Rise in mortality involving poisoning by medicaments other than narcotics, including poisoning by psychotropic and sedative-hypnotic drugs in different age/racial groups in the US

Edward Goldstein[1,*]

1. Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA 02115 USA.

*. Corresponding author, egoldste@hsph.harvard.edu

Abstract

Background: Life expectancy in white Americans has dropped during the last two decades compared to other major racial groups, and increase in mortality for poisoning, particularly by narcotics, is known to have been one of the contributing factors. However, the contribution of medicaments other than narcotics to mortality in different racial/age groups is less studied.

Methods: We regressed annual rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics (ICD-10 codes T36-39.xx or T41-50.8 but not T40.xx present as either underlying or contributing causes of death), as well as the annual rates of other mortality outcomes, including mortality involving poisoning by psychotropic drugs but not narcotics and psychodysleptics (ICD-10 codes T43.xx but not T40.xx present as either underlying or contributing causes of death) in different age/racial groups for both the 2000-2011 period and the 2011-2017 period against calendar year.

Results: The biggest increases in the rates of mortality per 100,000 individuals involving poisoning by medicaments but not narcotics and psychodysleptics for both the 2000-2011 and 2011-2017 periods were in non-elderly Non-Hispanic Native Americans (with annual increases peaking at 0.41(0.18,0.64)/year for ages 35-44y between 2000-2011, and at 2.25(1.67,2.83)/year for ages 45-54y between 2011-2017), followed by Non-Hispanic whites (with annual increases peaking at 0.24(0.21,0.27)/year for ages 45-54y between 2000-2011, and at 0.58(0.45,0.7)/year for ages 45-54y between 2011-2017). Most of the increases in the rates of

mortality involving poisoning by medicaments but not narcotics and psychodysleptics came from increases in the rates of mortality involving poisoning by psychotropic drugs but not narcotics and psychodysleptics; the latter rates for the overall US population grew for the period of 2015-2017 vs. 2000-2002 by a factor of 3.22 for ages 25-34y, 2.75 for ages 35-44y, 3.48 for ages 45-54y, 5.37 for ages 55-64y, and 3.94 for ages 65-74y, with those increases exceeding the growth in the rates of prescribing for psychotropic medications during that period. Additionally, there were no correlations between state-specific rates of mortality involving poisoning by psychotropic drugs but not narcotics/psychodysleptics and state-specific rates of mortality involving poisoning by narcotics/psychodysleptics (with negative, non-significant correlations between those rates), suggesting potential differences in factors behind those two epidemics.

Conclusions: Rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics, particularly poisoning by psychotropic drugs increased in different racial/age groups, especially in non-elderly non-Hispanic Native Americans and Non-Hispanic whites. Further work is needed to better understand the effects of medication, particularly phychotropic medicine prescribing and misuse on various health-related outcomes, including mortality that does not involve poisoning being present on the death certificate in different racial/age groups with the aim of informing prescribing guidelines.

Introduction

During the last two decades, life expectancy in white Americans was dropping compared to other major racial groups (save for Native Americans). By 2006, life expectancy in Hispanics was about 2.1 years higher than in non-Hispanic whites; by 2014, that gap has grown to about 3.2 years (Figure 4 in [1]). Life expectancy in African Americans is consistently lower than in whites, though the gap has decreased significantly in the recent years (Figure 4 in [2]; Figure 4 in [1]). In absolute terms, life expectancy in whites began to decline starting 2014 [1,3], together with the overall decline in life expectancy in the US starting 2015 [4] amid an ongoing epidemic of drug overdose deaths [5,6].

Several factors behind the relative decline in life expectancy in white Americans have been proposed, e.g. [4,7]. In particular, as suggested by a study that compared midlife mortality for the

2013-2015 period vs. the 1999-2001 period [8], major increases in mortality by poisoning, suicide, and liver disease took place in non-elderly white Americans compared to Hispanics and blacks. Moreover, those increases, particularly for deaths by poisoning, took place in both the Urban/Suburban and Rural Areas (Figure 1 in [8]). Those long-term trends, particularly in midlife deaths by poisoning and drug overdose [9,8], suggest that misuse of biological substances such as narcotics [5,6], and possibly medicaments other than narcotics may have pernicious health-related effects, including contribution to mortality in different population groups, particularly white Americans and Native Americans [9]. We note that the rates of consumption of certain medicaments in white Americans are higher than in other racial groups (excluding Native Americans) [10], including major differences in the rates of consumption of antibiotics [11] (with even higher rates of antibacterial uptake reported in Native Americans [12]), psychotropic drugs [13], including antidepressants [14,15], and sedative-hypnotic medications [16-18]. A number of studies, including meta-analyses, suggested elevated risks for mortality, including sudden cardiac death (SCD) associated with the use of various psychotropic drugs (both antipsychotics and antidepressants), as well as certain sedative-hypnotic drugs (benzodiazepines) [19-24], though firmly establishing causal links in such studies can be challenging [25]. For the case of antibiotics, our own work suggests an association between prescribing rates for certain antibiotics, particularly penicillins in the elderly, and mortality and hospitalization rates for septicemia [26,27], with that association presumably being mediated by antimicrobial resistance [28]. Further work is needed to gain a more comprehensive understanding of the effect of prescribing and misuse of different medication on health-related, including mortality outcomes.

In this paper, we study one of the more direct contributions of medication use to mortality, namely mortality that involves poisoning by medications. We note that the rise in the rates of mortality associated with narcotic, including opiate overdose is well-documented, e.g. [5,6,9]. However, trends in mortality involving poisoning by medicaments other than narcotics in the US are apparently not well studied. Here, we utilized the US CDC Wonder mortality database [29] to examine trends in mortality involving poisoning by medicaments other than narcotics in different age/racial groups in the US. We hope that this initial analysis will lead to further study of the contribution of medicament use to mortality outcomes, including mortality that does not involve poising by medicaments present on the death certificate (e.g. [19-24]).

Methods

Data

We've extracted annual mortality data between 2000-2017 stratified by age group (25-34y, 35-44y, 45-54y, 55-64y, 65-74y) and racial group (Hispanics, Non-Hispanic whites, Non-Hispanic blacks, Non-Hispanic Asian-Americans, Non-Hispanic Native Americans) from the US CDC Wonder database [29]. While the 1999 data are also available in [29], there are apparent incompatibilities between the 1999 and the 2000 data in [29] for certain age/racial groups (particularly non-whites), possibly having to do with transition from ICD-9 to ICD-10 coding around that time [30] and other factors relating to coding. Those data were extracted for five categories of deaths

1. Deaths involving poisoning by drugs, medicaments, and other biological substances: ICD-10 codes T36-50.xx present as either underlying or contributing causes of death
2. Deaths involving poisoning by narcotics and psychodysleptics: ICD-10 codes T40.xx present as either underlying or contributing causes of death
3. Deaths involving poisoning by specific drugs, medicaments, and other biological substances: ICD-10 codes T36-50.8 present as either underlying or contributing causes of death (with ICD-10 codes T50.9 representing poisoning by other and unspecified drugs, medicaments, and other biological substances)
4. Deaths involving poisoning by either psychotropic drugs (antipsychotic/neuroleptic drugs and antidepressants) or narcotics and psychodysleptics: ICD-10 codes T43.xx or T40.xx present as either underlying or contributing causes of death
5. Deaths involving poisoning by either sedative-hypnotic drugs (barbiturates and benzodiazepines) or narcotics and psychodysleptics: ICD-10 codes T42.3-43.4 or T40.xx present as either underlying or contributing causes of death

Those data were used to calculate the mortality rates for different causes used in the regression analyses:

A. Rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics (ICD-10 codes T36-39.xx or T41-50.8 but not T40.xx present as either

underlying or contributing causes of death) were obtained by subtracting mortality rates in category 2. above from the mortality rates in category 3. above.

