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RESEARCH ARTICLE

Obesity and Incident Prescription Opioid Use in the U.S., 2000–2015

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Introduction: Prior studies have identified associations between obesity and numerous conditions that increase risks for chronic pain. However, the impact of obesity on prescription opioid use is not well known. This study investigates the association between obesity and incidence of long-term prescription opioid use.

Methods: Fifteen panels of the Medical Expenditure Panel Survey from 2000 to 2015 were pooled to generate a sample of civilian non-institutionalized adults aged 30–84 years who were prescription opioid—naïve for approximately 9 months. Incident long-term prescription opioid use was defined as reporting use at 2 of 3 interviews during a 15-month follow-up. BMI was reported at baseline. Analyses were completed in 2019.

Results: Among opioid—naïve adults (n=89,629), obesity was strongly associated with incident long-term prescription opioid use. The association increased at progressively higher BMI values, with 24% elevated odds (95% CI=7%, 44%) in adults with overweight ($25-29.9 \text{ kg/m}^2$) and 158% increased odds (95% CI=106%, 224%) among adults with Class III obesity ($40-49.9 \text{ kg/m}^2$). These associations grew with higher-dosage opioids. Of the reasons for opioid use, joint pain, back pain, injury, and muscle/nerve pain contributed the most to the excess use observed among adults with obesity. At the population level, 27.0% of incident long-term prescription opioid use (95% CI=19.0%, 34.8%) was attributable to adults having a BMI above normal weight ($25-49.9 \text{ kg/m}^2$).

Conclusions: These findings suggest that obesity has contributed to prescription opioid use in the U.S. Future investments in chronic pain reduction may benefit from increased integration with obesity prevention and treatment.

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INTRODUCTION

S ince 1999, prescription opioid use has increased dramatically in the U.S.^{1,2} Accompanying these trends, deaths associated with prescription opioids quadrupled between 2000 and 2014^{3-5} and were involved in more than 17,000 of the estimated 47,600 opioid-related overdose deaths reported in the U.S. in 2017.⁶

The rise in prescription opioids has been attributed to a variety of factors, including aggressive marketing of opioids by pharmaceutical companies, changing norms toward the treatment of chronic noncancer pain in the medical community, and shifting expectations for pain relief among patients.^{7–10} Others have debated the From the ¹Department of Global Health, Boston University School of Public Health, Boston, Massachusetts; ²Robert Wood Johnson Foundation, Princeton, New Jersey; ³Department of Epidemiology, University of Minnesota School of Public Health, Minneapolis, Minnesota; ⁴Philadelphia VA Medical Center, Philadelphia, Pennsylvania; ⁵Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; ⁶Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and ⁷Department of Sociology and Population Studies Center, University of Pennsylvania, Philadelphia, Pennsylvania

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possible social and economic underpinnings of opioid use, tracing the rise to increasing levels of pain and despair related to stagnating wages, job loss, and declining social status.^{11–15}

Another potential factor that has received less attention is the obesity epidemic. In 2015–2016, approximately 40% of U.S. adults had a BMI in the obese range (BMI \geq 30 kg/m²).^{16,17} Numerous conditions that increase risk of chronic pain, such as arthritis, lower back pain, and muscle and nerve pain, are associated with obesity.^{18–20} The physiological mechanisms underlying these associations are increased joint loading, biomechanical effects on the spine, and adipose-derived inflammation.^{21–23} Obesity is further linked to depression and disrupted sleep, which may contribute to fatigue, inactivity, reduced mobility and exercise, and amplification of pain through greater pain sensitization.^{24–26}

Despite the strong association of obesity with chronic pain, the impact of obesity on prescription opioid use is not well established. Chronic pain is a strong prognostic factor for long-term opioid therapy, and thus it is plausible that obesity, through its association with chronic pain, represents an important underlying cause of long-term prescription opioid use.^{27–29}

In a prior study of the association between BMI and opioid use using data from the National Health and Nutrition Examination Survey, adults with obesity were found to be at higher risk of past-30-day opioid use than individuals with normal weight.³⁰ However, owing to the cross-sectional design, the observed associations could reflect confounding by illness or reverse causality between pain, opioid use, and weight status. Thus, this study aims to use a nationally representative longitudinal survey to prospectively examine the association between obesity and incident long-term prescription opioid use in an opioid—naïve sample.

METHODS

Study Sample

The Medical Expenditure Panel Survey (MEPS) is a nationally representative survey of the civilian non-institutionalized U.S. population drawn from the National Health Interview Survey.³¹ Since 1996, MEPS has interviewed approximately 15,000 households annually.³² Data are self-reported or proxy-reported by a single household informant. The survey employs a longitudinal panel design with 5 rounds of interviews that cover 2 calendar years. Each interview has a recall period of approximately 5 months that covers the time since the previous interview.³³

This study pooled data from 15 panels of MEPS spanning from 2000 to 2015. The sample was limited to adults aged 30–84 years with no history of prescription opioid use during their first 2 interview rounds and nonmissing values for all covariates. Respondents who had a current or recent cancer diagnosis (identified using clinical classification codes 11–45) or pregnancy (identified with codes

181–196) were excluded.³⁴ Respondents with a missing BMI or an extreme value $<17.5 \text{ kg/m}^2 \text{ or }>50 \text{ kg/m}^2$ were also dropped. These exclusions are detailed in Appendix Figure 1, available online, and compared with the sample in Appendix Table 1, available online. All analyses were completed in 2019.

