

# BMJ Open Consumption trends and prescription patterns of opioids from 2011 to 2016: a survey in a Chinese city

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## ABSTRACT

**Objective** Opioid consumption in China has been very less and has varied widely since 1995. The representatively high level of consumption in Mainland China has never been reported. Our aim was to describe the consumption trends and prescription patterns of opioids in Nanjing, a highly developed city of Mainland China, and compare the results with selected worldwide regions.

**Methods** Application data of opioids in 2011–2016 were extracted from the Jiangsu Medicine Information Institute. Six opioids were included. Consumption was expressed in terms of defined daily doses (DDDs), morphine equivalents (MEs) and expenditure. The correlation between consumption of opioids and gross domestic product (GDP), Human Development Index (HDI) and cancer incidence was analysed by Pearson's correlation test.

**Results** DDDs, expenditure and MEs of opioids were, respectively, 256.04, \$599.24 and 13.07 g in 2011, and increased to 361.27, \$1041.79 and 18.09 g in 2016. DDDs in Nanjing were 2.80-fold that in Mainland China, 1.42-fold that in East and South-East Asia, but only equivalent to 8.89% of the worldwide average level. From 2011 to 2016, the consumption had a linear correlation with GDP, HDI and cancer incidence ( $p < 0.05$ ). However, DDDs varied greatly in countries with similar GDP or HDI. Within 45 Asian countries, the GDP only contributed to 10.47% of change in DDDs, while the HDI contributed to 20.32%. Consumption of non-intravenous opioids or strong opioids always comprised majority of the total consumption. The opioids prescribed predominantly were fentanyl, oxycodone and morphine. Fentanyl and oxycodone account for most of the increase in consumption.

**Conclusion** Opioid consumption has increased >40% from 2011 to 2016, with consumption of fentanyl and oxycodone accounting for most of that increase. The consumption in Nanjing was higher than the average Chinese level, but lower than the global average. An increase in pain control services might be needed, but this need should be highly regulated.

## INTRODUCTION

An opioid is a type of substance that acts on opioid receptors to produce morphine-like effects and is indicated for the relief of mild-to-severe pain.<sup>1 2</sup> Opioids are effective for the treatment of acute pain (such as pain following surgery) and cancer pain, and have been identified by WHO

## Strengths and limitations of this study

- This is the first study investigating the consumption trends and prescription patterns of opioids in Nanjing, China, that has seen a huge increase in opioid consumption from 2011 to 2016.
- One of the strengths of this study is the cross-country comparison of opioid consumption between Nanjing and selected worldwide regions, reflecting the relatively low consumption in Nanjing as compared with the whole world.
- Another strength is Pearson's correlation test between consumption and influencing factors, which revealed that gross domestic product, Human Development Index and cancer incidence account for some changes in opioid use, but are not determinant factors.
- Our study provides valuable evidence to the Chinese government and health organisations for laying emphasis on the control of pain and expansion of pain services.
- The limitation of our data is that the term 'consumption' is used for the quantity of opioid prescribed but does not relate to how much is actually administered.

as 'indispensable for the relief of pain and suffering', so that their availability 'must be' ensured.<sup>3 4</sup> However, consumption of opioids varies widely between countries.<sup>5–8</sup> During 2011–2013 the annual global consumption, expressed as defined daily doses per million people per day (DDDs PMPPD), was 3027.<sup>7</sup> The average annual consumption in USA and Canada was up to 43 879 and 22 941, respectively,<sup>7</sup> while that in Asian countries was relatively low. Within Asia, the high level was 4664 in Israel, and the low level was less than 10 in Laos, Cambodia, Bangladesh, Yemen and so on.<sup>7</sup> The annual consumption in China was 96, which was the moderate level of Asia, but much lower than the worldwide average level.<sup>7 8</sup>

Consumption of opioids varies widely between cities because of the large diversity within China. The average DDDs in Macao

and Hong Kong, two cities in China, were, respectively, 221 and 175 in 2011–2013,<sup>7</sup> while the average DDD in Taiwan was 560 in 2007.<sup>9</sup> Their health service systems and cultural traditions are different from most cities in the Chinese mainland. The representatively high level of consumption in Mainland China has not been reported. Nanjing, a city in Eastern Mainland China, with a population of >8000 000, area of 6587 km<sup>2</sup> and gross domestic product (GDP) ranking eleventh among 338 cities in 2016,<sup>10</sup> is the political, economic and cultural centre of Southern China. The health service systems and cultural traditions of Nanjing are similar to most other cities in the Chinese mainland. Hence Nanjing has been chosen to represent the highly developed parts of China.

