



## Research Paper

## Spatial clustering of codeine use and its association with depression: a geospatial analysis of nationally representative South African data

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## A B S T R A C T

**Background:** There is an alarming trend in sub-Saharan Africa in the use of codeine-containing pharmaceuticals, but its risk of common comorbidities, such as mental health, remains unquantified at a national-level. We investigated the relationship between codeine use and onset of depression in South Africa at a population-level.

**Methods:** We used nationally representative panel data from the South Africa National Income Dynamic Study to investigate the relationship between exposure to codeine use in the community (i.e. residing in a codeine hotspot) and onset of depression. Geographical hotspots of codeine use were identified using Kulldorff spatial scan statistic in SaTScan. We quantified depression onset at Wave 5 (year 2017) between individuals residing inside and outside a codeine hotspot who were depression-free at enrolment (Wave 4: 2015) using generalised estimating equation (GEE) regression models.

**Results:** We identified four statistically significant hotspots of codeine use, mostly located at the northern part of the country. Among 13,020 participants who were depression-free at enrolment, residing within a codeine use hotspot was significantly associated with higher subsequent onset of depression (aRR=1.21, 95% CI:1.08-1.44).

**Limitations:** Data on diagnosis of depressive disorder were not available.

**Conclusion:** South Africa, a resource scarce nation with chronically limited mental health services, is not spared from the global opioid epidemic and its impact on depression. Targeted scale-up access to agonist therapy to effectively treat (opioid) addiction in communities at risk for high exposure to codeine use could reduce the risk of subsequent mental health challenges.

### 1. Introduction

Despite the attention given to the opioid crisis in the United States of America (USA) and other developed nations, some evidence points to an emerging opioid use and misuse epidemic in sub-Saharan Africa (SSA), including South Africa (SA) (Foley et al., 2018; Dada et al., 2015). Codeine, a type of prescription opioid, is a medically necessary opiate analgesic drug that is used to treat mild to moderate pain (Bowery, 2007). Although it is intended for short-term relief, misuse of codeine, as

a controlled substance, can lead to addiction and fatality (Iedema, 2011). The extent of the opioid crisis in the USA is concerning, with an estimated 50,000 individuals having died from opioid-involved overdoses in 2019 (CDC Wonder, 2020; DeWeerd, 2019). More people died from overdoses involving opioids in 2017 than from HIV-related illnesses at the peak of the HIV epidemic in the USA (DeWeerd, 2019). Despite the negative health consequences posed by opioid misuse documented elsewhere, the evidence of its use and health impacts remains scarce in other regions like SSA. A report led by the nationally

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representative SA Demographic and Health Survey (SA-DHS) study issued in 2019 indicates that 13% of men and 14% of women aged 15 and older used codeine-containing medications in the past 12 months (National Department of Health NDoH et al., 2019). The same report indicates that as many as 16.3% of male adults (19.3% in adult females) sought treatments for problems related to use of medicines for non-medical purposes in the past 12 months.

In addition to the issue of suicide and addiction, the association between opioid use and mental health conditions has also been reported (Hernández et al., 2021; Rosoff et al., 2021), including the increased risk of developing depression due to codeine misuse (Scherrer et al., 2016). Depression is a mental health disorder that causes a persistent feeling of sadness and loss of interest when left untreated (World Health Organization, 2021a). Depression can impair an individual's functioning to the extent that it leads to disability (Behrens-Wittenberg and Wedegaertner, 2020), or premature mortality from other related illnesses such as diabetes and hypertension (Rubio-Guerra et al., 2013; Bădescu et al., 2016) and/or suicide (Pompili, 2019).

The mechanism in which codeine can lead to the development of depression is not clear. However, in a review of studies, Lutz et al. (2020) reported opioids to contribute to both positive and negative experiences through the opioids receptors which either stimulate or inhibit reward. The study further reported that a similar modulation of reward by opioid receptors just as in the case of drug abuse has also been documented for natural stimuli such as social behaviors. For instance, receptors which stimulate reward were identified to promote proper attachment in infants and in turn positive behaviors later in life whilst those which inhibit reward have opposite effects. The changes in function of these receptors therefore could have the capacity of impacting regulation of social behaviors in adults who use opioids which may be associated with subsequent stressful life events and adverse social situations, ultimately contributing to the emergence of depressive symptoms.