This study examined the incidence of long-term prescription opioid use after a recent history of no opioid use. Given the inclusion criteria, respondents had no history of prescription opioid use during their first 2 interviews, which covered an average of 9 months. The time of the second interview, which was the end of the second recall period and the start of the third recall period, was considered baseline. Incident long-term prescription opioid use was defined as opioid use in at least 2 of the 3 interviews after baseline, which spanned an average of 15 months. Sites et al.³⁵ previously used this definition in MEPS to reduce classification of spurious prescription opioid use as chronic. Appendix Figure 2, available online, provides a visual description of the study design.

Measures

MEPS calculates BMI in units of kg/m² using self- or proxy-reported height and weight at baseline. BMI was categorized as underweight (17.5 \leq BMI \leq 19.9), normal weight (20 \leq BMI \leq 24.9), overweight (25 \leq BMI \leq 29.9), Obese I (30 \leq BMI \leq 34.9), Obese II (35 \leq BMI \leq 39.9), and Obese III (40 \leq BMI \leq 49.9). The normal weight category was modified from the standard range (18.5–24.9 kg/m²) to reduce bias from illness-associated weight loss.³⁶ Other covariates included age, which was collapsed into 5-year groups; sex traits (male and female); Census region (Northeast, Midwest, South, and West); race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, and non-Hispanic other/multiple races); education (less than high school, high school or equivalent, some college, and college or beyond); health insurance (any private, only public, and uninsured); and panel year collapsed into 3-panel groups.

MEPS used computer-assisted personal interviewing technology to identify prescription drugs filled in outpatient settings during the recall period since the last interview.³⁷ Pharmacy providers were contacted by mail to obtain medication name, National Drug Code, strength, and quantity. National Drug Codes linked the medications to the Multum Lexicon database from Cerner Multum Inc. and assigned therapeutic classes and subclasses. Ingredient category codes 60 (narcotic analgesics) and 191 (narcotic analgesic combinations) were used to identify prescription opioids.³⁸ Opiates used in the treatment of opioid disorders such as methadone and naloxone were excluded.³⁹

Prescription opioid strength was quantified using morphine milligram equivalents (MMEs). MMEs were calculated by multiplying drug strength in milligrams, quantity, and a conversion factor published by the Centers for Disease Control and Prevention.^{40,41} Average MMEs per recall period were determined by summing MMEs of all prescriptions during each recall period in which the respondent used opioids and taking the mean. Owing to missingness in exact fill dates, it was not possible to calculate average daily MMEs, and thus a statistical threshold was used to classify high dosage as the upper 10% of MME values. A 3-level indicator was then constructed to reflect no long-term use, low dosage use (<90% MME), and high dosage use (\geq 90% MME).

For each prescription medicine or refill, respondents were asked: *What health problem is this medicine prescribed for?* Professional coders converted their responses to ICD-9-CM codes.³⁴ For

confidentiality, specific ICD-9 codes were collapsed into 3-digit codes. Participants could have more than 1 reason for opioid use if they had multiple prescriptions or if a single prescription was linked to multiple conditions. All reported ICD-9 codes were classified using a typology adapted from Sherry and colleagues⁴² and listed in Appendix Table 2, available online.

Respondents were asked about their perceived mental health at Round 3 (*excellent/good/fair* and *poor*). They also completed a self-administered questionnaire containing the Short Form-12 during their first year. The Short Form-12 mental health summary score distribution was analyzed each year to produce a 6-level indicator using percentiles (lower 10th, 10th-30th, 30th-50th, 50th-70th, 70th-90th, and upper 90th), with lower scores indicating poorer health. Lastly, respondents were asked on the questionnaire if they currently smoke (*yes* or *no*).

Statistical Analysis

Multivariable logistic regression was used to evaluate the association of BMI category with incident long-term prescription opioid use, adjusting for age, sex, race/ethnicity, region, education, smoking, health insurance, and panel year. Multinomial logistic regression was used to examine the association of BMI category with the 3-level outcome for incident use incorporating opioid strength (no use, low dosage, and high dosage). To assess the possibility of a nonlinear relationship between BMI and incident use, BMI was modeled as a restricted cubic spline with 5 evenly spaced knots, and this model was used in a multivariable logistic regression to produce a smooth curve of the BMI-opioid association from 17.5 to 49.9 kg/m². Population attributable fractions were calculated to quantify the fraction of incident long-term prescription opioid use that could be avoided if adults with a BMI above normal weight instead had a normal BMI. Risk estimates for the population attributable fractions were obtained using a multivariable logistic regression with dichotomous underweight, overweight, Obese I, Obese II, and Obese III variables. As the outcome was rare, ORs approximated RRs.43,44

Next, predicted probabilities for reporting incident use and each pain condition (alone or in combination with other conditions) as the reason for use were estimated using multivariable logistic regression. Predicted probabilities were reported for the population overall and for the normal weight, overweight, and obese categories. The absolute difference in incidence for each pain condition reported as a reason for use by obesity status was determined by subtracting the probability for adults with normal weight from the probability for adults with obesity.

In the primary analysis, mental health status was not included as a model covariate, as mental health may be a key mediator of the association between obesity and prescription opioid use through disrupted sleep, mobility limitation, and stigma and discrimination.^{24,25} Thus, in a sensitivity analysis, perceived mental health and Short Form–12 mental health summary scores were introduced as covariates. A second sensitivity analysis examined potential confounding by smoking status by limiting the regression to nonsmoking adults. A final sensitivity analysis used multinomial logistic regression to assess the association between BMI category and incident prescription opioid use incorporating chronicity (no use, acute use, and long-term use).