According to the China Food and Drug Administration (CFDA) criterion,<sup>11</sup> opioids as prescription medicines are legally sold in hospitals only in order to avoid abuse. There are only 34 hospitals authorised by CFDA in Nanjing. Pain and addiction are assessed by doctors before prescription. Opioid abuse or misuse of opioid is supervised by CFDA. The abuse/utilisation rate of opioids prescribed in hospitals in this area was 0.01%–1.00% in 2016.<sup>12</sup> Opioids prescribed in hospitals are considered to be used for legal medical purposes. In this study, Nanjing has been chosen as a representative of the highly developed parts of China, to investigate consumption trends and prescription patterns of opioids from 2011 to 2016, and compare the results with selected regions worldwide.

## METHODS

### Data sources

Data on opioids were provided by the Jiangsu Medical Information Institute. According to the CFDA criterion,<sup>11</sup> every opioid prescription in Nanjing should be reported by the hospital to this institute. Each hospital has a designated reporter, usually a pharmacist, who is responsible for registering the consumption of drugs. The reporter collects information for each opioid including dosage form, package dose, manufacturer, price, monthly expenditure and monthly consumption (in terms of grams). The designated reporter reports data on a monthly basis. A specific network system has also been designed for data uploading, summarising, analysing and storage. The designated reporter imports data to the network system, and the network system automatically sends data to the Jiangsu Medicine Information Institute. A designated statistical officer collects, summarises and analyses data from different hospitals.

Eight kinds of opioids are used in Nanjing city; they are morphine, fentanyl, oxycodone, codeine, hydromorphone, pethidine, buprenorphine and methadone. Dextropropoxyphene, ketobemidone, tilidine and trimeperidine are not available in China. Methadone and buprenorphine were excluded because their use for pain relief cannot be distinguished from their predominant use for treatment of dependence on illicit opioid.<sup>7</sup> Therefore, morphine, fentanyl, oxycodone, codeine,

hydromorphone and pethidine were included and analysed in our study.

The institute reported the consumption of opioid in terms of grams and prices. We estimated them in terms of DDDs, morphine equivalents (MEs) and expenditures. The DDDs of opioids in other regions and countries were reported by Berterame *et al.*<sup>7</sup> GDP and Human Development Index (HDI) in other countries were retrieved from the World Bank<sup>13</sup> and the Human Development Report.<sup>14</sup> The population, GDP, HDI and cancer incidence in Nanjing were obtained from the statistical yearbook of the Nanjing Statistics Bureau.<sup>10</sup>

### Statistical analysis

DDD is a statistical unit defined by the WHO Collaborating Centre (WHOCC) for Drug Statistics Methodology.<sup>15</sup> In our study, DDDs were shown as the values PMPPD and calculated with the following formula:

$$\text{DDD} = (\sum(\text{Total dose used})/\text{DDD})/365/\text{population}$$

ME is another measuring unit for the consumption recommended by International Association for Hospice and Palliative Care (IAHPC).<sup>16 17</sup> ME ratios are recommended by WHOCC for Drug Statistics Methodology.<sup>18</sup> In our study, MEs were shown as the values PMPPD and calculated using the following formula:

$$\text{MEs} = (\sum(\text{Total dose used}) * (\text{ME ratio}))/365/\text{population}$$

The expenditure of opioids was recorded in Renminbi (RMB) and then converted to US dollars. Expenditure was shown as expenditure PMPPD and calculated using the following formula:

$$\text{Expenditure} = (\text{expenditure})/\text{dollar exchange rate}/365/\text{population}$$

GDP was shown as GDP PMPPD and was calculated using the following formula:

$$\text{GDP} = (\text{total GDP})/365/\text{population}$$

The correlation between consumption of opioids and GDP, HDI and cancer incidence was analysed by applying Pearson's correlation test and linear regression analysis using SPSS V.21 (IBM Corporation, Armonk, New York, USA). A value of  $p < 0.05$  was considered to show a statistically significant linear correlation.

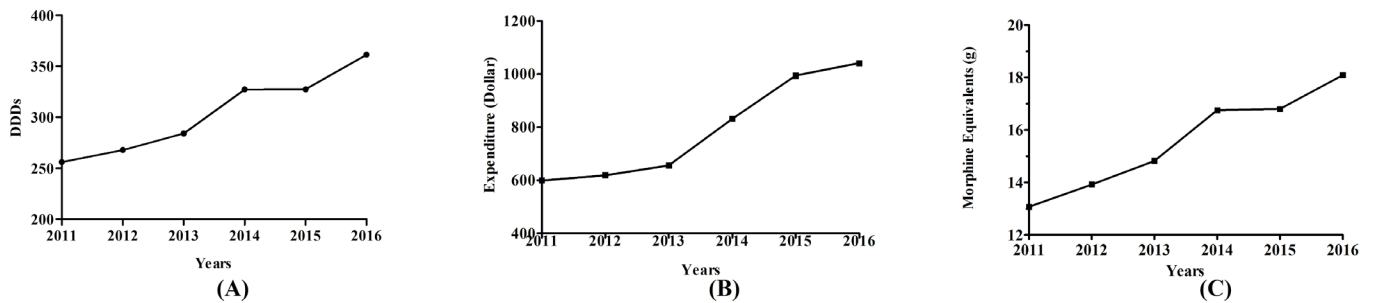
### Patient and public involvement

Patients were not involved because this study included no human participants.

