). At a crude level, the geographic distribution of crude DALYs was concentrated in Asian (41%) and European regions (15%). North America, high-income (Canada and the United States) accounted for a further 10% of global opioid dependence DALYs.

There was also geographic variation in the contribution of years lived with disability versus years of life lost due to opioid dependence (Fig. 4, Table 3). In the vast majority of regions, burden was due mainly to years lived with disability, but in North America, eastern Europe and southern SSA there was substantial burden due to years of life lost (greater than 50% of DALYs attributable to YLLs; Table 3).

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Table 1 Estimated age-standardized prevalence (%) and number of people who were opioid-dependent in 2010 (with comparison for 1990 for total estimates), by sex and global burden of disease (GBD) region.

	FEMALES			*MALES*			*TOTAL*					
	2010			*2010*			*1990*			*2010*		
	n	*%*	*95% UI*	*n*	*%*	*95% UI*	*n*	*%*	*95% UI*	*n*	*%*	*95% UI*
Asia Pacific high-income	147 000	0.19	(0.10–0.34)	308 500	0.37	(0.19–0.66)	436 000	0.26	(0.16–0.40)	456 000	0.28	(0.17–0.44)
Asia Central	62 000	0.15	(0.10–0.21)	146 500	0.34	(0.23–0.51)	137 000	0.21	(0.15–0.27)	209 000	0.24	(0.18–0.33)
Asia East	746 000	0.1	(0.04–0.22)	1 434 000	0.18	(0.08–0.36)	1 843 000	0.14	(0.08–0.25)	2 180 000	0.14	(0.08–0.24)
Asia South	1 291 500	0.16	(0.13–0.20)	3 039 500	0.36	(0.28–0.44)	2 698 000	0.25	(0.21–0.30)	4 331 000	0.26	(0.22–0.31)
Asia South East	282 500	0.09	(0.06–0.13)	673 500	0.21	(0.14–0.31)	579 000	0.13	(0.10–0.18)	956 000	0.15	(0.11–0.20)
Australasia	30 500	0.25	(0.22–0.31)	79 500	0.66	(0.57–0.78)	80 000	0.38	(0.34–0.44)	110 000	0.46	(0.41–0.53)
Caribbean	35 500	0.17	(0.11–0.25)	74 000	0.35	(0.23–0.54)	74 000	0.22	(0.16–0.31)	109 000	0.26	(0.18–0.36)
Europe central	66 500	0.11	(0.08–0.15)	163 500	0.27	(0.19–0.39)	185 000	0.16	(0.12–0.20)	230 000	0.19	(0.15–0.26)
Europe eastern	192 500	0.17	(0.09–0.31)	414 500	0.38	(0.21–0.69)	456 000	0.21	(0.13–0.32)	607 000	0.27	(0.17–0.44)
Europe western	346 000	0.18	(0.16–0.21)	972 500	0.52	(0.46–0.58)	1 278 000	0.34	(0.30–0.38)	1 318 000	0.35	(0.32–0.39)
Latin America, Andean	48 000	0.18	(0.10–0.31)	105 000	0.38	(0.21–0.63)	88 000	0.25	(0.15–0.37)	153 000	0.28	(0.18–0.42)
Latin America central	181 000	0.15	(0.09–0.25)	391 000	0.34	(0.20–0.55)	330 000	0.21	(0.15–0.31)	572 000	0.24	(0.17–0.35)
Latin America southern	63 500	0.21	(0.11–0.39)	144 500	0.48	(0.26–0.84)	135 000	0.29	(0.19–0.45)	208 000	0.35	(0.22–0.54)
Latin America tropical	161 500	0.14	(0.06–0.29)	329 500	0.31	(0.13–0.61)	305 000	0.20	(0.11–0.34)	491 000	0.23	(0.12–0.39)
North Africa/Middle East	392 500	0.17	(0.12–0.23)	981 000	0.39	(0.28–0.56)	601 000	0.23	(0.18–0.29)	1 374 000	0.29	(0.22–0.37)
North America high-income	270 500	0.17	(0.13–0.22)	688 500	0.43	(0.34–0.54)	609 000	0.21	(0.17–0.25)	959 000	0.30	(0.25–0.36)
Oceania	6000	0.13	(0.07–0.23)	12 500	0.26	(0.13–0.47)	9000	0.18	(0.11–0.29)	19 000	0.20	(0.12–0.31)
Sub-Saharan Africa central	39 000	0.09	(0.05–0.16)	79 000	0.2	(0.10–0.35)	58 000	0.13	(0.08–0.20)	118 000	0.15	(0.09–0.23)
Sub-Saharan Africa East	149 000	0.09	(0.07–0.13)	339 500	0.21	(0.15–0.29)	239 000	0.14	(0.11–0.18)	488 000	0.15	(0.12–0.19)
Sub-Saharan Africa South	50 500	0.14	(0.07–0.26)	106 500	0.28	(0.13–0.53)	72 000	0.15	(0.09–0.24)	157 000	0.21	(0.13–0.35)
Sub-Saharan Africa West	137 000	0.09	(0.06–0.14)	298 500	0.2	(0.13–0.31)	216 000	0.13	(0.10–0.18)	435 000	0.15	(0.11–0.20)
Global	4 698 500	0.14	(0.12–0.16)	10 781 000	0.31	(0.27–0.35)	10 429 000	0.20	(0.18–0.23)	15 479 000	0.22	(0.20–0.25)