Despite the link at an individual-level between codeine use and depression, and warning signs of an emerging opioid crisis in SA, the extent of codeine use in the community and its impact, based on national-level evidence on depression remains unknown. Depression is one of the leading mental disorders affecting people globally (Liu et al., 2020; Santomauro et al., 2021) and has been reported as one of the top five diseases contributing to the global burden of disease since 1990 (Salleh, 2018). In SA, depression also contributes considerably to poor mental health (Cuadros et al., 2019), with some studies estimating that 9.8% of the adult population experience depression sometime in their lifetime (Herman et al., 2009; Lund et al., 2010), but with only 3.9% accessing the mental health care that they need (Docrat et al., 2019). Considering the above facts, and the lack of national evidence, we first identified the spatial structuring of codeine use in SA, and then quantified the relationship between living in a community with increased levels of opioid use and onset of depression, using data from the SA National Income Dynamic Study (SA NIDS) (National Income Dynamic Study, 2020). As a panel study and the first nationally representative survey, SA-NIDS is exceptional in SSA as it holds geospatial data that enables longitudinal insights into the relationship between codeine use (which requires geolocations) and onset of depression in SA.

## 2. Methods

Data from the SA National Income Dynamics Study (SA-NIDS), wave 4 (2015) and wave 5 (2017) (National Income Dynamic Study, 2020), were used. The SA-NIDS is the first panel survey of a nationally representative sample of households in SA. Due to it being a panel study, it provides comprehensive data about living conditions and well-being trends of the population that is rarely observed in similar developing nations. To obtain a sample that is representative of the national household, it employed a two-stage stratified cluster sample design, with further details on the study design being described elsewhere

(Leibbrandt et al., 2009).

### 2.1. Measures

#### 2.1.1. Depression

The main study outcome was onset of depression, with information being obtained from the SA-NIDS adult questionnaire, which is based on the 10-item abridged version of the Center for Epidemiologic Studies Depression Scale (CES-D) (Andresen et al., 1994). This captures self-reported depression-associated symptoms during the past week and whilst the CES-D might have its limitations (Carleton et al., 2013), it is a commonly used valid/reliable psychometric instrument (Björgvinsson et al., 2013; Cole et al., 2004). The CES-D consists of likert scale questions with four possible responses that range from 0 = rarely/none of the time (less than 1 day) to 3 = almost/all of the time (5–7 days). Depression symptomatology is based on a composite score of the 10 items (Cronbach's  $\alpha = 0.75$ ) and a total score of  $\geq 10$  (out of a possible 30) is classified as a cut off to indicate significant depressive symptoms, which is consistent with a previous study (Andresen et al., 1994).

To better isolate the effect of exposure to codeine (i.e. residing in a codeine hotspot) at baseline following depression onset, our study constructed an *incident cohort* based on methods similarly used in previous studies (Tomita et al., 2017; Tomita and Manuel, 2020), thus minimizing the probability of reverse causation. The incident cohort was constructed to ensure that the observed participants were initially free of depression so as to enable the risk of depression onset over time on the individuals exposed and those unexposed to codeine use to be tracked over time. We right censored the data, either at the initial observation at which a participant eventually screened positive, or at the last observation, if the participant did not eventually screen positive for depression. The SA-NIDS study obtained written informed consent from all study participants. The University of KwaZulu-Natal Biomedical Research Ethics Committee provided approval to use the SA-NIDS data.

#### 2.1.2. Geographical clusters ("hotspots") of codeine use

The main source of codeine use data was the publicly available (de-identified) information from the South Africa Demographic and Health (National Department of Health NDoH et al., 2019). Similar to the SA-NIDS, the SA-DHS is also a nationally representative sample of households that employs a stratified, two-stage cluster sampling design. Although the SA-DHS is not a panel, it does contain data from codeine use that is not available in the SA-NIDS. We used the binary "yes" or "no" answer to the question "have you used codeine-contained medication in the past 12 months?" as a measure of codeine exposure. The Kulldorf spatial scan statistic (Kulldorff, 1997) implemented in the SaTScan software (Kulldorff et al., 2005; Kulldorff, 2005) was used to identify the geographical clusters ("hotspots") of codeine use. The permutation model was used to identify clusters that were unlikely to have arisen by chance by testing whether they were significantly adjacent in space. The scan statistical analysis applies a circular window with varying radii continuously for each global positioning system (GPS) coordinate of the SA-DHS households located throughout SA. The analysis identifies a number of distinct potential clusters of codeine use, with the statistical significance of each being tested using a likelihood ratio test. The strength of the codeine use hotspot was compared with use outside the hotspot and estimated using relative risk (RR). The map of spatial clusters of codeine use was overlaid with the SA-NIDS household GPS coordinates that is available from the University of Cape Town's Data First's Secure Data Centre. Individuals were either classified as exposed or unexposed to the codeine hotspot depending on whether they resided within or outside the identified geographical clusters of codeine use.