## RESULT

### Opioid consumption had an increasing tendency

The consumption of opioids in Nanjing city increased year by year from 2011 to 2016. DDD was 256.04 in 2011; it increased by 7.13% per year and reached 361.27 in 2016 (figure 1A). The average DDD was 302.24 during 2011–2016. The expenditure was \$599.24 in 2011, increased by 11.70% per year and reached \$1041.79 in 2016 (figure 1B). The average expenditure was \$781.99 during 2011–2016. ME was 13.07g in 2011, increased by 6.72%



**Figure 1** Consumption of opioids in Nanjing from 2011 to 2016. (A) DDDs of opioids. (B) Expenditure on opioids. (C) MEs of opioids. DDD, defined daily dose; ME, morphine equivalent.

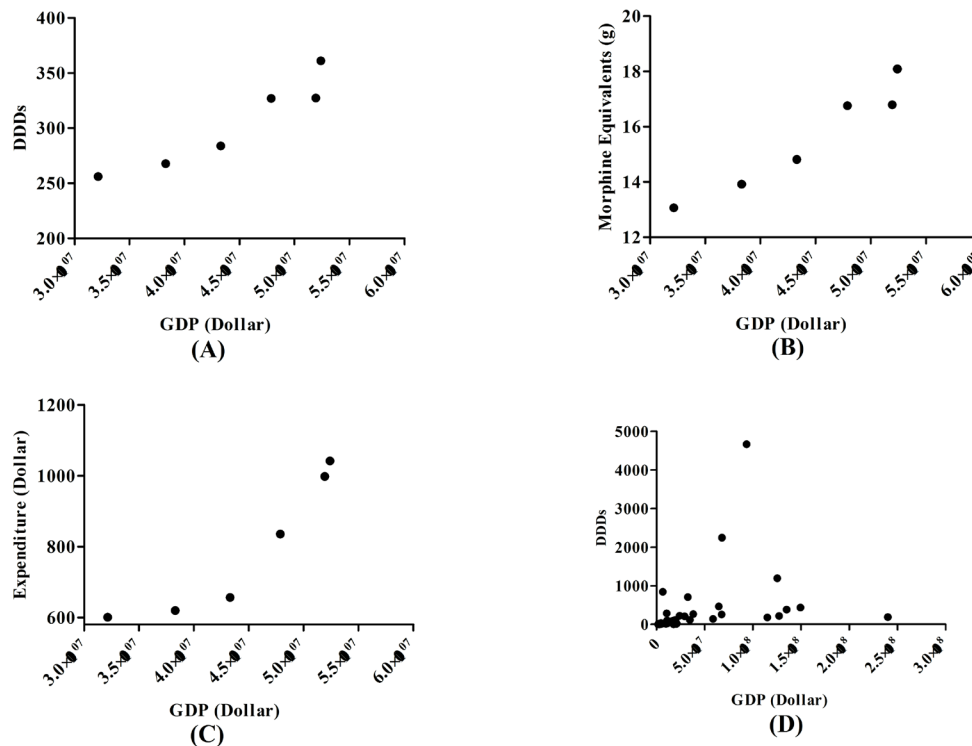
per year and reached 18.09 g in 2016 (figure 1C). The average ME was 15.58 g during 2011–2016.

### Consumption in Nanjing is relatively low in the world

Within China, the annual average DDD in Nanjing was 269, which is about 2.80-fold of that in the Chinese mainland (online supplementary table S1) and slightly higher than that in Macau (221) and Hong Kong (175) during 2011–2013.<sup>7</sup> Nanjing is a city in the East and South-East of Asia, so we compared the DDD in Nanjing with that of the other countries in this area. During 2011–2013, DDD in Nanjing was 1.42-fold of the average value in East and South-East Asia, but much lower than the DDDs

in South Korea, Japan, Singapore (online supplementary table S1).

In order to reveal the level of opioid consumption of Nanjing in the whole world, we compared the DDDs of Nanjing with the average value of the whole world and every main region. DDD in Nanjing was only 8.89% of the worldwide average level, 0.86% of North America, 2.89% of West and Central Europe, 2.94% of Oceania and 24.45% of South-East Europe. It was close to the average level in South America and West Asia, but higher than the average level in East and South-East Asia, East Europe, Central America, Africa and South Asia (online supplementary table S2).