B. Rates of mortality involving poisoning by psychotropic drugs but not narcotics and psychodysleptics (ICD-10 codes T43.xx but not T40.xx present as either underlying or contributing causes of death) were obtained by subtracting mortality rates in category 2. above from the mortality rates in category 4. above.
C. Rates of mortality involving poisoning by sedative-hypnotic drugs but not narcotics (ICD-10 codes T42.3-42.4 but not T40.xx present as either underlying or contributing causes of death) were obtained by subtracting mortality rates in category 2. above from the mortality rates in category 5. above.
D. Rates of mortality involving poisoning by narcotics and psychodysleptics were obtained as mortality rates in category 2. above.

Trends in mortality rates

For each age/racial group, we have regressed the corresponding annual rates of mortality involving poisoning by (A) medicaments but not narcotics and psychodysleptics; (B) psychotropic drugs but not narcotics and psychodysleptics; (C) sedative-hypnotic drugs but not narcotics and psychodysleptics; (D) narcotics and psychodysleptics (see previous subsection) against the calendar year. Given the apparent uptick in the trends for mortality involving poisoning by medicaments (including psychotropic drugs) but not narcotics and psychodysleptics in certain age/racial groups starting around 2012 (Figures 3,4), the regression analyses were performed separately for the 2000-2011 period and the 2011-2017 period. The regression coefficient for the calendar year estimates the annual increase in the rate of mortality involving poisoning by corresponding substances in the given age/racial group during the corresponding time period.

Relative changes in mortality rates

In addition to the evaluation of trends in mortality for the different categories of deaths in different age/racial groups, we also calculated the relative (fold) increases in the rates of mortality involving poisoning by different substances for different age groups in the overall population of US adults. The mortality categories are (i) medicaments but not narcotics and psychodysleptics; (ii) psychotropic drugs but not narcotics and psychodysleptics; (iii) sedative-hypnotic drugs but not narcotics and psychodysleptics; (iv) narcotics and psychodysleptics. We

considered changes in average annual mortality rates for the 2015-2017 period vs. 2000-2002 period, as well as for the 2011-2014 period vs. 2000-2002 period (to allow for the comparison with changes in prescribing rates for different medications in [31]).

Spatial variability in the rates of mortality involving poisoning by different substances

In addition to temporal changes in the rates of mortality involving poisoning by different substances, we also look at state-specific rates of mortality involving poisoning by psychotropic drugs but not narcotics/psychodysleptics, as well as mortality involving poisoning by narcotics/psychodysleptics, including correlations between those state-specific rates.

Results

Figure 1 plots the annual rates of mortality (per 100,000 individuals) involving poisoning by drugs, medicaments, and other biological substances between 2000-2017 for the different age/racial groups. Figure 2 plots the annual rates of mortality involving poisoning by narcotics and psychodysleptics between 2000-2017 for the different age/racial groups. We note that most deaths involving poisoning by drugs, medicaments, and other biological substances are deaths involving poisoning by narcotics and psychodysleptics (Figure 2 vs. 1). For rates of deaths involving poisoning by narcotics and psychodysleptics, the biggest rises in the younger age groups (25-34y, 35-44y and 45-54y) took place in Non-Hispanic whites and Native Americans. Those rises are very significant, particularly during the more recent years. For example, for Non-Hispanic whites, by 2017 about a third of all deaths in aged 25-34y, and about 20% of all deaths in aged 35-44y involved poisoning by narcotics and psychodysleptics. The biggest rises in mortality rates involving poisoning by narcotics and psychodysleptics in older age groups (55-64y and 65-74y), particularly during the most recent years, took place in non-Hispanic blacks (Figure 2).

Figure 3 plots the annual rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics between 2000-2017 for the different age/racial groups. We note that those rates are lower than the rates of mortality involving poisoning by narcotics and psychodysleptics (Figure 3 vs. Figure 2). The biggest increases in mortality rates involving poisoning by medicaments but not narcotics and psychodysleptics were in Non-Hispanic Native

Americans, though for the initial time period (2000-2011), for the three oldest age groups (45-54y, 55-64y, 65-74y), the increases in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics in Non-Hispanic whites were similar to the corresponding increases in Non-Hispanic Native Americans. Figures 4 and 5 plot the annual rates of mortality involving poisoning by psychotropic drugs but not narcotics and psychodysleptics (Figure 4) and sedative-hypnotic drugs but not narcotics and psychodysleptics (Figure 5) between 2000-2017 for the different age/racial groups. The majority of deaths involving poisoning by medicaments but not narcotics and psychodysleptics, as well as most of the increases in those death rates were for deaths involving poisoning by psychotropic drugs but not narcotics and psychodysleptics (Figure 3 vs. 4). We also note that rates of mortality involving poisoning by psychotropic drugs but not narcotics and psychodysleptics are generally higher in Non-Hispanic Native Americans than in Non-Hispanic whites, while rates of mortality involving poisoning by sedative-hypnotic drugs but not narcotics and psychodysleptics in Non-Hispanic whites are on par with the corresponding rates for Non-Hispanic Native Americans (Figures 5 and 4).

Rates of mortality involving poisoning by drugs, medicaments and other biological substances