### 2.2. Statistical analysis

A descriptive analysis of the socio-demographic details of the incident cohort was conducted, after the codeine hotspots were identified.

Thereafter, we quantified the risk of depression onset at Wave 5 between individuals exposed and unexposed to high codeine use communities (i.e. residing inside or outside of a codeine hotspot) who were depression-free at enrolment (Wave 4) using generalised estimating equation (GEE) regression models. The regression model was adjusted for socio-demographic variables, such as age, race, gender, educational attainment, employment status, income, marital status and urban/rural residence. Due to the complexity of the SA-NIDS data, all the analyses involving proportion and regression were adjusted by post-stratification weight to enable the results to appropriately represent the South African population. The post-stratification weight construction by the SA-NIDS is documented elsewhere (Wittenberg, 2009).

### 3. Results

A total number of 13,020 people participated in the survey SA-NIDS, of whom at least 59.1% were female, the majority (82.5%) being African. Over half of the participants (57.9%) had never been married, almost two thirds had completed high school, and two thirds were unemployed. A slight majority (52.5%) lived in rural areas, and 86.0% resided outside the codeine hotspots. Detailed information on the participants' socio-demographic data is presented in Table 1.

**Table 1**  
Sociodemographic profiles of study participants in the incident cohort (N = 13,020).

		n	%
Gender:	Male	5327	40.9%
	Female	7691	59.1%
Race:	African	10,747	82.5%
	White	1898	14.6%
	Coloured	111	0.9%
	Asian/Indian	264	2.0%
Age category:	15–19	2326	17.9%
	20–24	1896	14.6%
	25–29	1617	12.4%
	30–34	1296	10.0%
	35–64	4855	37.3%
	65+	1025	7.9%
Marital status:	Married	3169	24.4%
	Living with partner	938	7.2%
	Widow/Widower	1100	8.5%
	Divorced or separated	267	2.1%
	Never married	7540	57.9%
Highest educational attainment:	Below HS	994	7.6%
	Completed HS	8562	65.8%
	Beyond HS	3459	26.6%
Employment Status:	Unemployed	7889	60.7%
	Employed	5108	39.3%
Location:	Rural	6838	52.5%
	Urban formal	5279	40.5%
	Urban informal	903	6.9%
Exposure to codeine hotspot:	Residing outside hotspot community	10,667	86.0%
	Residing inside hotspot community	1736	14.0%

HS stands for high school. % adjusted for post-stratification weight. The "coloured" is term used by Statistics South Africa (Statistics South Africa, 2004), South African ethnic label that includes children/descendants from black–white, black-Asian, black, colored, and white-Asian unions (Brown, 2000). Due to missing data, the total number of participants differ by variable.

#### 3.1. Geographical clusters ("hotspots") of codeine

We estimated a codeine-containing medication use prevalence of 23.4%. Kulldorf clustering analysis identified four statistically significant clusters of codeine use, mostly located at the northern part of the country, among the provinces of North West, Gauteng, and Mpumalanga (Fig. 1/Table 2). Individuals living within the codeine clusters had a RR of codeine exposure between 1.6 and 2.4. Prevalence of codeine-containing medication use within the hotspots was 21.2% compared to 10.4% outside the hotspots.

#### 3.2. Relationship between codeine exposure and depression

The onset of depression was 25.4% in wave 5 among the cohort without depression at enrolment (wave 4). The results of the regression analysis indicated that residing in a codeine clusters was significantly associated with higher onset of depression (adjusted relative risk [aRR]= 1.21, 95% confidence interval [CI]: 1.08-1.44), even after controlling for various socio-economic factors of age, marital and employment status, as well as household income (Table 3).