**Figure 2** Correlation of GDP and consumption of opioids in Nanjing from 2011 to 2016. (A) Correlation between GDP and DDDs of opioids in Nanjing from 2011 to 2016. (B) Correlation between GDP and expenditure on opioids in Nanjing from 2011 to 2016. (C) Correlation between GDP and MEs of opioids in Nanjing from 2011 to 2016. (D) Linear regression analysis of GDP and DDDs in 45 Asian countries. DDD, defined daily dose; GDP, gross domestic product; ME, morphine equivalent.

**Table 1** Opioid consumption in regions with similar GDP

Regions	Average GDP (2011–2013) (USD )	Average DDDs (2011–2013)
Worldwide	28 808 219	3027
Panama	29 035 616	309
Kazakhstan	35 863 014	120
Hungary	36 928 767	3984
Seychelles	37 197 260	184
Poland	37 268 493	1916
Croatia	37 764 384	2733
Nanjing	38 049 315	269
Latvia	38 879 452	1122
Lithuania	40 550 685	1237
Chile	41 643 836	747

DDDs are shown as the values per million people per day.  
GDPs are shown as the GDP per million people per day.  
DDD, defined daily dose; GDP, gross domestic product.

### Factors influencing the consumption of opioid

Previous studies have reported that GDP and HDI are important determinants of opioid consumption.<sup>7</sup> GDP has increased at an annual rate of 10.26% from 2011 to 2016 (figure 2), so correlation analysis was carried out. GDP had a linear correlation with DDDs ( $R^2=0.94$ ,  $p=0.005$ ) (figure 2A), MEs ( $R^2=0.97$ ,  $p=0.002$ ) (figure 2B) and expenditure ( $R^2=0.92$ ,  $p=0.008$ ) (figure 2C). However, DDDs of opioids varied greatly in countries with similar

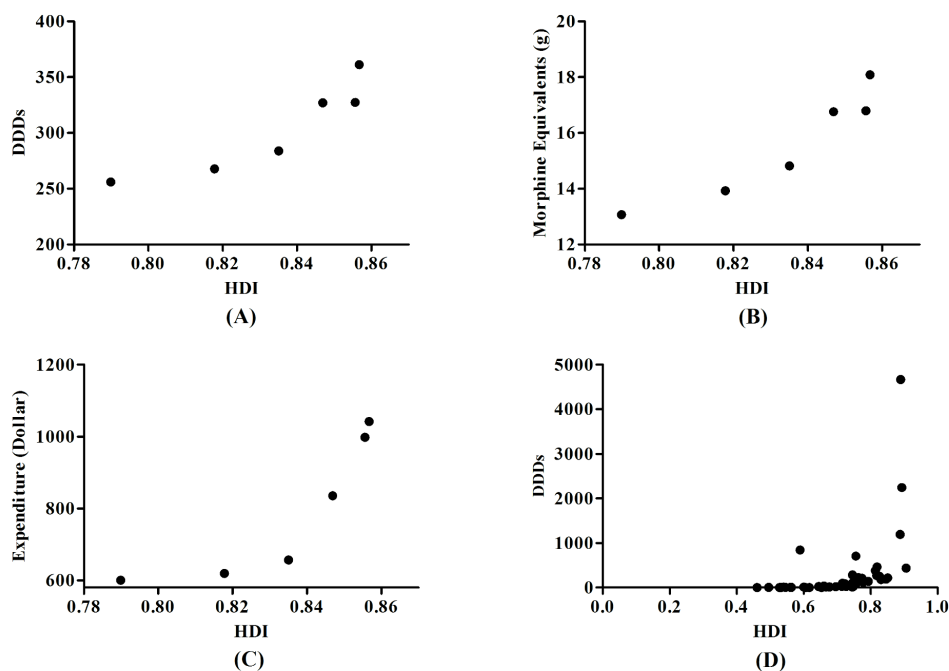
GDPs (\$28–\$42 million) (table 1). DDDs in Nanjing were significantly lower than in some European countries, such as Hungary, Poland, Croatia and Latvia, but higher than in Kazakhstan (Asia) and Seychelles (Africa) (table 1). GDP only contributed to 10.47% of change in DDDs in a linear regression model of 45 Asian countries ( $R^2=0.1047$ ,  $p=0.0301$ ) (figure 2D).