UI = uncertainty interval.

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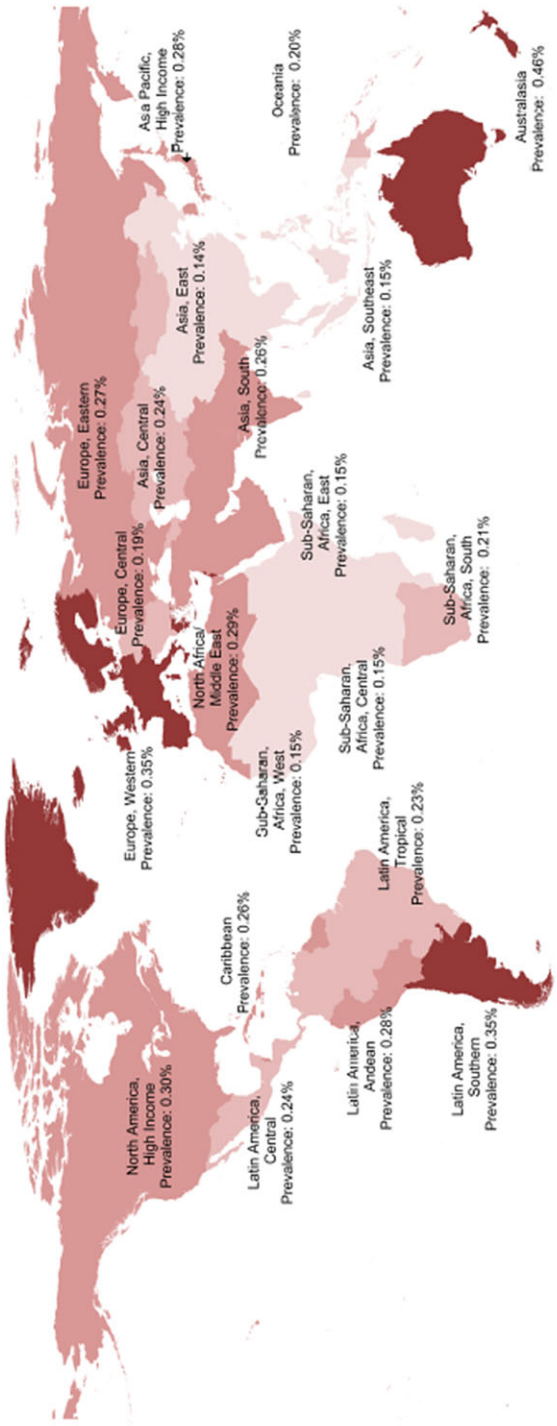

Figure 2 Pooled regional prevalence of opioid dependence, 2010

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Table 2 Estimated disability-adjusted life years (DALYs) (*n* and age-standardized rates per 100 000 population) for opioid dependence, by sex and global burden of disease (GBD) region, 2010 (totals shown for 1990 for comparison).