### 4. Discussion

In this study, we focused on finding out the association between codeine use and depression onset in initially depression free individuals. We identified a significant association between high exposure to codeine use, measured as residing in a codeine hotspot, and the onset of depression, even after controlling for possible confounding factors. Our finding is consistent with other studies conducted outside SA, which identified high codeine use as increasing the risk of developing depression (Rosoff et al., 2021; Scherrer et al., 2016).

Interestingly, codeine clusters are concentrated in the northern parts of South Africa; that is Gauteng, Mpumalanga and the North West provinces. It is not clear why high codeine use is concentrated in the northern parts of the country but we discuss the possible reasons below. Firstly, Gauteng is the most urbanized and populous province in SA (Baffi et al., 2018; Statistics South Africa, 2020). As a result of being overburdened, the province is not spared from some of the common challenges which result from overcrowding such as poor housing, unemployment and poverty (Nhamo et al., 2021; Turok, 2012), all of which collectively, are known to increase the risk of drug use (Rummage, 2019) including codeine. Other studies have also identified Gauteng Province to be one of the areas where substance abuse is more common in SA (Peltzer et al., 2010).

The other possible reason for the concentration of codeine clusters in northern parts of the country could be related to frequent use of codeine-containing medicines in Mpumalanga and the proximity of the two provinces to Gauteng. Mpumalanga has poor air quality as a result of coal mining making it home to various respiratory infections (Human Rights Watch, 2022) some of which are usually treated with over the counter medicines which contain codeine such as Benylin (Essack et al., 2020). North West Province is largely characterized by rural areas and shortage of medicines has been reported in most SA rural areas (Zuma, 2022) hence access to codeine here is more surprising. However, due to the geographical proximity of both regions particularly North West to Gauteng province, there is a possibility of migration to and from Gauteng, particularly for job seeking, exposing people from the adjacent provinces to the codeine containing medicines in Gauteng. The reasons for the accumulation of codeine clusters in the Northern parts of SA is inconclusive, and the nature of our data could not enable us to determine depression incidence independently for each area making it hard to have a clearer picture. Therefore, future studies could further look at codeine use in these areas which is particularly important for targeted interventions.

The evidence from our study, emanating from the field of spatial mental health research that is largely overlooked in Africa, highlights