HDI increased by 1.64% per year. HDI was also correlated with DDDs of ( $R^2=0.90$ ,  $p=0.014$ ) (figure 3A), MEs of ( $R^2=0.94$ ,  $p=0.006$ ) (figure 3B) and expenditures ( $R^2=0.86$ ,  $p=0.028$ ) (figure 3C) on opioids from 2011 to 2016. In countries with similar HDI (0.79–0.83), DDDs of opioids varied greatly. DDD in Nanjing was remarkably higher than in some European countries such as Hungary, Croatia, Latvia, Portugal and Montenegro, but mildly lower than in some Asian countries such as Bahrain and Kuwait (table 2). GDP only contributed to 20.32% of change in DDDs in a linear regression model of 45 Asian countries ( $R^2=0.1686$ ,  $p=0.0019$ ) (figure 3D).

Cancer incidence increased by 6.28% per year from 2011 to 2016 (figure 4). Cancer incidence was correlated with DDDs of ( $R^2=0.98$ ,  $p=0.001$ ) (figure 4A), MEs of ( $R^2=0.98$ ,  $p=0.001$ ) (figure 4B) and expenditures on ( $R^2=0.97$ ,  $p=0.002$ ) (figure 4C) opioids from 2011 to 2016.

### Prescription pattern of opioids

Consumption of non-intravenous opioids accounted for majority of the total consumption from 2011 to 2016. The DDDs of non-intravenous opioids increased by 6.81% per



**Figure 3** Correlation of HDI and consumption in Nanjing from 2011 to 2016. (A) Correlation between HDI and DDDs of opioids in Nanjing from 2011 to 2016. (B) Correlation between HDI and expenditure on opioids in Nanjing from 2011 to 2016. (C) Correlation between HDI and MEs of opioids in Nanjing from 2011 to 2016. (D) Linear regression analysis of HDI and DDDs in 45 Asian countries. DDD, defined daily dose; HDI, Human Development Index; ME, morphine equivalent.

**Table 2** Opioid consumption in regions with similar HDI

Regions	Average HDI (2011–2013)	Average DDDs (2011–2013)
Portugal	0.827	2302
Chile	0.826	747
Hungary	0.824	3984
Bahrain	0.819	465
Nanjing	0.818	269
Latvia	0.814	1122
Croatia	0.816	2733
Kuwait	0.814	383
Montenegro	0.799	1498
Belarus	0.795	300

DDDs are shown as values per million people per day. DDD, defined daily dose; HDI, Human Development Index.

year (figure 5A), while their expenditure increased by 7.34% per year (figure 5B). Consumption of intravenous opioids accounted for a minor part of the total consumption from 2011 to 2016. The DDDs of and expenditure on intravenous opioids, respectively, increased by 9.33% (figure 5A) and 27.18% per year (figure 5B).

Strong opioids took more than 99% of the total consumption. The annual growth rates of DDDs and expenditures were 7.18% (figure 6A) and 11.69%, respectively (figure 6B). The proportion of weak opioids was always low, though it increased steadily.

Consumption of fentanyl, which was the most widely applied type of opioid, accounted for more than 50% of the total consumption during 2011–2016. DDDs of, MEs of and expenditures on fentanyl increased from 2011 to 2014, but decreased in 2015 (figures 7A–C). Fentanyl accounted for most of the increase in consumption during 2011–2014. In our study, the DDDs of transdermal fentanyl were 157.38, 175.70, 192.16, 214.89, 194.90 and 205.35, and the DDDs of fentanyl injection were 23.46, 25.81, 29.79, 34.13, 36.21 and 36.95 from 2011 to 2016, respectively. The DDDs of transdermal fentanyl were higher than those of fentanyl injection during our study period.

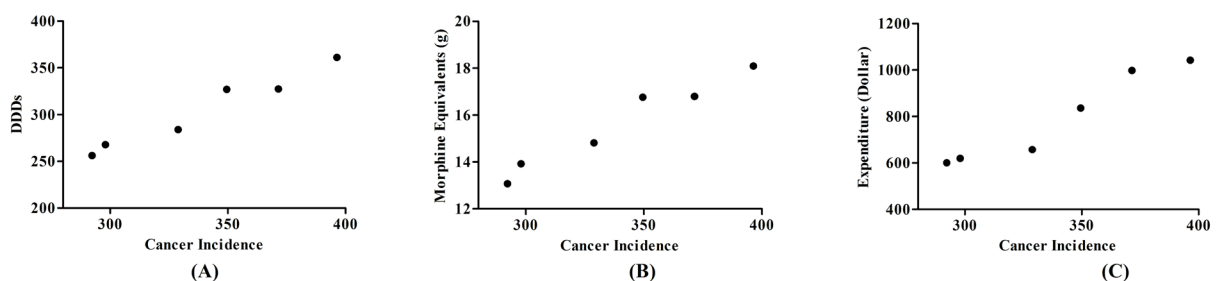
Consumption of oxycodone, which accounted for more than 10% of the total consumption, decreased from 2011 to 2013, but increased from 2013 to 2016. Oxycodone accounted for most of the increase in consumption during 2011–2014 (figures 7A–C). Consumption of morphine changed little and accounted for more than 10% of the total consumption in 2011–2016 (figure 7). Consumption of other opioids such as codeine, pethidine and hydromorphone was low in 2011–2016 (figures 7A–C).