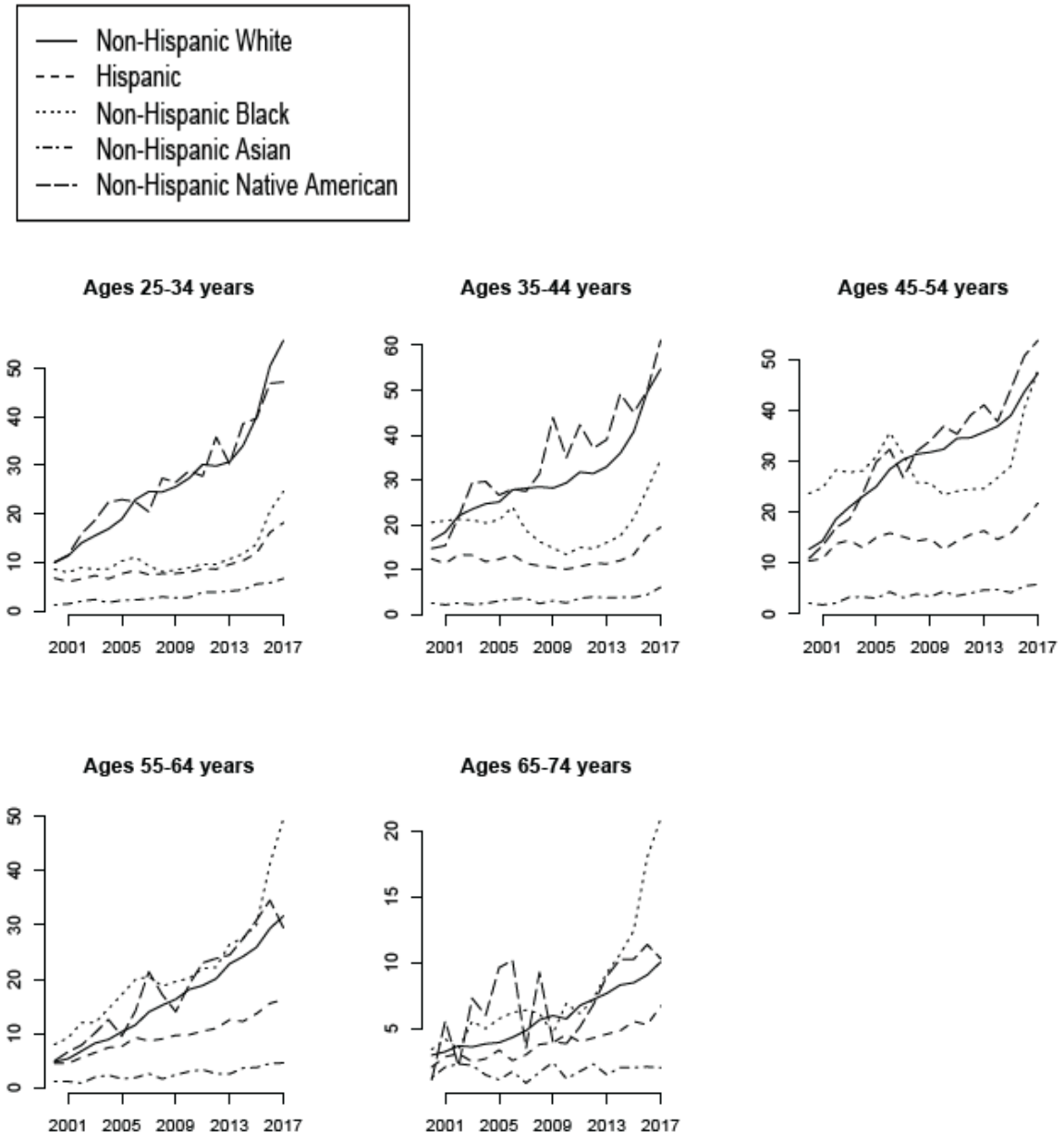

Figure 1: Annual rates of mortality involving poisoning by drugs, medicaments and other biological substances (ICD-10 codes T36-50.xx present as either underlying or contributing causes of death) between 2000-2017 per 100,000 individuals in different age/racial groups.

Rates of mortality involving poisoning by narcotics and psychodysleptics

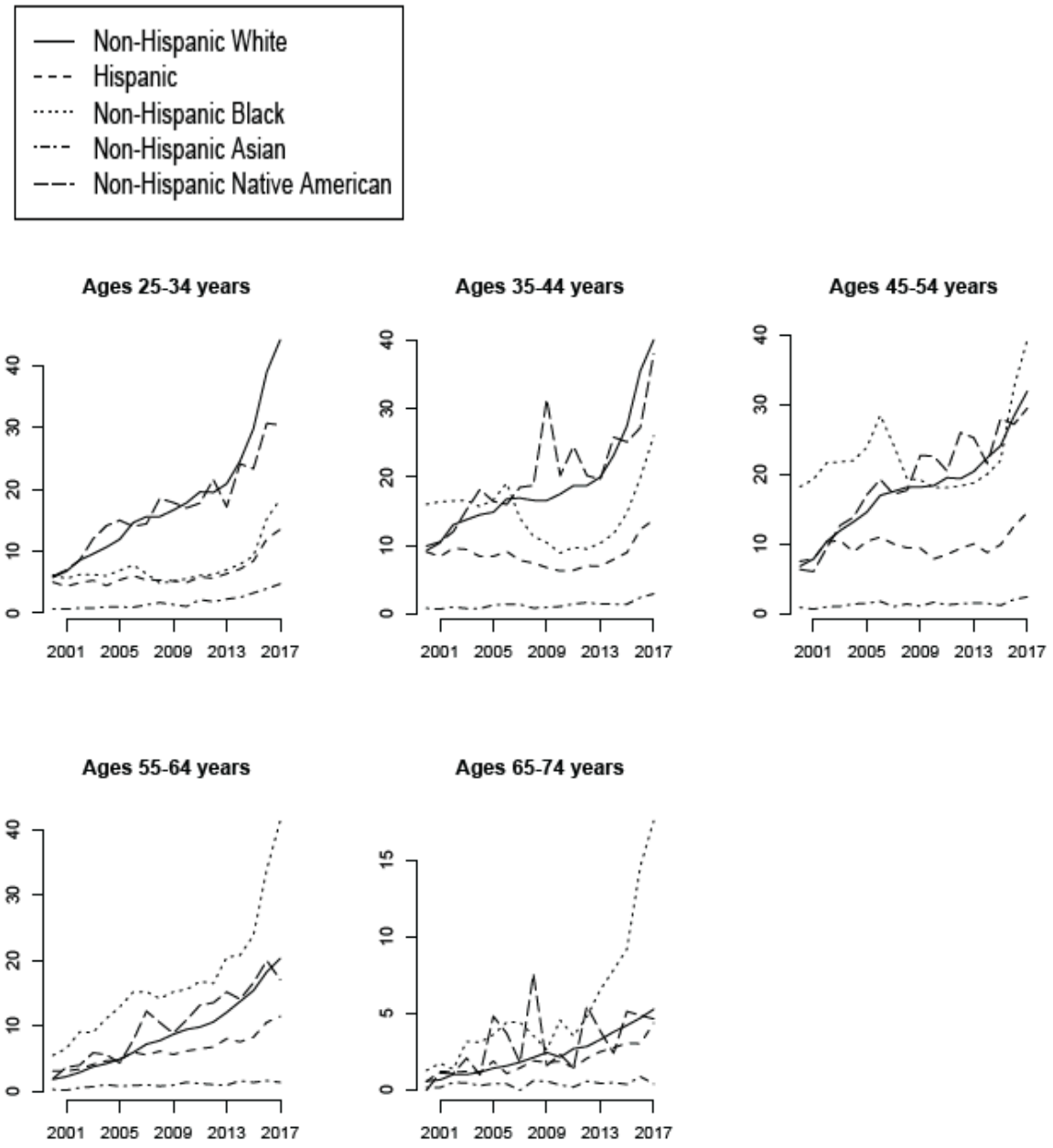

Figure 2: Annual rates of mortality involving poisoning by narcotics and psychodysleptics (ICD-10 codes T40.xx present as either underlying or contributing causes of death) between 2000-2017 per 100,000 individuals in different age/racial groups.

Rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics

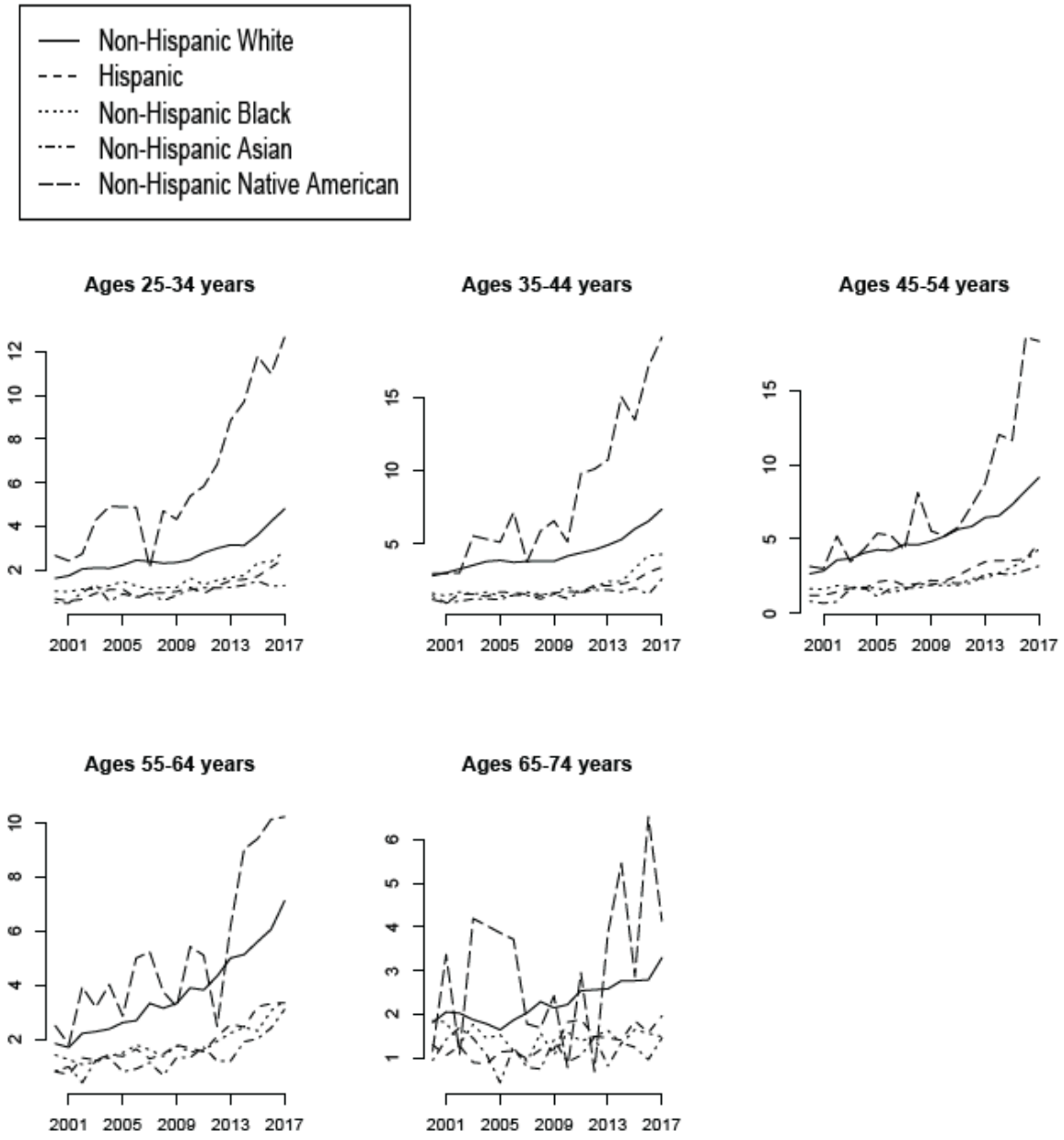

Figure 3: Annual rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics (ICD-10 codes T36-39.xx or T41-50.8 but not T40.xx not present as either underlying or contributing causes of death) between 2000-2017 per 100,000 individuals in different age/racial groups.

Rates of mortality involving poisoning by psychotropic drugs but not narcotics and psychodysleptics

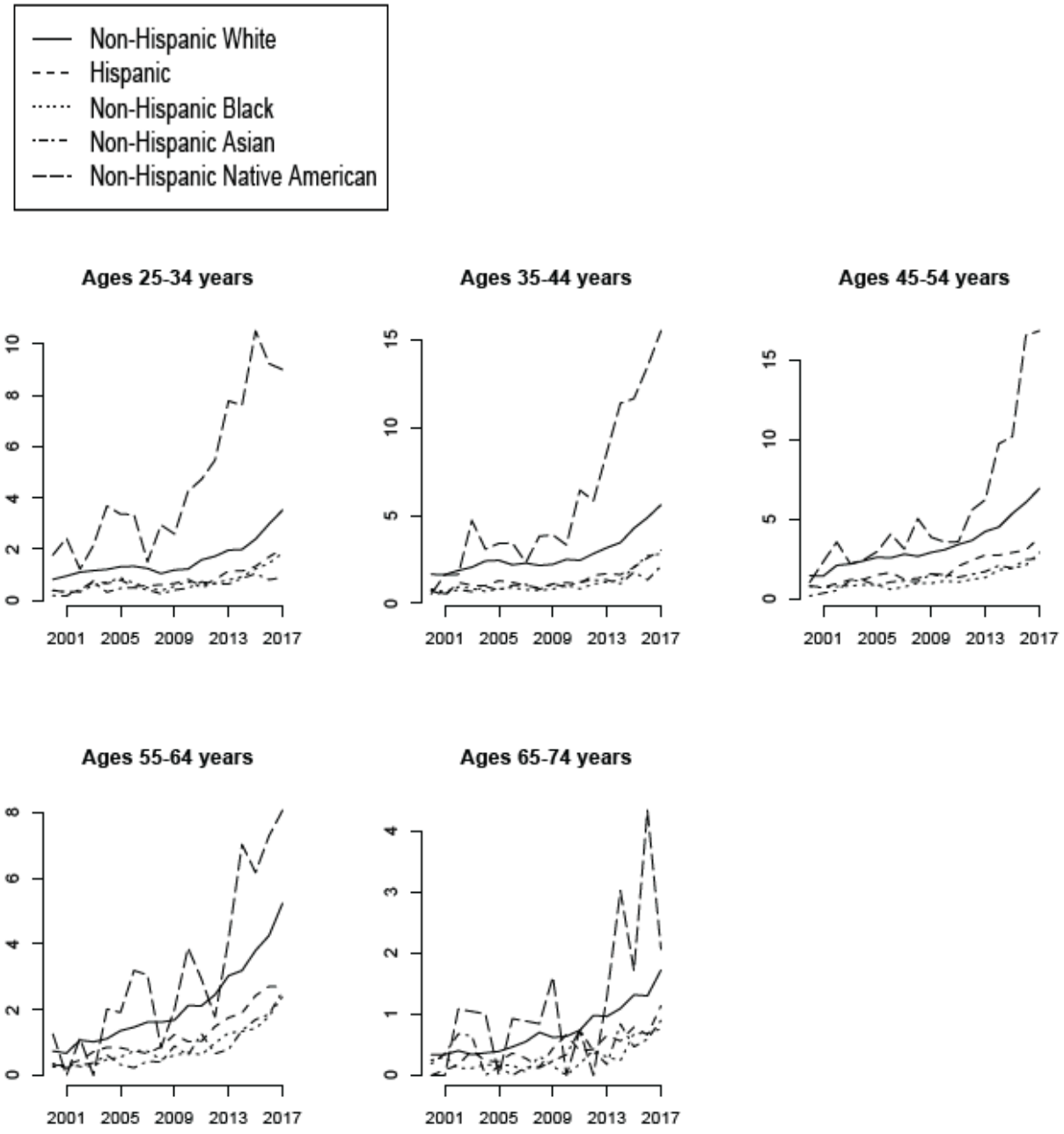

Figure 4: Annual rates of mortality involving poisoning by psychotropic drugs but not narcotics and psychodysleptics (ICD-10 codes T43.xx but not T40.xx not present as either underlying or contributing causes of death) between 2000-2017 per 100,000 individuals in different age/racial groups.