Stata, version 15 was used for all analyses. Restricted cubic spline models were plotted using the xbrcspline package.⁴⁵

Population attributable fractions were calculated with the punafcc package.⁴⁶ Analyses were sample weighted using MEPS longitudinal weights, and 95% CIs were reported. Per MEPS analytic guidelines, sample weights were divided by 15 to account for pooling longitudinal panels. Variance primary sampling units and strata were also specified to account for the complex survey design, which included clustering, stratification, and oversampling of priority populations. IRB approval was not required for these analyses of publicly available, de-identified data.

RESULTS

The sample included 89,629 adults. Among them, 1,985 (2.2%) developed incident long-term prescription opioid use (Table 1).

The overall incidence of long-term prescription opioid use in the sample increased substantially with obesity (Figure 1). Adults who were overweight or obese had elevated odds of incident use compared with adults with normal weight after adjusting for covariates (overweight: OR=1.24, 95% CI=1.07, 1.44; Obese I: OR=1.74, 95% CI=1.49, 2.03; Obese II: OR=2.10, 95% CI=1.69, 2.59; Obese III: OR=2.58, 95% CI=2.06, 3.24) (Appendix Table 3, available online).

At the population level, 27.0% (95% CI=19.0%, 34.8%) of incident long-term prescription opioid use was attributable to having a BMI above normal (Appendix Table 4, available online). Thus, approximately one quarter of all incident long-term prescription opioid use in the U.S. could be averted in a scenario in which all individuals with a BMI of overweight or obese instead lost weight and entered the normal BMI category.

The association between obesity and incident use of high-dosage opioids (\geq 90% MME) was stronger than the association between obesity and low dosage use (<90% MME) (Table 2). Adults in the Obese III category were 6.38 times more likely (95% CI=3.16, 12.87) to receive high-dosage prescription opioids but only 2.32 times more likely (95% CI=1.83, 2.95) to receive a low dosage compared with individuals with normal weight (Appendix Table 5, available online).

The pain conditions most frequently cited as reasons for initiating long-term prescription opioid use were joint pain, back pain, and injury. Figure 2 shows the adjusted proportion of reporting incident use and each pain condition among respondents with normal and obese BMI, respectively. Overall, joint pain (difference for obese versus normal: 0.68%, 95% CI=0.49, 0.88), back pain (difference for obese versus normal: 0.45%, 95% CI=0.29, 0.61), injury (difference for obese versus normal: 0.41%, 95% CI=0.25, 0.57), and muscle/nerve pain (difference for obese versus normal: 0.20%, 95% CI=0.10, 0.30) contributed most to the absolute difference in incident use among adults with obesity

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Table 1. Baseline Demographics for Adults Aged 30–84 Years With No History of Opioid Use, MEPS 2000–2015

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Demographics		Incident opioid use ^a (<i>n</i> =1,985)	incidence proportion, %	
Age, years, mean (SD)	50.9 (±13.7)	54.1 (±13.1)	-	
Sex traits, n (%)				
Male	42,869 (50.2)	798 (42.8)	1.9	
Female	46,760 (49.8)	1,187 (57.2)	2.6	
Race/ethnicity, n (%)				
White, NH	45,888 (69.3)	1,166 (74.4)	2.4	
Hispanic	21,558 (12.9)	304 (8.5)	1.5	
Black, NH	14,853 (10.9)	405 (12.4)	2.6	
Other/multiple races, NH	7,330 (6.8)	110 (4.7)	1.5	
Census region, n (%)				
Northeast	14,391 (19.0)	258 (14.0)	1.7	
Midwest	17,640 (22.2)	433 (23.0)	2.3	
South	34,170 (36.3)	835 (41.0)	2.5	
West	23,428 (22.5)	459 (21.9)	2.2	
Educational attainment, n (%)				
Less than high school	20,178 (14.8)	494 (18.6)	2.8	
High school or equivalent	27,617 (30.4)	666 (33.9)	2.5	
Some college	19,698 (24.1)	487 (26.3)	2.4	
College degree or beyond	22,136 (30.6)	338 (21.3)	1.6	
Insurance status, n (%)				
Any private insurance	57,601 (72.9)	1,146 (65.0)	2.0	
Only public insurance	15,547 (13.6)	619 (24.9)	4.1	
Uninsured	16,481 (13.5)	220 (10.1)	1.7	
Current smoking, <i>n</i> (%)				
Does not currently smoke	72,176 (80.4)	1,377 (70.1)	2.0	
Currently, smokes	17,453 (19.6)	608 (29.9)	3.4	
SF-12 mental health summary score, n				
Lower 10th percentile	7,860 (8.0)	398 (18.2)	5.1	
10th to 30th percentile	17,177 (17.5)	471 (21.6)	2.8	
30th to 50th percentile	17,895 (20.2)	347 (18.6)	2.1	
50th to 70th percentile	17,847 (21.7)	306 (16.9)	1.7	
70th to 90th percentile	19,797 (23.6)	306 (16.9)	1.6	
Upper 90th percentile	9,053 (9.0)	157 (7.9)	2.0	
Perceived mental health, n (%)		- (-)		
Excellent/Good/Fair health	88,497 (98.9)	1,902 (96.0)	2.2	
Poor health	1,132 (1.1)	83 (4.0)	8.0	
Year of incident use, n (%)				
2001–2003	18,051 (19.3)	332 (16.0)	1.9	
2004–2006	17,615 (19.8)	393 (19.5)	2.2	
2007–2009	17,143 (19.6)	362 (18.8)	2.1	
2010-2012	18,521 (20.6)	417 (21.1)	2.3	
2013-2015	18,299 (20.6)	481 (24.6)	2.7	
BMI category (kg/m ²), n (%)	_0,200 (20.0)			
Underweight (17.5–19.9)	3,044 (3.7)	49 (2.8)	1.7	
Normal (20–24.9)	24,820 (29.3)	416 (21.8)	1.7	
Overweight (25–29.9)	33,740 (37.4)	655 (33.0)	2.0	
Obese I (30–34.9)	17,615 (18.6)	443 (23.5)	2.8	
Obese II (35–34.9)	6,844 (7.2)	255 (11.5)	3.6	
Obese III (40-49.9)	3,566 (3.7)	167 (7.5)	4.5	