## DISCUSSION

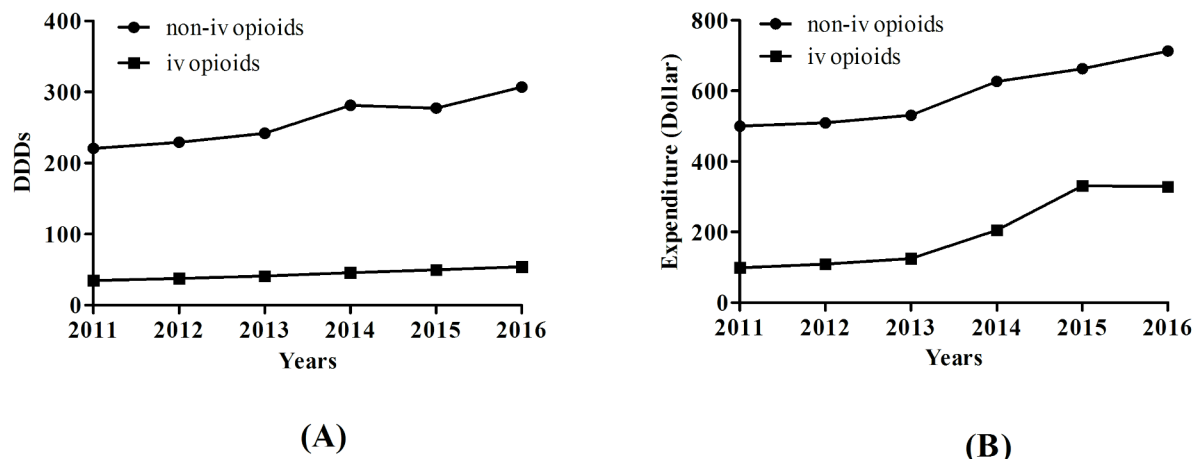
Consumption of opioids in China has been very low and has varied widely since 1995.<sup>7 8 19</sup> Because of the unbalanced development in the different regions in China, Nanjing was chosen as a representative of the highly developed part of China. In our study, the DDD in Nanjing was higher than that in Macau and Hong Kong, and was about 2.80-fold that of the Chinese average level during 2011–2013, reflecting the high level of opioid consumption in China. Two major findings of the present study are the continuous increase in the consumption of opioids in Nanjing in the recent past and the change in the consumption pattern.

Though opioid consumption in Nanjing increased gradually reflecting the continuous progress in pain relief, the level is still low compared with the selected worldwide regions. Within East and South-East Asia, the DDD in Nanjing was much lower than that of South Korea, Japan and Singapore. Around the world, the DDD in Nanjing was much lower than the average levels in North America, West and Central Europe, Oceania and South-East Europe. Previous studies have demonstrated the low opioid consumption in China.<sup>7 8</sup> In our study, the DDD in Nanjing, which reflected the high consumption level in China, was relatively low in comparison to other regions worldwide.

Previous studies have reported that GDP and HDI are important determinants of opioid consumption.<sup>7</sup> So a correlation analysis was carried out. As expected, the consumption in Nanjing correlated with its GDP and HDI. The GDP and HDI in Nanjing are higher than the average



**Figure 4** Correlation between cancer incidence and consumption in Nanjing from 2011 to 2016. (A) Correlation between cancer incidence and DDDs of opioids. (B) Correlation between cancer incidence and expenditure on opioids. (C) Correlation between cancer incidence and MEs of opioids. DDD, defined daily dose; ME, morphine equivalent.



**Figure 5** Consumption of intravenous (iv) and non-intravenous opioids in Nanjing from 2011 to 2016. (A) DDDs of intravenous or non-intravenous opioids. (B) Expenditure on intravenous or non-intravenous opioids. DDD, defined daily dose.