	Females			*Males*			*Total*					
	2010			*2010*			*1990*			*2010*		
	n	*%*	*95% UI*	*n*	*%*	*95% UI*	*n*	*%*	*95% UI*	*n*	*%*	*95%UI*
Asia Pacific high-income	73 500	80.9	(40.26–148.9)	151 500	173.4	(88.15–329.49)	205 863	122.9	(69.4–198.8)	225 000	126.3	(74.04–211.41)
Asia central	41 500	101.6	(66.72–165.37)	114 000	290.9	(195.55–474.05)	81 494	119.8	(80.3–181.8)	155 500	194.3	(138.85–294.66)
Asia East	385 000	57.2	(25.36–115.7)	696 000	96.2	(40.84–192.2)	923 299	72.6	(39.1–125.4)	1 081 500	77.4	(40.96–130.51)
Asia South	614 000	78.4	(53.16–109.41)	1 464 500	176.7	(117.75–247.11)	1 224 961	116.6	(80.3–155.8)	2 078 500	128.9	(89–173.45)
Asia South East	136 500	44.5	(26.64–70.69)	349 000	115.1	(73.68–179.2)	283 328	62.9	(40.9–91.1)	486 000	79.6	(53.27–177.51)
Australasia	19 500	149.9	(220.27–104.63)	52 500	409.1	(286.88–596.48)	45 273	214.9	(158.8–279.3)	72 000	278.6	(203.7–379.76)
Caribbean	22 000	99.8	(62.78–152.38)	42 500	196.9	(125.68–305.72)	42 194	116.6	(74.4–172.8)	64 500	148.0	(102.79–212.8)
Europe central	36 000	59.0	(39.04–84.86)	99 500	172.5	(114.68–250.93)	90 699	77.7	(52.6–110.8)	136 000	114.1	(79.88–155.6)
Europe eastern	156 000	139.8	(81.77–230.09)	441 500	461.3	(249.93–797.11)	280 341	129.4	(76.1–239.9)	597 500	288.4	(176.09–458.78)
Europe western	197 000	92.9	(69.46–118.26)	632 000	309.8	(231.1–387.25)	723 914	191.0	(143.2–240.1)	829 000	199.3	(151.83–246.51)
Latin America Andean	30 000	112.1	(66.83–179.69)	63 500	236.6	(139.51–393.34)	51 110	137.0	(84.5–214.2)	93 500	174.4	(113.67–262.42)
Latin America central	93 000	79.7	(47.05–127.59)	215 500	188.8	(112.67–303.3)	166 327	107.4	(67.9–161.9)	308 500	133.5	(85.05–197.56)
Latin America southern	33 500	109.5	(59.48–190.9)	74 000	251.0	(131.56–449.12)	66 509	143.0	(83.4–238.3)	107 500	178.8	(106.12–285.51)
Latin America tropical	77 000	75.4	(31.44–157.21)	170 000	171.1	(73.19–342.52)	143 863	93.8	(47.5–169.6)	247 000	122.5	(62.72–213.79)
North Africa/Middle East	221 500	101.6	(63.82–148.65)	616 500	270.6	(174.67–425.85)	318 799	118.4	(78.0–170.9)	838 000	188.0	(130.67–268.36)
North America high-income	268 000	155.7	(101.82–204.62)	725 000	431.9	(272.58–598.92)	310 619	106.7	(74.0–145.2)	993 000	292.1	(201.86–377.76)
Oceania	4000	83.4	(49.29–141.73)	7500	149.5	(83.1–261.38)	5981	101.8	(56.5–169.9)	11 500	117.1	(76.04–184.89)
Sub-Saharan Africa central	23 000	47.3	(24.02–93.39)	45 500	94.8	(46.18–188.13)	29 650	65.5	(37.6–104.0)	68 500	70.9	(38.88–129.37)
Sub-Saharan Africa East	103 500	58.1	(30.76–97.14)	234 000	132.2	(75.05–225.87)	139 973	76.1	(49.1–110.1)	337 500	95.0	(56.72–145.75)
Sub-Saharan Africa South	62 000	174.6	(109.77–271.36)	123 500	354.1	(163.51–794.31)	39 868	80.9	(44.5–137.9)	185 500	263.5	(155.58–493.79)
Sub-Saharan Africa West	80 500	48.2	(27.82–77.07)	169 000	99.8	(61.16–153.15)	109 456	63.5	(40.9–95.2)	249 000	74.2	(47.79–104.81)
Global	2 677 000	78.4	(57.61–101.67)	6 488 500	186.7	(139.39–240.8)	5 283 521	99.7	(71.7–129.4)	9 165 500	133.0	(102.04–166.41)

UI = uncertainty interval.