Rates of mortality involving poisoning by sedative-hypnotic drugs (barbiturates or benzodiazepines) but not narcotics and psychodysleptics

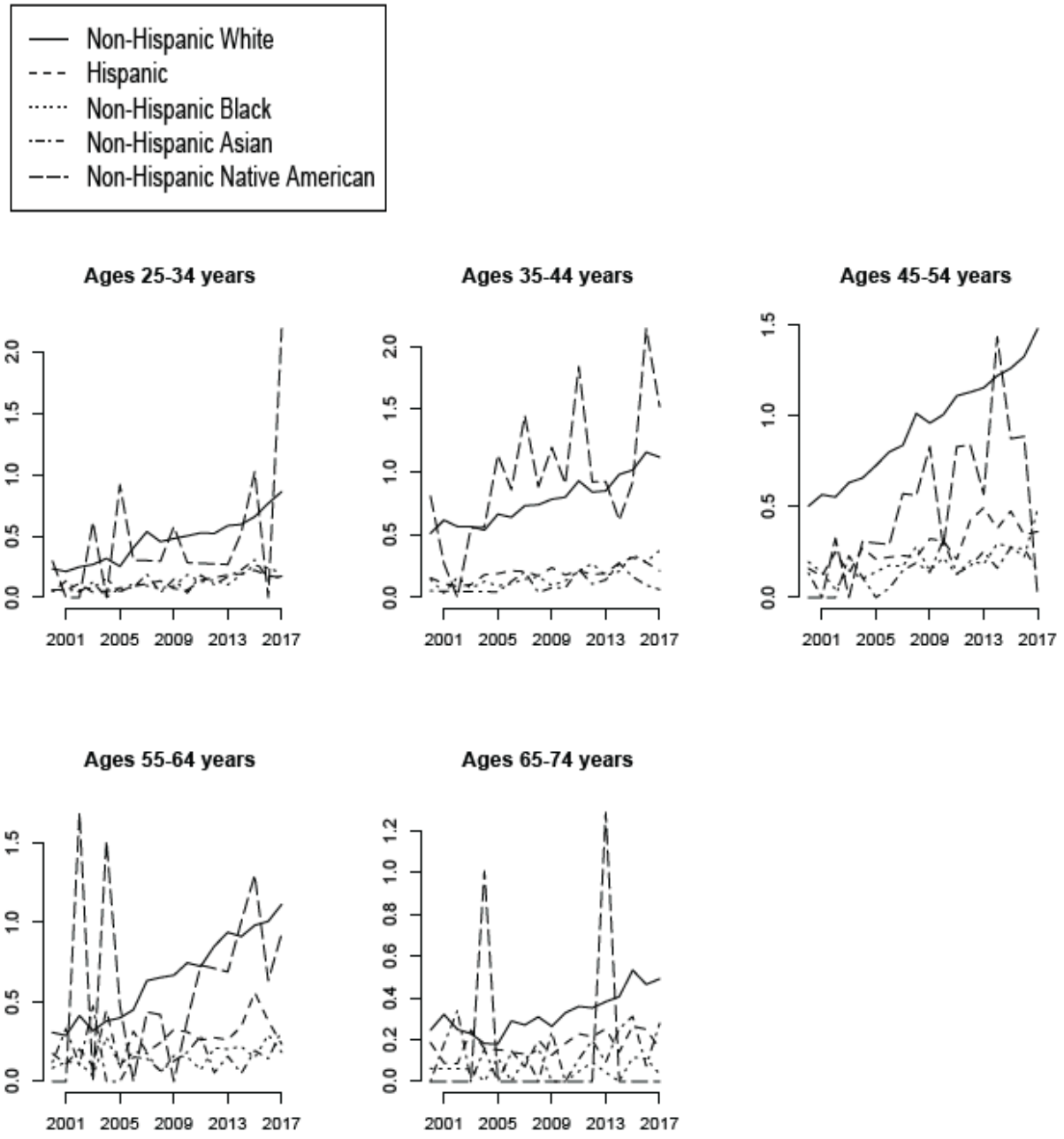

Figure 5: Annual rates of mortality involving poisoning by sedative-hypnotic drugs but not narcotics and psychodysleptics (ICD-10 codes T42.3-42.4 but not T40.xx not present as either underlying or contributing causes of death) between 2000-2017 per 100,000 individuals in different age/racial groups.

Figures 3 and 4 suggest an apparent uptick in the trends for mortality involving poisoning by medicaments (including psychotropic drugs) but not narcotics and psychodysleptics in certain age/racial groups starting around 2012. Table 1 gives the estimates of the annual increase in the rate of mortality involving poisoning by medicaments but not narcotics and psychodysleptics in different age/racial groups between 2000-2011, as well as between 2011-2017 (Methods). Annual increases in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics between 2011-2017 are significantly higher than the corresponding increases during the 2000-2011 period, with the biggest relative change between the two time periods being in Non-Hispanic blacks. The greatest increases in rate of mortality involving poisoning by medicaments but not narcotics and psychodysleptics during each time period are in non-elderly Non-Hispanic Native Americans, followed by Non-Hispanic whites. Increases in mortality rates involving poisoning by medicaments but not narcotics and psychodysleptics for non-elderly Non-Hispanic whites are significantly higher than for non-elderly Hispanics, Non-Hispanic blacks, and Non-Hispanic Asian-Americans, except for the 2011-2017 period, when increases for aged 25-44y in Non-Hispanic whites were comparable to the corresponding increases in Hispanics (for aged 25-34y) and Non-Hispanic blacks (Table 1). For the 2000-2011 period, increases in the rate of mortality involving poisoning by medicaments but not narcotics and psychodysleptics are generally lowest in Non-Hispanic blacks, while for the 2011-2017 period, those increases are generally lowest in Non-Hispanic Asians. Finally, for persons aged 65-74y, rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics increased in Hispanics and Non-Hispanic whites during the 2000-2011 period, and in Non-Hispanic whites during the 2011-2017 period, albeit more modestly compared to the younger age groups.