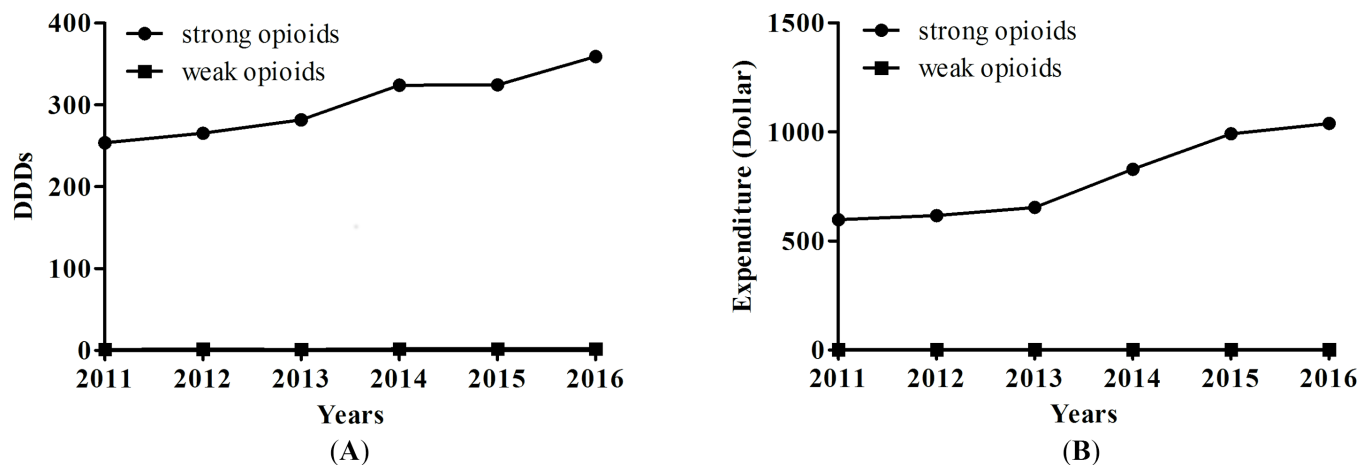
Chinese levels, which might explain the high consumption of opioids. However, countries with similar GDP or HDI have significantly different opioid consumptions. In 45 Asian countries, GDP contributed to only 10.47% change in DDD, while HDI contributed to 20.32%. So GDP and HDI do not seem to play a crucial role in the diversity between regions and countries; this has also been demonstrated in our previous study.<sup>8</sup>

Opioids are commonly prescribed for pain.<sup>20</sup> Chronic non-cancer pain can be due to various diseases, and it is difficult to determine its incidence. Hence, we only analysed the relationship between opioid consumption and cancer pain. Data on cancer prevalence in Nanjing are not available, so cancer incidence was substituted for cancer prevalence. Opioid consumption was correlated with cancer incidence from 2011 to 2015 in Nanjing, suggesting that cancer incidence accounted for some changes in opioid use.

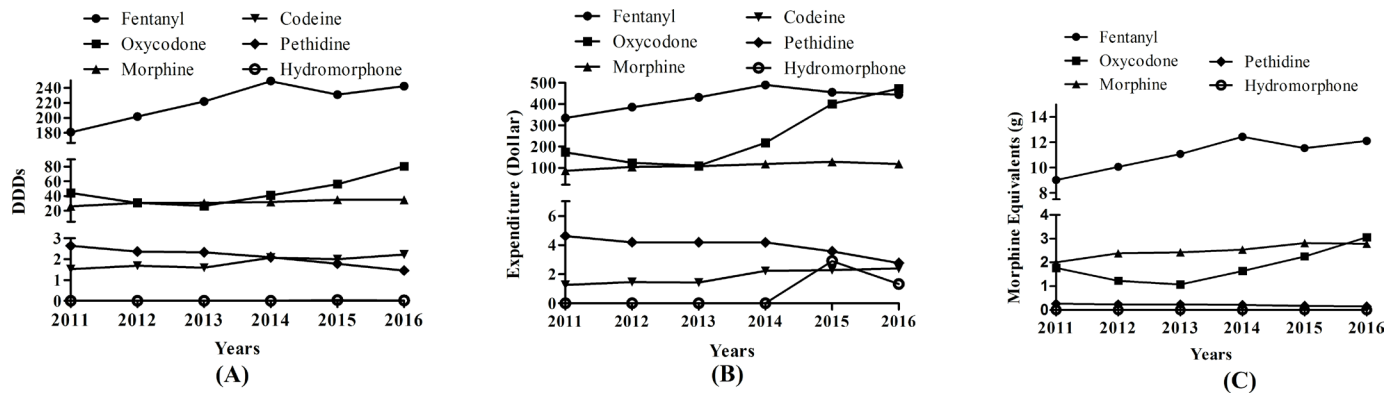
Other impediments also influenced opioid application, such as reimbursement policies and prescription

regulations, availability of pain services, and so on.<sup>9 21–23</sup> In China, all types of opioids have been covered by insurance, but the reimbursement ratio varies with the different types of insurance. Reimbursement policies and prescription regulations of opioids did not change in Nanjing from 2011 to 2016, and their effect on opioid consumption was small. Expansion of pain services could be other possible contributors to this increase. The National Health and Family Planning Commission of the People's Republic of China launched the 'Good Pain Management Programme (GPM programme)' across the country since 2011.<sup>24</sup> Twenty-nine hospitals in Nanjing have enrolled in this programme since 2012.<sup>25</sup> The GPM programme has proved to improve the pain management of patients with cancer.<sup>26</sup>

WHO's cancer pain ladder for adults and the National Comprehensive Cancer Network (NCCN) guidelines highlight non-invasive administration of opioids.<sup>27 28</sup> Therefore, a major part of the total consumption was of non-intravenous opioids, and this consumption tended to increase in Nanjing from 2011 to 2016.