Note: Proportions weighted using MEPS longitudinal sample weights to be nationally representative.

^aIncident long-term prescription opioid use = any opioid use reported in at least 2 of 3 interviews over approximately 15 months after a recent history of no opioid use during the respondent's first 2 interviews, which covered approximately 9 months.

MEPS, Medical Expenditure Panel Survey; NH, non-Hispanic; SF-12, Short Form-12.

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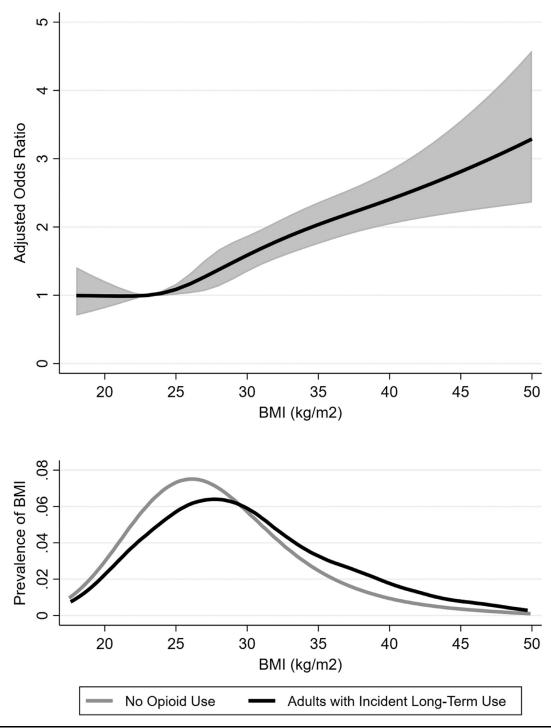


Figure 1. Incident long-term prescription opioid use by BMI in adults aged 30–84 years, MEPS 2000–2015 (*n*=89,629). ORs were calculated using a multivariable logistic regression with BMI modeled as a restricted cubic spline. Results adjusted for age, sex, race/ethnicity, region, education, current smoking, health insurance, and panel year. MEPS, Medical Expenditure Panel Survey.

compared with normal weight (Appendix Table 6, available online).

A sensitivity analysis including mental health variables as covariates yielded similar results to the main regression (overweight: OR=1.23, 95% CI=1.06, 1.41; Obese I: OR=1.69, 95% CI=1.44, 1.97; Obese II: OR=2.00, 95% CI=1.61, 2.47; Obese III: OR=2.43, 95% CI=1.94, 3.05) (Appendix Table 7, available online). A

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 Table 2.
 Association of BMI and Incident Long-Term Prescription Opioid Use Incorporating Opioid Strength in Adults Aged
 30–84 Years, MEPS 2000–2015 (n=89,629)
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	BMI category (kg/m ²)							
Variable	Underweight (17.5–19.9)	Normal (20–24.9)	0verweight (25–29.9)	Obese I (30–34.9)	Obese II (35–39.9)	Obese III (40–49.9)		
Overall use (any dosage)								
OR ^a (95% CI)	0.94 (0.64, 1.36)	ref	1.24 (1.07, 1.44)	1.74 (1.49, 2.03)	2.10 (1.69, 2.59)	2.58 (2.06, 3.24)		
<i>p</i> -value	0.73	_	0.004	<0.001	<0.001	<0.001		
Low dosage use (<90% MME)								
RRR ^b (95% CI)	0.88 (0.58, 1.33)	ref	1.19 (1.01, 1.40)	1.65 (1.41, 1.94)	2.02 (1.63, 2.51)	2.32 (1.83, 2.95)		
p-value	0.54	_	0.03	<0.001	<0.001	<0.001		
High dosage use (≥90% MME)								
RRR ^b (95% CI)	1.77 (0.78, 4.05)	ref	1.99 (1.17, 3.40)	2.94 (1.67, 5.19)	3.15 (1.63, 6.07)	6.38 (3.16, 12.87		
<i>p</i> -value	0.17	_	0.01	<0.001	<0.001	<0.001		

Note: Boldface indicates statistical significance (p<0.05). MME was calculated by multiplying strength in milligrams, quantity, and a conversion factor associated with the prescription opioid's national drug code. Prescriptions and refills were summed for each of the 2 or 3 recall periods when the respondent used prescription opioids to calculate average MME per recall period. High dosage use was indicated by reporting an average MME per recall period value in the upper 10% of values.