Table 2 and 3 give the estimates of the annual increase in the rate of mortality involving poisoning by psychotropic drugs but not narcotics and psychodysleptics (Table 2) and sedative-hypnotic drugs but not narcotics and psychodysleptics (Table 3) in different age/racial groups between 2000-2011 as well as between 2011-2017. Table 2 suggests that most of increases in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics were for mortality involving poisoning by psychotropic drugs but not narcotics and psychodysleptics. Similarly to mortality involving poisoning by medicaments but not narcotics and psychodysleptics, the greatest increases in the rates of mortality involving poisoning by psychotropic drugs but not narcotics and psychodysleptics during each time period

are in non-elderly Non-Hispanic Native Americans, followed by Non-Hispanic whites. For mortality involving poisoning by sedative-hypnotic drugs, the corresponding increases for the two time periods are similar (Tables 3), with the increases for the 2011-2017 period being considerably lower compared to the corresponding increases for psychotropic drugs but not narcotics and psychodysleptics.

2000-2011 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**0.08 (0.06,0.1)**	**0.11 (0.08,0.14)**	**0.24 (0.21,0.27)**	**0.20 (0.17,0.23)**	**0.05 (0.02,0.08)**
Hispanics	**0.03 (0.01,0.06)**	**0.05 (0.02,0.07)**	**0.11 (0.08,0.14)**	**0.07 (0.04,0.11)**	**0.05 (0.01,0.1)**
Non-Hispanic blacks	**0.03 (0.01,0.06)**	0.02 (-0.01,0.05)	0.02 (-0.01,0.05)	**0.04 (0.01,0.07)**	-0.04 (-0.09,0)
Non-Hispanic Asian Americans	0.03 (-0.01,0.08)	**0.04 (0.01,0.06)**	**0.12 (0.08,0.17)**	**0.06 (0.01,0.11)**	-0.03 (-0.09,0.03)
Non-Hispanic Native Americans	**0.23 (0.07,0.4)**	**0.41 (0.18,0.64)**	**0.26 (0.08,0.44)**	**0.23 (0.08,0.37)**	-0.05 (-0.26,0.17)
2011-2017 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**0.32 (0.22,0.42)**	**0.50 (0.41,0.59)**	**0.58 (0.45,0.7)**	**0.50 (0.41,0.58)**	**0.10 (0.05,0.16)**
Hispanics	**0.24 (0.19,0.29)**	**0.26 (0.19,0.33)**	**0.28 (0.17,0.4)**	**0.30 (0.22,0.38)**	0.03 (-0.06,0.12)
Non-Hispanic blacks	**0.25 (0.19,0.31)**	**0.47 (0.37,0.58)**	**0.38 (0.29,0.46)**	**0.28 (0.21,0.36)**	0.02 (-0.03,0.06)
Non-Hispanic Asian Americans	0.03 (-0.01,0.06)	0.08 (-0.04,0.2)	**0.19 (0.12,0.25)**	**0.27 (0.12,0.41)**	0.02 (-0.08,0.12)
Non-Hispanic Native Americans	**1.13 (0.87,1.39)**	**1.6 (1.12,2.08)**	**2.25 (1.67,2.83)**	**1.21 (0.64,1.78)**	0.51 (-0.12,1.13)

Table 1: Annual change in mortality rates involving poisoning by medicaments but not narcotics and psychodysleptics (ICD-10 codes T36-39.xx or T41-50.8 but not T40.xx not present as either underlying or contributing causes of death) between 2000-2011 and between 2011-2017 per 100,000 individuals in different age/racial groups

2000-2011 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**0.04 (0.01,0.06)**	**0.07 (0.03,0.1)**	**0.16 (0.13,0.19)**	**0.13 (0.11,0.15)**	**0.04 (0.03,0.05)**
Hispanics	**0.03 (0,0.05)**	0.03 (0,0.07)	**0.08 (0.05,0.12)**	**0.07 (0.05,0.09)**	**0.04 (0.01,0.06)**
Non-Hispanic blacks	0.02 (-0.01,0.04)	0.01 (-0.01,0.03)	**0.03 (0.01,0.05)**	**0.04 (0.02,0.06)**	-0.01 (-0.02,0.01)
Non-Hispanic Asian Americans	0.02 (0,0.05)	**0.04 (0.02,0.06)**	**0.11 (0.07,0.14)**	**0.06 (0.02,0.1)**	0 (-0.04,0.05)
Non-Hispanic Native Americans	**0.20 (0.05,0.34)**	**0.31 (0.13,0.5)**	**0.20 (0.08,0.33)**	**0.24 (0.08,0.4)**	0.04 (-0.05,0.13)
2011-2017 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**0.31 (0.22,0.4)**	**0.52 (0.44,0.61)**	**0.59 (0.49,0.68)**	**0.49 (0.41,0.57)**	**0.14 (0.1,0.18)**
Hispanics	**0.22 (0.19,0.26)**	**0.29 (0.21,0.36)**	**0.24 (0.17,0.32)**	**0.29 (0.24,0.34)**	**0.10 (0.05,0.15)**
Non-Hispanic blacks	**0.21 (0.18,0.25)**	**0.36 (0.27,0.45)**	**0.28 (0.21,0.35)**	**0.25 (0.19,0.32)**	**0.10 (0.05,0.15)**
Non-Hispanic Asian Americans	0.04 (0,0.09)	**0.11 (0.01,0.22)**	**0.20 (0.15,0.25)**	**0.26 (0.12,0.4)**	0.04 (-0.06,0.14)
Non-Hispanic Native Americans	**0.82 (0.4,1.25)**	**1.62 (1.3,1.95)**	**2.34 (1.81,2.87)**	**1.02 (0.62,1.42)**	**0.47 (0.05,0.89)**

Table 2: Annual change in mortality rates involving poisoning by psychotropic drugs but not narcotics and psychodysleptics (ICD-10 codes T43.xx but not T40.xx present as either underlying or contributing causes of death) between 2000-2011 and between 2011-2017 per 100,000 individuals in different age/racial groups

2000-2011 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**0.03 (0.02,0.04)**	**0.03 (0.02,0.04)**	**0.06 (0.05,0.06)**	**0.05 (0.04,0.06)**	0.01 (0,0.02)
Hispanics	0 (0,0.01)	**0.01 (0,0.02)**	**0.01 (0,0.02)**	0.01 (0,0.03)	0 (-0.01,0.01)
Non-Hispanic blacks	**0.01 (0,0.01)**	0.01 (0,0.01)	0.01 (0,0.02)	0 (-0.01,0.01)	0 (-0.01,0.01)
Non-Hispanic Asian Americans	0.01 (-0.01,0.02)	**0.01 (0,0.02)**	0.01 (0,0.03)	0 (-0.03,0.02)	0 (-0.02,0.02)
Non-Hispanic Native Americans	0.02 (-0.03,0.06)	**0.10 (0.04,0.16)**	**0.07 (0.04,0.09)**	-0.01 (-0.11,0.09)	-0.01 (-0.06,0.04)
2011-2017 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**0.06 (0.04,0.07)**	**0.05 (0.02,0.07)**	**0.06 (0.04,0.07)**	**0.05 (0.04,0.07)**	**0.03 (0.01,0.04)**
Hispanics	0 (-0.01,0.01)	0.01 (-0.01,0.03)	0.01 (-0.03,0.05)	0.02 (-0.03,0.06)	0 (-0.02,0.01)
Non-Hispanic blacks	**0.02 (0,0.04)**	**0.02 (0,0.04)**	**0.04 (0.02,0.07)**	0.02 (-0.01,0.04)	0 (-0.01,0.02)
Non-Hispanic Asian Americans	0.01 (-0.02,0.03)	-0.02 (-0.04,0.01)	0.01 (-0.01,0.03)	0.01 (-0.03,0.05)	0.02 (-0.02,0.05)
Non-Hispanic Native Americans	0.21 (-0.03,0.45)	0.05 (-0.17,0.28)	-0.07 (-0.24,0.09)	0.04 (-0.05,0.13)	-0.05 (-0.24,0.15)