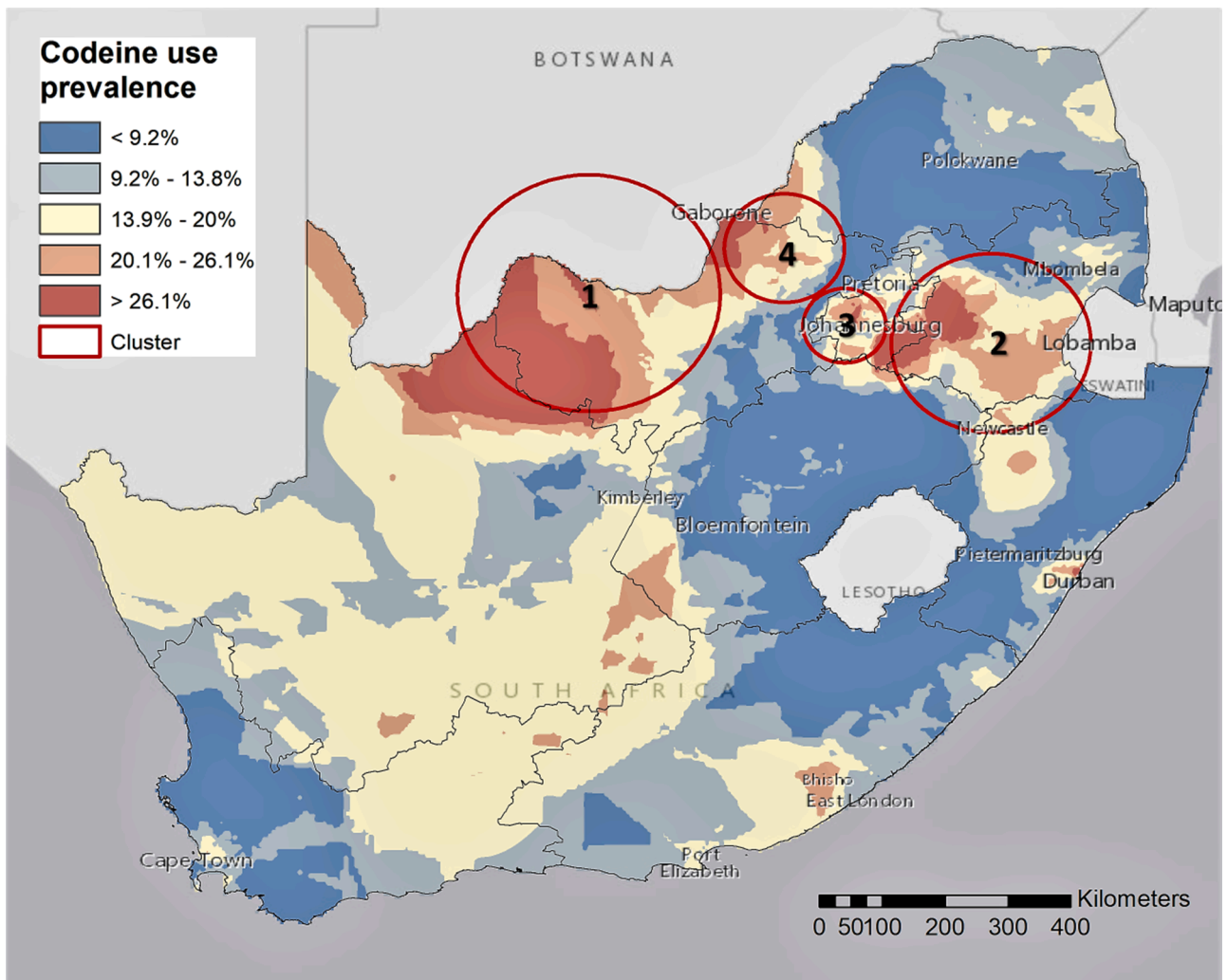


Fig. 1. Spatial distribution and cluster identification of codeine-containing medications in South Africa. Locations of the codeine use clusters (hotspots) illustrated in red circles, superimposed into a continuous surface map of codeine use prevalence generated using kernel interpolation technique.

Table 2  
Cluster information of codeine-containing medications in South Africa.

Cluster number	Radius (km)	Observed cases	Expected cases	Relative risk	Prevalence (%)	P-value
1	187.9	92	40	2.4	26.4	< 0.005
2	141.8	134	79	1.8	22.2	<0.005
3	59.1	105	67	1.6	22.1	<0.005
4	86.8	97	62	1.6	19.6	0.013

Cluster number corresponds to Fig. 1.

several important issues that have policy and practice implications. Firstly, based on nationally representative data, the findings indicate a spatial pattern of clustering of codeine use in SA, suggesting that there are discrete regions and communities at risk for significant opioid abuse. The implication is that the opioid substance abuse epidemic extends well beyond developed nations, but that risk may not be evenly distributed within countries. Importantly therefore, policymakers in countries like South Africa, should focus on educating all communities on the potential dangers of excessive opiate use, but should arguably also develop strategies to target specific communities that may be at particular risk of epidemic opioid misuse.

Secondly, based on the application of the depression incident cohort, the data highlights the increased risk of depression associated with high community exposure to prescription opioids in SA. South Africa faces many complex challenges, such as poverty, hunger and HIV (Gassner

et al., 2019; World Health Organization, 2021b), which are well-recognized threats to population mental health (Tomita et al., 2020; Rubin and Maki, 2019). Our results serve to highlight an additional, somewhat overlooked, public health problem that contributes to the mental health burden. Collectively, all these risk factors for poor mental health threaten the efforts to achieve Goal 3 of the Sustainable Development Goals adopted by all the world’s governments in 2016 (United Nations, 2016). Goal 3 aims to achieve good health and well-being, with targets to prevent, treat and promote mental health. Furthermore, in addition to the design and implementation of effective prevention measures aimed at reducing opiate misuse in SA, we argue that the up-scaling of agonist therapy to effectively treat opioid addiction should be prioritized in communities at specific risk for high codeine misuse. Such strategies would ultimately contribute to improved population mental health.



**Table 3**  
Regression examining the association between exposure to codeine hotspot and depression in incident cohort.