^aORs calculated using multivariable logistic regression and a 2-level outcome variable (no use, incident long-term prescription opioid use) with BMI modeled categorically, adjusting for age, sex, race/ethnicity, region, education, current smoking, health insurance, and panel year. Appendix Table 3, available online, presents the complete regression results.

^bRRRs calculated using multinomial logistic regression with BMI modeled categorically and a 3-level outcome variable (no opioid use, low dosage use, high dosage use), adjusting for age, sex, race/ethnicity, region, education, current smoking, health insurance, and panel year. Appendix Table 5, available online, presents the complete regression results.

MEPS, Medical Expenditure Panel Survey; MME, morphine milligram equivalence.

sensitivity analysis that limited the sample to nonsmoking adults found an even stronger association (overweight: OR=1.32, 95% CI=1.09, 1.59; Obese I: OR=1.87, 95% CI=1.54, 2.28; Obese II: OR=2.56, 95% CI=2.01, 3.25; Obese III: OR=3.20, 95% CI=2.47, 4.14) (Appendix Table 8, available online). Lastly, a sensitivity analysis incorporating chronicity identified a larger association for incident long-term use than acute use (Appendix Table 9, available online).

DISCUSSION

In this nationally representative longitudinal study, a strong association was identified between obesity and incident long-term prescription opioid use during approximately 15 months of follow-up. The association increased at progressively higher BMI values. At the population level, approximately one quarter of incident use was attributable to having overweight or obese BMI.

One explanation for this association is that individuals experience different types of chronic pain related to obesity. Four categories of pain—joint pain, back pain, injury, and muscle and nerve pain—emerged as the most important conditions in explaining the gap in incident use between the obese and normal weight categories. Obesity is a well-established and prominent risk factor for osteoarthritis and other joint disorders including several conditions leading to chronic lower back pain, including spondylosis, and internal disc disruption.^{20,47} Risk of these disorders may stem from altered biomechanics, excessive joint loading, and upregulation of inflammatory pathways in individuals with excessive adiposity.^{21–23,48} With respect to injury, prior studies have reported higher rates of strains, sprains, and occupational injuries in individuals with obesity.⁴⁹ Additionally, previous studies have found significant associations of obesity with muscle and nerve pain, including neuropathy and disorders of muscle ligaments.⁵⁰

Obesity is also associated with increased depression, pain perception, and disturbed sleep,^{25,51–53} which could present additional pathways through which BMI affects chronic pain and opioid use.⁵⁴ Although increased chronic pain and prescription opioid use are closely associated with depression and poor mental health, this study revealed that adults living with obesity were at heightened risk for long-term prescription opioid use, even after adjusting for mental health.

This study further identified increased usage of higherdosage opioids among adults with obesity. Although these observations might reflect differences in dosing related to weight-based efficacy,⁵⁵ they may also suggest more rapid dose escalation in adults with obesity. Early dose escalation is associated with increased healthcare utilization and risk of substance use disorders.⁵⁶

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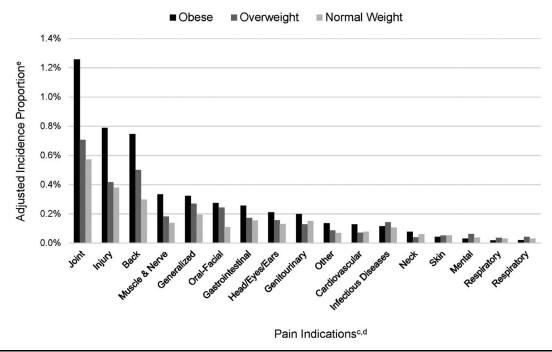


Figure 2. Pain indications reported as reasons for incident long-term prescription opioid use by BMI category in adults aged 30–84 years, MEPS 2000–2015 (n=86,585). BMI category was defined as obese (30–49.9 kg/m²), overweight (25–29.9 kg/m²), and normal weight (20–24.9 kg/m²). Underweight (17.5–20 kg/m²) was excluded. Results adjusted for age, sex, race/ethnicity, region, education, current smoking, health insurance, and panel year. Respondents could attribute opioid use to multiple pain indications. Appendix Table 2, available online, provides ICD-9-CM codes included in each indication category. Sample interpretation: 1.3% of the sample with obesity, 0.7% of the sample that is overweight, and 0.6% of the sample that is normal weight reported incident long-term prescription opioid use and attributed that use to joint pain alone or in combination with other pain indications. MEPS, Medical Expenditure Panel Survey.

Although prescription opioids are not recommended as a first-line treatment for chronic pain owing to risks for long-term dependence and overdose, nonsteroidal anti-inflammatory drugs are contraindicated in patients with cardiovascular disease,⁴¹ which occurs disproportionally with obesity.⁵⁷ Therefore, primary prevention and secondary treatment of obesity among adults with chronic pain may be useful in reducing the use of prescription opioids in this population.

This study is broadly relevant to trends in U.S. mortality and life expectancy. Case and Deaton^{11,58} recently described a constellation of trends that include rising death rates from drug overdose, suicide, and alcohol abuse as well as increasing levels of chronic pain. They did not, however, include rising obesity as a possible factor in these trends. By contrast, Preston et al.⁵⁹ concluded that rising levels of obesity reduced rates of improvement in U.S. death rates by 30% from 1988 to 2011. This study suggests that trends in obesity, pain, and demand for opioids may be more closely linked than heretofore acknowledged. However, this does not diminish the role of supply-side factors such as aggressive marketing by

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manufacturers in increasing the availability of opioids for adults with chronic pain.^{8,60}

Future research is needed to determine if the association between BMI and prescription opioid use is related to greater prevalence of pain conditions among adults with obesity or increased likelihood of receiving an opioid conditional on pain conditions. Another important topic is if BMI affects the likelihood of illicit opioid dependence, opioid use disorders, and overdose.