Table 3: Annual change in mortality rates involving poisoning by sedative-hypnotic drugs but not narcotics and psychodysleptics (ICD-10 codes T42.3-42.4 but not T40.xx present as either underlying or contributing causes of death) between 2000-2011 and between 2011-2017 per 100,000 individuals in different age/racial groups

Table 4 presents the estimates of annual increases in mortality rates involving poisoning by narcotics and psychodysleptics between 2000-2011, as well as between 2011-2017. Some of the largest increases in those rates are notably higher than the increases in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics (Table 4 vs. 1). For the 2000-2011 period, for younger age groups (25-54y), the largest increases in mortality rates involving poisoning by narcotics and psychodysleptics were in Non-Hispanic Native Americans

and Non-Hispanic whites, with the corresponding rates of mortality in Hispanics and Non-Hispanic blacks decreasing for ages 35-44y; for older age groups (ages 55-74y), the largest increase between 2000-2011 was in Hon-Hispanic blacks. For the 2011-2017 period, for persons aged 25-44y, the biggest increases in the rates of mortality involving poisoning by narcotics and psychodysleptics were in Non-Hispanic whites, followed by Non-Hispanic Native Americans/Non-Hispanic Blacks; for persons aged over 45y, the biggest increases in the rates of mortality involving poisoning by narcotics and psychodysleptics between 2011-2017 were in Non-Hispanic blacks, followed by Non-Hispanic whites, then Non-Hispanic Native Americans. Increases in the rates of mortality involving poisoning by narcotics and psychodysleptics between 2011-2017 were lowest in Non-Hispanic Asians.

2000-2011 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**1.24 (1.15,1.34)**	**0.76 (0.59,0.92)**	**1.17 (0.98,1.37)**	**0.78 (0.74,0.83)**	**0.19 (0.17,0.21)**
Hispanics	0.07 (0,0.15)	**-0.28 (-0.38,-0.18)**	0.01 (-0.19,0.21)	**0.33 (0.27,0.4)**	**0.08 (0.03,0.13)**
Non-Hispanic blacks	-0.05 (-0.18,0.08)	**-0.73 (-1.08,-0.37)**	-0.1 (-0.64,0.43)	**1.01 (0.8,1.22)**	**0.23 (0.09,0.37)**
Non-Hispanic Asian Americans	**0.10 (0.06,0.15)**	**0.04 (0,0.08)**	**0.05 (0,0.1)**	**0.08 (0.05,0.11)**	0.01 (-0.02,0.04)
Non-Hispanic Native Americans	**1.11 (0.84,1.39)**	**1.4 (0.85,1.96)**	**1.52 (1.18,1.85)**	**0.94 (0.69,1.2)**	0.21 (-0.13,0.54)
2011-2017 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**4.34 (3.04,5.65)**	**3.74 (2.62,4.86)**	**2.1 (1.47,2.73)**	**1.79 (1.54,2.04)**	**0.44 (0.4,0.49)**
Hispanics	**1.35 (0.88,1.82)**	**1.24 (0.82,1.66)**	**0.86 (0.39,1.34)**	**0.81 (0.54,1.08)**	**0.40 (0.28,0.52)**
Non-Hispanic blacks	**2.05 (1.22,2.87)**	**2.64 (1.61,3.67)**	**3.39 (1.76,5.03)**	**4.00 (2.53,5.47)**	**2.3 (1.74,2.86)**
Non-Hispanic Asian Americans	**0.46 (0.31,0.6)**	**0.21 (0.05,0.37)**	**0.15 (0.03,0.27)**	0.08 (-0.01,0.16)	0.04 (-0.04,0.12)
Non-Hispanic Native Americans	**2.22 (1.2,3.24)**	**2.14 (0.54,3.74)**	**1.15 (0.25,2.04)**	**0.93 (0.38,1.47)**	0.34 (-0.19,0.88)

Table 4: Annual change in mortality rates involving poisoning by narcotics and psychodysleptics (ICD-10 codes T40.xx present as either underlying or contributing causes of death) between 2000-2011 and between 2011-2017 per 100,000 individuals in different age/racial groups

Table 5 presents relative (fold) increases in the average annual rates of mortality involving poisoning by different substances for different age groups in the overall population of US adults for the 2015-2017 period vs. 2000-2002 period, as well as for the 2011-2014 period vs. 2000-2002 period. Table 5 shows significant increases in mortality involving poisoning, particularly by narcotics and psychodysleptics (especially in persons aged 55-74y), as well as psychotropic medications, particularly for adults aged 45-64y. Increases in the rates of mortality involving poisoning by psychotropic medications but not narcotics and psychodysleptics for the 2011-2014 period vs. 2000-2002 period were greater than the corresponding increases in the rates of prescribing for those medications, particularly for adults aged 45-64y (Table 5 vs. [31]). Increases in the rates of mortality involving poisoning by sedative-hypnotic medications but not narcotics and psychodysleptics for the 2011-2014 period vs. 2000-2002 period were greater than the corresponding increases in the rates of prescribing for those medications for adults aged 45-64y (Table 5 vs. [31]).

There were no correlations between state-specific rates of mortality involving poisoning by psychotropic drugs but not narcotics/psychodysleptics and state-specific rates of mortality involving poisoning by narcotics/psychodysleptics during the 2013-2017 period; those correlation were -0.06(-0.33,0.22) for persons aged 45-64y, and -0.16(-0.42,0.12) for persons aged 25-44y. Table 6 presents the 20 states with the highest rates of mortality involving poisoning by psychotropic drugs but not narcotics/psychodysleptics, as well as the 20 states with the highest rates of mortality involving poisoning by narcotics/psychodysleptics per 100,000 persons aged 45-64y during the 2013-2017 period. Those lists of states are quite different, with a notable presence of westerns states among those with the highest rates of mortality involving poisoning by psychotropic drugs but not narcotics/psychodysleptics vs. a notable presence of eastern (particularly northeastern) states among those with the highest rates of mortality involving poisoning by narcotics/psychodysleptics.