	RR	aRR	SE	95% CI	
Exposure to codeine hotspot: [Residing outside hotspot]	ref				
Residing inside hotspot	1.21	1.25	0.09	1.08	1.44
Gender: [Male]	ref				
Female	1.14	1.07	0.06	0.96	1.2
Race: [White]	ref				
African	1.41	1.11	0.25	0.72	1.72
Coloured	1.11	1.05	0.25	0.66	1.66
Asian/Indian	0.59	0.77	0.33	0.33	1.77
Age category: [15-19]	ref				
20-24	1.65	1.67	0.19	1.33	2.09
25-29	1.81	2.02	0.24	1.6	2.55
30-34	1.94	2.25	0.29	1.75	2.89
35-64	2.16	2.55	0.29	2.04	3.19
65+	2.16	2.14	0.3	1.62	2.83
Marital status: [Married]	ref				
Living with partner	0.82	0.77	0.1	0.61	0.99
Widow/Widower	1.84	1.56	0.15	1.29	1.89
Divorced or separated	1.87	1.8	0.27	1.34	2.41
Never married	1.13	1.28	0.1	1.1	1.5
Highest educational attainment: [Below HS]	ref				
Completed HS	0.73	0.91	0.09	0.75	1.1
Beyond HS	0.66	0.95	0.11	0.76	1.19
Employment Status: [Unemployed]	ref				
Employed	0.89	0.83	0.05	0.74	0.94
Household income: [1st quintile]	ref				
2 <sup>nd</sup> quintile	0.94	0.99	0.08	0.85	1.17
3 <sup>rd</sup> quintile	0.85	0.91	0.08	0.78	1.07
4 <sup>th</sup> quintile	0.64	0.67	0.06	0.57	0.79
5 <sup>th</sup> quintile	0.51	0.55	0.05	0.45	0.66
Location: [Rural]	ref				
Urban formal	1.03	1.09	0.07	0.96	1.23
Urban informal	1.15	1.13	0.11	0.94	1.37

The "coloured" is term used by Statistics South Africa (Statistics South Africa, 2004), a South African ethnic label that includes children/ descendants from black-white, black-Asian, black, colored, and white-Asian unions (Brown, 2000). The regression model adjusted based on post stratification weight (from final observation of the individual panel) to reflect more recent population estimates produced by Statistics South Africa. HS stands for high school. Red highlights indicate  $p < 0.05$ .

One of the main limitations of our study was that depression was measured using a screening rather than a diagnostic tool. However, despite depression not being clinically determined, our study was the first and a nationally representative analysis to identify a significant association between a high prevalence of codeine use and the incident depression in South Africa. Another limitation is our use of a measure of codeine use that relies on a simple 'yes'/'no' to a survey question "have you used codeine-contained medication in the past 12 months?" A single use in the course of a year, therefore, generates a 'yes' response. Of course this cannot be equated with codeine misuse or addiction. However, there is some evidence that suggests that higher population usage of codeine does predict a higher prevalence of codeine misuse in the same population (Algarni et al., 2021). We argue then that our use of this variable on simple codeine usage as a proxy for risk of misuse in the same population is at least partly justified, while acknowledging that we are not measuring codeine misuse itself. We also acknowledge that there

is evidence around the abuse of prescription opioids to alleviate depression symptoms (Grattan et al., 2012). However, an incident cohort was constructed to ensure that participants were depression free initially before using codeine. Finally, the relationship between living in an area with elevated opioid use and onset of depression is an ecological one and as such cannot be used to infer a direct causal relationship. Thus, higher opioid use may not necessarily be occurring in those participants who had onset of depression during the period of follow-up.

Notwithstanding these limitations our study highlights the seemingly overlooked but significant prevalence of prescription opioid use in some regions of SA and its association with the onset of depression in those populations. While the Sub-Saharan region continues to address overwhelming challenges to its people including hunger, poverty and various infectious diseases, the importance of mental ill-health should not be underestimated or ignored, as it too will have a considerable negative effect on regional development if immediate action is not taken. Our study suggests the need for South Africa to enhance its mental health promotion policies, in particular the scaling-up of appropriate interventions that can restrict unnecessary access to opioids and the implementation of suitable interventions to treat opioid addiction in communities at risk.

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### CRediT authorship contribution statement

**Princess Nyoni:** Investigation, Methodology, Writing – original draft, Writing – review & editing. **Diego F. Cuadros:** Investigation, Formal analysis, Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Andrew Gibbs:** Investigation, Writing – review & editing. **Frank Tanser:** Investigation, Writing – review & editing. **Rob Slotow:** Investigation, Writing – review & editing. **Jonathan K Burns:** Investigation, Writing – review & editing. **Andrew Tomita:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

### Declaration of Competing Interest

None.

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