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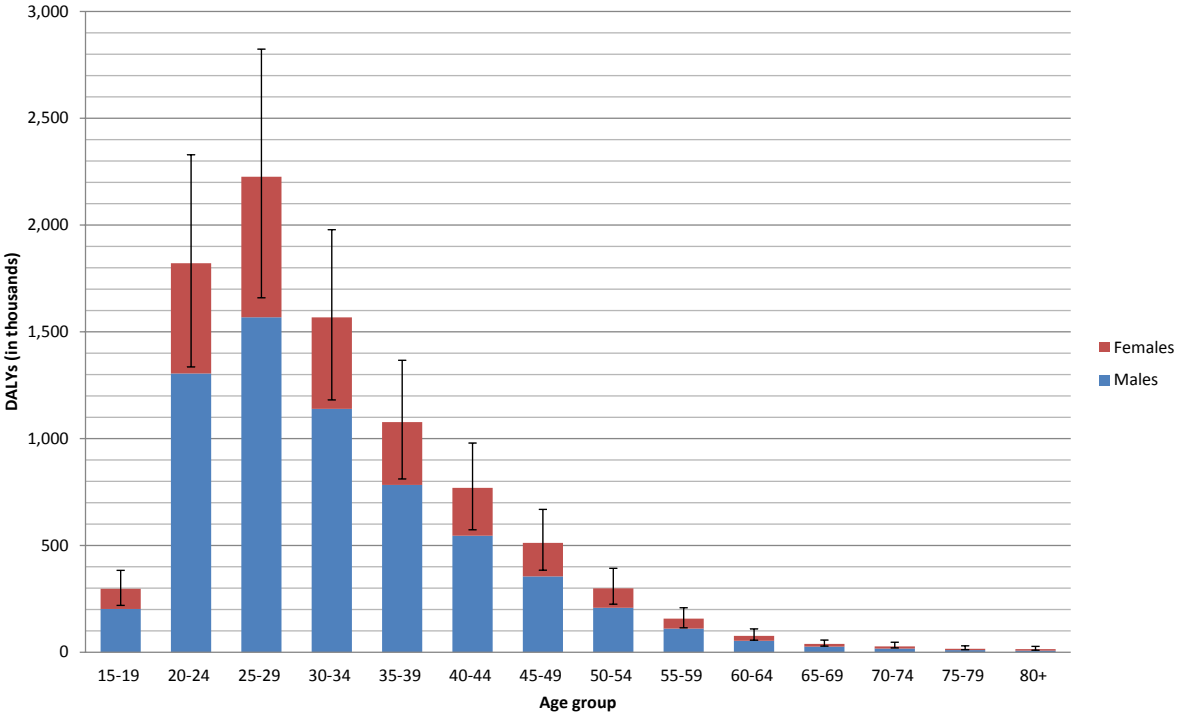

Figure 3 Global opioid dependence disability-adjusted life years (DALYs) by age and sex, in thousands, 2010

DISCUSSION

These first estimates of the burden of disease attributable to opioid dependence revealed considerable geographic variation in the prevalence of opioid dependence, in the total burden attributable to this disorder and in the relative contribution that years of life lost made to overall disease burden. Prevalence was higher among males than females, and peaked between the ages of 25 to 29 years.

Globally, a total of 9.2 million DALYs were attributed to opioid dependence in 2010: 0.37% of global DALYs. This burden was estimated to have increased markedly over time, with increased prevalence of dependence the predominant driver of increased burden, rather than changes in the age structure or size of the global population. Opioid dependence is clearly an increasing source of global disease burden.

The substantial regional variation in burden attributable to opioid dependence largely reflected prevalence levels. Overall, the highest burden was in several regions containing high-income countries, and in North Africa and the Middle East.

There were also striking variations in the contribution made by YLLs to regional-level opioid burden. In particular, North America, eastern Europe and southern SSA had greater than 50% of DALYs attributable to YLLs. In many countries in eastern Europe and Africa, there is limited access to interventions that reduce mortality among opioid-dependent people, such as opioid substitution therapy (OST), needle and syringe programmes (NSPs) and HIV treatment for those who are HIV-positive [33]; this may have contributed to this estimated loss of life. There is also variable access to these interventions across the United States; it is difficult to determine the level of availability of these interventions at a national level in the United States [33].