**Figure 6** Consumption of strong and weak opioids in Nanjing from 2011 to 2016. (A) DDDs of strong and weak opioids. (B) Expenditures on strong and weak opioids. DDD, defined daily dose.



**Figure 7** Consumption of main opioids in Nanjing from 2011 to 2016. (A) DDDs of main opioids. (B) Expenditures on main opioids. (C) MEs of main opioids. DDD, defined daily dose; ME, morphine equivalent.

The WHO three-step ‘ladder’ had recommended weak opioids for patients with moderate pain since 1986.<sup>27</sup> Recent research has revealed that passing directly from step 1 to step 3 of the WHO analgesic ladder is more effective than the traditional three-step strategy for mild-to-moderate chronic cancer pain.<sup>28–29</sup> Nowadays, the European Association for Palliative Care guidelines recommend a small dose of strong opioid instead of weak opioid in patients with refractory moderate pain.<sup>30</sup> The NCCN Adult Cancer Pain Guideline (V.1.2015) recommends opioid for all levels of pain.<sup>31</sup> This could explain the overwhelming use of strong opioids in Nanjing during 2011–2016.

Consumption of morphine remains stable, while consumption of fentanyl, oxycodone and methadone has increased in many countries;<sup>32–34</sup> this suggests changes in the prescription pattern of opioids for pain management. In Nanjing transdermal fentanyl has come into use since 1999, and controlled-release oxycodone since 2004. The consumption of fentanyl might have been overestimated in our study. The DDD value for fentanyl used in this study was 0.6 mg, which was recommended by WHO and International Narcotics Control Board, but the daily dose is usually 1.2–2.4 mg/day in practice. In order to compare the consumption with other regions and countries, we chose 0.6 mg as the DDD value of fentanyl.

In our study, the DDD of transdermal fentanyl was much higher than that of fentanyl injection during the study period. Transdermal patch is the mostly used species, and accounted for most of the increasing of consumption in 2011–2014. We retrospectively analysed the application of fentanyl in 2016 in our hospital. Fentanyl is mainly used for the treatment of cancer pain, but is also used sometimes for relief from acute postoperative pain, rheumatoid arthritis, osteoporosis and postherpetic neuralgia.

Transdermal fentanyl has some advantages in the management of cancer pain, such as very long half-life<sup>35</sup> and much fewer opioid-related gastrointestinal side effects, such as nausea, vomiting and constipation.<sup>36–38</sup> Fentanyl has been reported to be used in the treatment of patients with chronic non-cancer pain such as rheumatoid arthritis, osteoporosis and postherpetic neuralgia.<sup>39–40</sup>

The consumption of oxycodone has increased since 2013, and accounts for most of the increase in consumption during 2015–2016. Oxycodone is mostly used in the controlled-release form, which has a lower rate of constipation, nausea and vomiting than controlled-release morphine.<sup>41–42</sup> A previous study has reported that the rescue analgesic dose of controlled-release oxycodone is smaller than that of controlled-release morphine.<sup>43–44</sup> So consumption of morphine has changed little and has always been lower than that of fentanyl and oxycodone. Consumption of other opioids such as pethidine, codeine and hydromorphone was always low. In one word, the prescription pattern of opioids was generally reasonable.

Our work has some limitations. The data contain no information on compliance with therapy; the term ‘consumption’ is used for the quantity of drug prescribed but does not relate to how much is actually administered. Second, data on cancer prevalence in Nanjing are not available, so we just analysed the association of cancer incidence and consumption.

## CONCLUSION

In conclusion, during the past few years, the consumption of opioids in Nanjing has increased remarkably, although the level of consumption remains low in comparison with selected worldwide regions. The large increase in the consumption of fentanyl and oxycodone is most likely the main feature of this consumption, whereas the use of morphine is stable. GDP, HDI or cancer incidence, all affected consumption, but were not decisive factors. The Chinese government has initiated steps to emphasise the control of pain and expand pain services, but more needs to be done in the future. However, there has been an opioid crisis in USA and Canada, and expansion of pain services in China needs to be highly regulated.

**Contributors** XL revised the manuscript. CL drafted the manuscript. HD was responsible for acquisition of data. WF analysed the data and performed the statistical analysis. All authors have read and approved the final manuscript.

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**Patient consent for publication** Obtained.

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**Data sharing statement** The data used and/or analysed during the current study are available from the corresponding author on reasonable request.

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