Limitations

This study had several limitations. The period for establishing an opioid-naïve cohort was limited to an average of 9 months, and thus some individuals could have a history of opioid use that was not captured. MEPS also only reports prescription opioids filled in outpatient settings.⁶¹ Second, the sample was not chronic pain—naïve, which may have introduced bias associated with illness-related weight gain, leading to overestimation of the obesity opioid association. By contrast, the incidence of most major diseases is associated with weight loss rather than weight gain.⁶² Thus, if certain illnesses simultaneously acted to reduce BMI and increase risk of opioid use 8

because of chronic pain, underestimation is also possible. Third, the Obese Class IV category, which includes BMI $>50 \text{ kg/m}^2$, was not examined but may represent an important high-risk group. Finally, this analysis was based on BMI data reported by a single household informant, which could introduce bias in the estimation of ORs.

CONCLUSIONS

This study suggests that obesity contributed significantly to incident long-term prescription opioid use in the U.S. from 2000 to 2015. Joint pain, back pain, injury, and muscle/nerve pain, which prior studies have linked with obesity, emerged as important types of pain in explaining excess prescription opioid use among adults with obesity. Future investments in chronic pain reduction may benefit from increased integration with obesity prevention and treatment. As the BMI distribution in the U.S. grows increasingly overweight and obese, a comprehensive response is needed to prevent an even greater contribution of obesity to the opioid epidemic.

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AS and DL had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. AS designed the study, interpreted the data, and wrote the manuscript. DL performed the analyses and contributed to interpreting the data and writing the manuscript. KMB and KH contributed to the study design and interpretation of the data and reviewed and edited the manuscript. JFB and SHP reviewed the manuscript and contributed to the introduction and discussion.

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SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j. amepre.2019.12.018.

REFERENCES

- Guy GP, Zhang K, Bohm MK, et al. Vital signs: changes in opioid prescribing in the United States, 2006–2015. MMWR Morb Mortal Wkly Rep. 2017;66(26):697–704. https://doi.org/10.15585/mmwr. mm6626a4.
- Schuchat A, Houry D, Guy GP. New data on opioid use and prescribing in the United States. *JAMA*. 2017;318(5):425–426. https://doi.org/ 10.1001/jama.2017.8913.

- Rudd RA, Aleshire N, Zibbell JE, Matthew Gladden R. Increases in drug and opioid overdose deaths–United States, 2000–2014. *Am J Transplant*. 2016;16(4):1323–1327. https://doi.org/10.1111/ajt.13776.
- Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999–2017. NCHS Data Brief. 2018;(329):1–8. www. ncbi.nlm.nih.gov/pubmed/30500323. Accessed February 9, 2020.
- 5. Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science*. 2018;361(6408): eaau1184. https://doi.org/10.1126/science.aau1184.
- Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and opioidinvolved overdose deaths — United States, 2013–2017. MMWR Morb Mortal Wkly Rep. 2018;67(5152):1419–1427. https://doi.org/ 10.15585/mmwr.mm675152e1.
- Dasgupta N, Beletsky L, Ciccarone D. Opioid crisis: no easy fix to its social and economic determinants. *Am J Public Health.* 2018;108 (2):182–186. https://doi.org/10.2105/AJPH.2017.304187.
- Hadland SE, Rivera-Aguirre A, Marshall BDL, Cerdá M. Association of pharmaceutical industry marketing of opioid products with mortality from opioid-related overdoses. *JAMA Netw Open.* 2019;2(1): e186007. https://doi.org/10.1001/jamanetworkopen.2018.6007.
- Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A brief history of the opioid epidemic and strategies for pain medicine. *Pain Ther*. 2018;7(1):13–21. https://doi.org/10.1007/s40122-018-0097-6.
- Hadland SE, Cerdá M, Li Y, Krieger MS, Marshall BDL. Association of pharmaceutical industry marketing of opioid products to physicians with subsequent opioid prescribing. *JAMA Intern Med.* 2018;178 (6):861–863. https://doi.org/10.1001/jamainternmed.2018.1999.
- Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci U S A.* 2015;112(49):15078–15083. https://doi.org/10.1073/ pnas.1518393112.
- Graham C, Pinto S. Unequal hopes and lives in the USA: optimism, race, place, and premature mortality. *J Popul Econ*. 2019;32(2):665– 733. https://doi.org/10.1007/s00148-018-0687-y.
- Currie J, Jin JY, Schnell M. U.S. Employment and Opioids: Is There a Connection? NBER Work Pap Ser. 2018:24440. https://doi.org/ 10.3386/w24440.
- Hollingsworth A, Ruhm CJ, Simon K. Macroeconomic conditions and opioid abuse. NBER Work Pap Ser. 2017:23192. https://doi.org/ 10.3386/w23192.
- Ruhm CJ. Deaths of Despair or Drug Problems? NBER Work Pap Ser. 2018:24188. https://doi.org/10.3386/w24188.
- Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015–2016. NCHS Data Brief. 2017(288):1–8. https://www.cdc.

gov/nchs/data/databriefs/db288.pdf. Accessed February 9, 2020.

- Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in U.S. youth and adults by sex and age, 2007–2008 to 2015–2016. *JAMA*. 2018;319(16):1723– 1725. https://doi.org/10.1001/jama.2018.3060.
- Okifuji A, Hare BD. The association between chronic pain and obesity. J Pain Res. 2015;8:399–408. https://doi.org/10.2147/JPR.S55598.
- Kulkarni K, Karssiens T, Kumar V, Pandit H. Obesity and osteoarthritis. *Maturitas*. 2016;89:22–28. https://doi.org/10.1016/j.maturitas. 2016.04.006.
- Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between obesity and low back pain: a meta-analysis. *Am J Epidemiol.* 2010;171(2):135–154. https://doi.org/10.1093/aje/kwp356.
- Koonce RC, Bravman JT. Obesity and osteoarthritis: more than just wear and tear. J Am Acad Orthop Surg. 2013;21(3):161–169. https:// doi.org/10.5435/JAAOS-21-03-161.
- Urban H, Little CB. The role of fat and inflammation in the pathogenesis and management of osteoarthritis. *Rheumatology(Oxford)*. 2018;57 (suppl 4):iv10-iv21. https://doi.org/10.1093/rheumatology/kex399.

- Ghezelbash F, Shirazi-Adl A, Plamondon A, Arjmand N, Parnianpour M. Obesity and obesity shape markedly influence spine biomechanics: a subject-specific risk assessment model. *Ann Biomed Eng.* 2017;45 (10):2373–2382. https://doi.org/10.1007/s10439-017-1868-7.
- Jantaratnotai N, Mosikanon K, Lee Y, McIntyre RS. The interface of depression and obesity. *Obes Res Clin Pract.* 2017;11(1):1–10. https:// doi.org/10.1016/j.orcp.2016.07.003.
- Katz P, Margaretten M, Trupin L, Schmajuk G, Yazdany J, Yelin E. Role of sleep disturbance, depression, obesity, and physical inactivity in fatigue in rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2016;68(1):81–90. https://doi.org/10.1002/acr.22577.
- Okifuji A, Donaldson GW, Barck L, Fine PG. Relationship between fibromyalgia and obesity in pain, function, mood, and sleep. *J Pain*. 2010;11(12):1329–1337. https://doi.org/10.1016/j.jpain.2010.03.006.
- Shah A, Hayes CJ, Martin BC. Factors influencing long-term opioid use among opioid naive patients: an examination of initial prescription characteristics and pain etiologies. J Pain. 2017;18(11):1374– 1383. https://doi.org/10.1016/j.jpain.2017.06.010.
- Quinn PD, Hur K, Chang Z, et al. Incident and long-term opioid therapy among patients with psychiatric conditions and medications: a national study of commercial health care claims. *Pain.* 2017;158 (1):140–148. https://doi.org/10.1097/j.pain.00000000000730.
- Katz C, El-Gabalawy R, Keyes KM, Martins SS, Sareen J. Risk factors for incident nonmedical prescription opioid use and abuse and dependence: results from a longitudinal nationally representative sample. *Drug Alcohol Depend.* 2013;132(1-2):107-113. https://doi.org/ 10.1016/j.drugalcdep.2013.01.010.
- Stokes A, Berry KM, Collins JM, et al. The contribution of obesity to prescription opioid use in the United States. *Pain*. 2019;160(10):2255– 2262. https://doi.org/10.1097/j.pain.000000000001612.
- Cohen JW, Monheit AC, Beauregard KM, et al. The Medical Expenditure Panel. The Medical Expenditure Panel Survey: a national health information resource. *Inquiry*. 1996;33(4):373–389. www.jstor.org/stable/29772654.
- 32. Ezzati-Rice TM, Rohde F, Greenblatt J. Sample Design of the Medical Expenditure Panel Survey Household Component, 1998–2007. Methodology Report # 22. Rockville, MD: Agency for Healthcare Research and Quality. https://meps.ahrq.gov/data_files/publications/mr22/ mr22.pdf. Published 2008. Accessed December 16, 2019.
- Cohen SB. Design strategies and innovations in the Medical Expenditure Panel Survey. *Med Care*. 2003;41(7suppl):III5–III12. https://doi. org/10.1097/01.MLR.0000076048.11549.71.
- Machlin S, Cohen J, Elixhauser A, Beauregard K, Steiner C. Sensitivity of household reported medical conditions in the Medical Expenditure Panel Survey. *Med Care*. 2009;47(6):618–625. https://doi.org/10.1097/ MLR.0b013e318195fa79.
- 35. Sites BD, Harrison J, Herrick MD, Masaracchia MM, Beach ML, Davis MA. Prescription opioid use and satisfaction with care among adults with musculoskeletal conditions. *Ann Fam Med.* 2018;16(1):6–13. https://doi.org/10.1370/afm.2148.
- Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med. 2010;363(23):2211–2219. https://doi.org/10.1056/NEJMoa1000367.
- Medical Expenditure Panel Survey. Panel 20, Rounds 3–5, Panel 21, Rounds 1–3; prescribed medicines (PM). Medical Expenditure Panel survey. https://meps.ahrq.gov/survey_comp/hc_survey/2016/Pm-111416.pdf. Published 2016. Accessed February 10, 2019.
- Kea B, Fu R, Lowe RA, Sun BC. Interpreting the National Hospital Ambulatory Medical Care Survey: United States Emergency Department opioid prescribing, 2006–2010. Acad Emerg Med. 2016;23 (2):159–165. https://doi.org/10.1111/acem.12862.
- Bart G. Maintenance medication for opiate addiction: the foundation of recovery. J Addict Dis. 2012;31(3):207–225. https://doi.org/10.1080/ 10550887.2012.694598.

- CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors. CDC. www.cdc.gov/drugoverdose/resources/ data.html. Published 2018. Accessed December 16, 2019.
- Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA. 2016;315 (15):1624–1645. https://doi.org/10.1001/jama.2016.1464.
- 42. Sherry TB, Sabety A, Maestas N. Documented pain diagnoses in adults prescribed opioids: results from the National Ambulatory Medical Care Survey, 2006–2015. Ann Intern Med. 2018;169(12):892–894. https://doi.org/10.7326/M18-0644.
- Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA*. 1998;280 (19):1690–1691. https://doi.org/10.1001/jama.280.19.1690.
- Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health*. 1998;88(1):15–19. https:// doi.org/10.2105/ajph.88.1.15.
- Orsini N. XBRCSPLINE: Stata module to tabulate differences in predicted responses after restricted cubic spline models. *Stat Softw Compon.* 2019:S457092. https://ideas.repec.org/c/boc/bocode/s457092. html. Accessed December 16, 2019.
- Newson R. PUNAFCC: Stata module to compute population attributable fractions for case-control and survival studies. Stat Softw Compon. 2011:S457354. https://ideas.repec.org/c/boc/bocode/s457354. html. Accessed December 16, 2019.
- 47. Reyes C, Leyland KM, Peat G, Cooper C, Arden NK, Prieto-Alhambra D. Association between overweight and obesity and risk of clinically diagnosed knee, hip, and hand osteoarthritis: a population-based cohort study. *Arthritis Rheumatol.* 2016;68(8):1869–1875. https://doi. org/10.1002/art.39707.
- King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. *Indian J Med Res.* 2013;138(2):185–193. www.ncbi.nlm.nih.gov/ pubmed/24056594. Accessed December 16, 2019.
- Gu JK, Charles LE, Andrew ME, et al. Prevalence of work-site injuries and relationship between obesity and injury among U.S. workers: NHIS 2004–2012. J Saf Res. 2016;58:21–30. https://doi.org/10.1016/j. jsr.2016.06.001.
- Hozumi J, Sumitani M, Matsubayashi Y, et al. Relationship between neuropathic pain and obesity. *Pain Res Manag.* 2016;2016:2487924. https://doi.org/10.1155/2016/2487924.
- Beydoun MA, Wang Y. Pathways linking socioeconomic status to obesity through depression and lifestyle factors among young U.S. adults. J Affect Disord. 2010;123(1-3):52-63. https://doi.org/10.1016/ j.jad.2009.09.021.
- 52. Tyrrell J, Mulugeta A, Wood AR, et al. Using genetics to understand the causal influence of higher BMI on depression. *Int J Epidemiol.* 2019;48(3):834–848. https://doi.org/10.1093/ije/dyy223.
- 53. Torensma B, Oudejans L, van Velzen M, Swank D, Niesters M, Dahan A. Pain sensitivity and pain scoring in patients with morbid obesity. *Surg Obes Relat Dis.* 2017;13(5):788–795. https://doi.org/10.1016/j. soard.2017.01.015.
- Sullivan MD. Depression effects on long-term prescription opioid use, abuse, and addiction. *Clin J Pain*. 2018;34(9):878–884. https://doi.org/ 10.1097/AJP.0000000000603.
- Patanwala AE, Edwards CJ, Stolz L, Amini R, Desai A, Stolz U. Should morphine dosing be weight based for analgesia in the emergency department. J Opioid Manag. 2012;8(1):51–55. https://doi.org/ 10.5055/jom.2012.0096.
- Henry SG, Wilsey BL, Melnikow J, Iosif AM. Dose escalation during the first year of long-term opioid therapy for chronic pain. *Pain Med.* 2015;16(4):733–744. https://doi.org/10.1111/pme.12634.
- Varga Z, Sabzwari SRA, Vargova V. Cardiovascular risk of nonsteroidal anti-inflammatory drugs: an under-recognized public health issue. *Cureus.* 2017;9(4):e1144. https://doi.org/10.7759/cureus.1144.

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- Case A, Deaton A. Mortality and morbidity in the 21st century. *Brookings Pap Econ Act.* 2017;2017:397–476. https://doi.org/10.1353/eca.2017.0005.
- Preston SH, Vierboom YC, Stokes A. The role of obesity in exceptionally slow U.S. mortality improvement. *Proc Natl Acad Sci U S A*. 2018;115(5):957–961. https://doi.org/10.1073/pnas.1716802115.
- Van Zee A. The promotion and marketing of OxyContin: commercial triumph, public health tragedy. Am J Public Health. 2009;99(2):221– 227. https://doi.org/10.2105/AJPH.2007.131714.
- Miller GE, Moriya AS. Any use and frequent use of opioids among non-elderly adults in 2015–2016, by socioeconomic characteristics. Statistical Brief #515. Rockville, MD: Agency for Healthcare Resarch and Quality. https://meps.ahrq.gov/data_files/publications/st515/stat515.shtml. Published 2001. Accessed December 16, 2019.
- Vierboom YC, Preston SH, Stokes A. Patterns of weight change associated with disease diagnosis in a national sample. *PLoS One.* 2018;13 (11):e0207795. https://doi.org/10.1371/journal.pone.0207795.