These data have important implications for policies to reduce opioid dependence burden at global, regional and country levels. The primary, and most highly resourced, response of most governments has been to attempt to reduce opioid supply through prohibition and law enforcement. Clearly, this approach has not been sufficient to prevent illicit opioid dependence from becoming a global problem. Burden may be worsened by the criminal status and stigmatization of illicit drug use, high rates of imprisonment and a lack of political commitment to funding health-care interventions to reduce these risks [34–36].

More effective strategies to reduce the burden of disease attributable to opioid dependence include maintenance opioid substitution treatment (OST) and HIV antiretroviral therapy [34,37]. Both methadone and buprenorphine (the two most commonly used medications) have been listed on the WHO's *List of Essential Medicines* [38] for the treatment of opioid dependence [39,40]. OST reduces mortality among opioid-dependent people [41–46], with time spent in treatment halving mortality compared to that in time spent out of treatment

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Table 3 Contrast of years of life lived with disability (YLDs), years of life lost (YLLs) and disability-adjusted life years (DALYs) for opioid dependence (*n* and age-standardized rates per 100 000 population, by global burden of disease (GBD)region, 2010

	Years lived with disability (YLDs)			*Years of life lost (YLLs)*			*Disability-adjusted life years (DALYs)*		
	n	*Rate Per 100 000*	*95% UI*	*n*	*Rate Per 100 000*	*95% UI*	*n*	*Rate Per 100 000*	*95% UI*
Asia Pacific high-income	213 500	120.0	(68.2–205.33)	11 500	6.4	(3.8–10.34)	225 000	126.3	(74.04–211.41)
Asia central	96 000	119.6	(75.39–177.49)	60 000	74.7	(48.47–174.16)	155 500	194.3	(138.85–294.66)
Asia East	1 010 000	72.3	(36.33–126.04)	71 500	5.1	(3.46–10.65)	1 081 500	77.4	(40.96–130.51)
Asia South	2 013 000	124.9	(85.31–170.15)	65 000	4.1	(0.76–11.14)	2 078 500	128.9	(89–173.45)
Asia South East	443 000	72.6	(46.28–109.61)	43 000	7.0	(3.9–13.5)	486 000	79.6	(53.27–177.51)
Australasia	51 000	196.8	(138.76–257.02)	21 000	81.7	(45.56–173.96)	72 000	278.6	(203.7–379.76)
Caribbean	50 500	116.4	(73.08–178.99)	14 000	31.6	(20.26–48.39)	64 500	148.0	(102.79–212.8)
Europe central	106 500	89.6	(58.22–129.99)	29 000	24.5	(11.86–32.57)	136 000	114.1	(79.88–155.6)
Europe eastern	275 000	132.7	(73.41–227.54)	322 500	155.7	(72.05–316.13)	597 500	288.4	(176.09–458.78)
Europe western	613 500	147.4	(103.89–191.75)	216 000	51.9	(29.62–72.04)	829 000	199.3	(151.83–246.51)
Latin America Andean	70 000	131.0	(75.55–210.44)	23 000	43.4	(30.12–85.49)	93 500	174.4	(113.67–262.42)
Latin America central	264 500	114.6	(67.69–177.72)	44 000	19.0	(11.47–40.05)	308 500	133.5	(85.05–197.56)
Latin America southern	96 500	160.5	(88.52–265.33)	11 000	18.2	(11.97–39.22)	107 500	178.8	(106.12–285.51)
Latin America tropical	226 500	112.4	(52.27–204.28)	20 500	10.2	(4.67–22.72)	247 000	122.5	(62.72–213.79)
North Africa/Middle East	652 500	146.4	(94.69–213.5)	185 500	41.6	(26.98–99.26)	838 000	188.0	(130.67–268.36)
North America high-income	444 500	130.7	(87.45–174.02)	548 500	161.4	(72.63–231.51)	993 000	292.1	(201.86–377.76)
Oceania	8500	85.8	(48.24–141.72)	3000	31.3	(18.34–56.22)	11 500	117.1	(76.04–184.89)
Sub-Saharan Africa central	53 500	55.5	(31.21–91.81)	15 000	15.4	(2.61–67.46)	68 500	70.9	(38.88–129.37)
Sub-Saharan Africa East	223 500	62.9	(41.08–89.99)	114 000	32.1	(5.27–78.28)	337 500	95.0	(56.72–145.75)
Sub-Saharan Africa South	71 000	100.7	(54.2–173.75)	114 500	162.8	(71.68–389.7)	185 500	263.5	(155.58–493.79)
Sub-Saharan Africa West	200 000	59.6	(37.38–88.76)	49 000	14.6	(4.19–26.51)	249 000	74.2	(47.79–104.81)
Global	7 184 000	104.3	(74.51–134.54)	1 981 500	28.8	(17.89–45.48)	9 165 500	133.0	(102.04–166.41)

UI = uncertainty interval.

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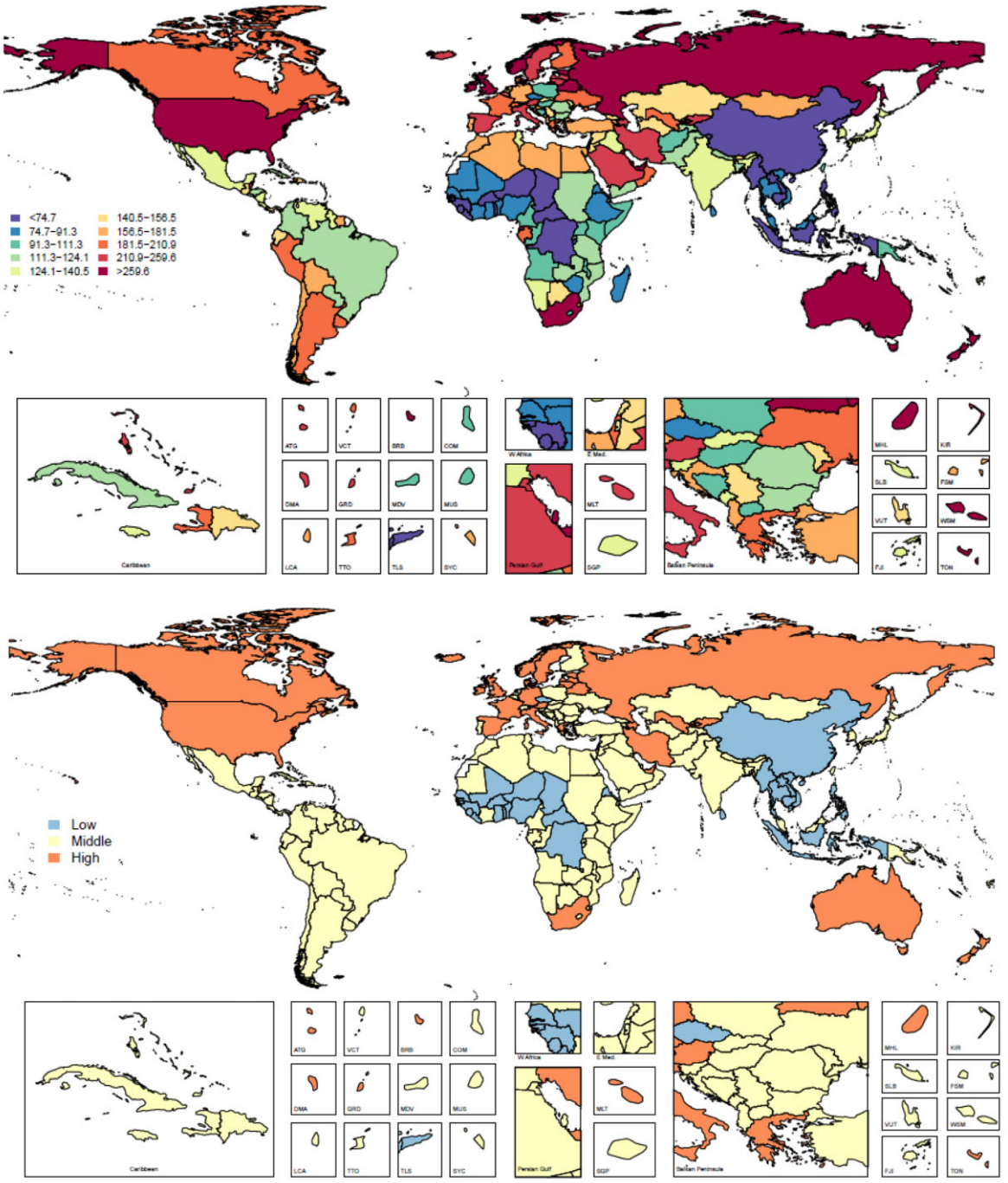

Figure 4 Country-level disability-adjusted life years (DALYs) per 100 000 population for opioid dependence, age-standardized, for 2010. Low: shows countries with statistically lower DALY rates than global mean; middle: shows countries with DALY rates that are not statistically different to global mean; high: shows countries with statistically higher DALY rates than global mean

[16]. A large evaluation study in multiple countries, including low- and middle-income countries, has demonstrated that OST is effective in reducing opioid use and injecting risk behaviours and improving physical and mental wellbeing [47].

There is also scope for reducing the risk of overdose among people who continue to use opioids. There is increasing evidence that the provision of the opioid antagonist naloxone to opioid users enables peers to intervene effectively if overdoses occur [48,49]. Additional strategies may include: education of users about the risks of overdose (especially high-risk periods, such as post-release from prison or after a period of abstinence), and motivational interviews with users who have recently overdosed [50]. Safe injecting rooms have been proposed as an additional strategy to reduce overdose,

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although their population reach is likely to be more limited [51].

It is important to note that there will be a need to tailor responses to opioid dependence to different settings. Interventions delivered country-wide or even region-wide will still have to take into consideration population differences and the need for a culturally sensitive approach, in addition to addressing the systemic and structural barriers to roll-out of treatment [35]. Systemic barriers include bans on the treatment of people who are still injecting drugs, stigmatization of clients in treatment and fees for treatment [35]. Structural barriers include the use of police registers of 'drug users', detention of drug users and harassment of patients and/or clinicians [35].

Limitations

We have made estimates based on the best available epidemiological data and used sophisticated modelling to incorporate different sources of uncertainty about the parameters used in our models. Our reviews identified major gaps in existing epidemiological data on opioid dependence. A significant amount of research is needed to document the epidemiology of opioid dependence in many countries. Until such work is conducted, considerable uncertainty will remain about the exact global burden of disease that is attributable to opioids. This is particularly the case for low-income countries, where there is typically limited information on use, even less on levels of use and often no data on the prevalence of dependence. There is a clear imperative to assess levels of dependent opioid use more effectively in these countries, whose populations may be experiencing higher levels of burden than were estimated conservatively here.

Although deaths were reassigned using standardized algorithms where the recorded cause of death was not likely to be the underlying cause of death, substance use deaths are often mischaracterized as accidental poisonings. Deaths coded as accidental poisonings due to narcotics, hallucinogens, sedative–hypnotic or psychotrophic drugs were recoded to be drug use disorder deaths (unless in children), but uncharacterized or mischaracterized poisonings may include additional opioid use deaths.

It is also important to acknowledge that the improved disability weights [19], involving surveys of the general population, have their limitations. As discussed elsewhere [19], it is unclear whether brief lay descriptions capture accurately the complexity of disability due to drug dependence. There is also the possibility that considerations other than health status may have influenced respondents' views of 'which state was healthier', because it was hard to describe the disability due to opioid dependence without mentioning opioids. None the less, this study has made significant improvements in methods and in the transparency with which burden estimates have been made.

CONCLUSIONS

Opioid dependence is a significant contributor to the global burden of disease. The challenge is to ensure that evidence-based strategies are implemented burden optimally and to scale to reduce this burden.

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Declaration of interests

L.D. has received untied educational grants from Reckitt Benckiser for the post-marketing surveillance of opioid substitution therapy medications in Australia, and the development of an opioid-related behaviour scale. L.D. has received untied educational grants from Mundi Pharma to conduct surveillance of the use of pharmaceutical opioids in Australia. All such studies' design, conduct and interpretation of findings were the work of the investigators; the funders had no role in those studies. These organizations had no knowledge of this paper.

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Supporting information

Additional Supporting information may be found in the online version of this article at the publisher's web-site:

Figure S1 Summary of epidemiological inputs for opioid dependence

Figure S2 Pooled regional prevalence of opioid dependence, 2010

Figure S3 Prevalence (proportion) of opioid dependence by age, sex and region, 2010

Table S1 Global burden of disease (GBD) region and country classifications.

Table S2 Estimated age-standardized opioid dependence prevalence and disability-adjusted life years (DALYs) by country, 2010.

Table S3 Estimated opioid dependence prevalence and disability-adjusted life years (DALYs) by country, 1990.

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