2015-2017 vs. 2000-2002 periods					
Category of substances	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
medicaments but not narcotics and psychodysleptics	2.33	2.07	2.56	3.1	1.43
psychotropic drugs but not narcotics and psychodysleptics	3.22	2.75	3.48	5.37	3.94
sedative-hypnotic drugs but not narcotics and psychodysleptics	3.06	1.75	2.27	2.75	1.73
narcotics and psychodysleptics	4.29	2.32	2.62	6.54	6.33
2011-2014 vs. 2000-2002 periods					
Category of substances	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
medicaments but not narcotics and psychodysleptics	1.64	1.48	1.92	2.24	1.27
psychotropic drugs but not narcotics and psychodysleptics	1.95	1.65	2.3	3.24	2.5
sedative-hypnotic drugs but not narcotics and psychodysleptics	2.26	1.47	2	2.31	1.35
narcotics and psychodysleptics	2.42	1.38	1.89	4.14	3.82

Table 5: Relative (fold) increases in the rates of mortality involving poisoning by different substances for different age groups in the overall population of US adults for the 2015-2017 period vs. the 2000-2002 period, as well as the 2011-2014 period vs. the 2000-2002 period

Psychotropic drugs but not narcotics/psychodysleptics			Narcotics/psychodysleptics	
State	Rate per 100,000		State	Rate per 100,000
Hawaii	16.5		District of Columbia	77.37
Nevada	14.04		West Virginia	55.3
Oklahoma	13.68		Rhode Island	39.38
Arizona	10.56		Ohio	37.52
Utah	9.25		Maryland	36.97
New Mexico	9.07		Kentucky	31.28
California	9.02		Nevada	30.88
Washington	7.49		New Mexico	30.57
Idaho	6.05		Massachusetts	30.57
Colorado	5.96		Connecticut	30.17
Wyoming	5.91		Tennessee	29.8
Alaska	5.91		Utah	29.45
Iowa	5.76		New Hampshire	28.24
Oregon	5.65		Delaware	26.58
West Virginia	5.27		Oklahoma	24.65
Kansas	4.86		Michigan	22.47
Rhode Island	4.76		Illinois	22.3
Missouri	4.54		Maine	22.18
Arkansas	4.25		South Carolina	21.79
Montana	4.15		New York	21.12

Table 6: 20 states with the highest rates of mortality involving poisoning by psychotropic drugs but not narcotics/psychodysleptics, as well as the 20 states with the highest rates of mortality involving poisoning by narcotics/psychodysleptics per 100,000 persons aged 45-64y during the 2013-2017 period.

Discussion

There is a long-term decline in life expectancy for Non-Hispanic whites relative to other major racial groups in the US (except for Native Americans) [1], and increases in midlife mortality by poisoning, suicide and liver disease in Non-Hispanic whites are known to have been greater than for other major racial groups [8]. This suggests that consumption and misuse of various biological substances contributes to the relative decline in life expectancy for Non-Hispanic whites (as well as Native Americans [9,3]). While the rise in mortality by narcotic, including

opiate poisoning, particularly during the most recent years in well documented ([5,9]), our understanding of the contribution of medicaments other than narcotics to mortality in different racial/age groups is more limited. In this study, we have shown significant increases in the rates of mortality involving poisoning by medicaments other than narcotics in different age/racial groups, both for the 2000-2011 period, and even more so for the 2011-2017 period. Those increases were particularly large in non-elderly Non-Hispanic Native Americans and whites. The majority of deaths involving poisoning by medicaments other than narcotics, as well as most of the increases in those death rates were for deaths involving poisoning by psychotropic medications. Significant increases in prescribing for antidepressants, antipsychotic and sedative-hypnotic drugs in different age subgroups of adults took place during the study period [31]. For example, for the 2011-2014 period, 17.5% of US adults aged 45-64y and 18.7% of those aged 65-74y reported receiving antidepressant medications during the last 30 days, compared to 10.5% and 9.3% correspondingly for the 1999-2002 period. At the same time, increases in the rates of mortality involving poisoning by psychotropic medications but not narcotics and psychodysleptics were greater than increases in prescribing for psychotropic medications, particularly for persons aged 45-64y (Table 5 vs. [31]), which might be different from the case of certain other countries, e.g. [32]. While rates of mortality involving poisoning by medicaments other than narcotics are lower than the rates of mortality involving poisoning by narcotics, medication use/misuse may have long-term pernicious effects on health, including mortality that does not involve poisoning by medicaments present on a death certificate. Indeed, a number of studies, e.g. [19-24] have suggested elevated risks for mortality and other health-related outcomes associated with the use of psychotropic medications (both antipsychotic medications and antidepressants) and sedative-hypnotic medications (benzodiazepines). Our own work suggests associations between rates of prescribing for penicillins, and rates of mortality and hospitalization for septicemia in older adults [25,26]. Additionally, rates of consumption of certain medications, particularly psychotropic drugs, sedative-hypnotic medications and antibiotics in Non-Hispanic whites are higher than in other major racial groups (save for Native Americans) [10-18], and those differences have an effect on health-related, including mortality outcomes [19-26]. Our results, as well as other work, e.g. [19-26] support the need for a comprehensive evaluation of the impact of prescribing/misuse of various medications on health, including mortality outcomes.

Our paper has some limitations. It might be that increases in the rates of mortality involving poisoning by medicaments other than narcotics came in tow with increases in the rates of mortality involving poisoning by narcotics/psychodysleptics, with a growing fraction of deaths having poisoning by medicaments but not poisoning by narcotics/psychodysleptics on a death certificate actually being partly affected by narcotic/psychodysleptic use, with poisoning by narcotics/psychodysleptics not appearing on some of those death certificates. We do not believe that this could largely explain our results as there are no correlations between state-specific rates of mortality involving poisoning by psychotropic drugs but not narcotics/psychodysleptics and state-specific rates of mortality involving poisoning by narcotics/psychodysleptics during the 2013-2017 period (Results; Table 6). Additionally, there are notable discrepancies in trends for mortality involving poisoning by narcotics and psychodysleptics vs. mortality involving poisoning by medicaments other than narcotics, particularly for Hispanics and Non-Hispanic blacks. For example, rates of mortality involving poisoning by medicaments, including sedative-hypnotic drugs but not narcotics/psychodysleptics in Hispanics aged 35-44y increased between 2000-2011 (Tables 1,3), while rates of mortality involving poisoning by narcotics and psychodysleptics in that population declined between 2000-2011 (Table 4 and Figure 2); for persons aged 55-64y, increases in mortality involving poisoning by narcotics and psychodysleptics were greater in Non-Hispanic blacks than in Non-Hispanic whites for both the 2000-2011 and the 2011-2017 periods (Table 4), with the opposite being true for increases in mortality involving poisoning by medicaments but not narcotics and psychodysleptics (Table 1), etc. Another possible contributing factor to the increase in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics is change in diagnostic/coding criteria. However, it is unlikely that such changes, if they indeed took place, would be very different for different population groups, while growth in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics is notably higher for some age/racial groups compared to others. For example, there were no discernible changes in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics in Non-Hispanic blacks aged 34-54y between 2000-2011 (Table 1), while major changes in the corresponding mortality rates took place in Non-Hispanic whites and Non-Hispanic Native Americans. Another example is Non-Hispanic whites aged 55-64y vs. Non-Hispanic whites aged 65-74y. In the beginning of the study period, rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics were similar for the two age groups; however, subsequently those rates followed quite different trends for the two age

groups (Figure 3). We believe that those differences in trends for different population groups are unlikely to be explained by differences in changes in diagnostic/coding criteria for those population groups, but rather by genuine differences in mortality trends. Finally, we don't know whether increases in prescribing or misuse have contributed to the increases in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics. Significant increases in medication prescribing rates, particularly for sedative-hypnotic and antipsychotic drugs in adults aged 25-44y, and antidepressants in adults aged 45-74y did take place during the study period [31]. At the same time, increases in mortality involving poisoning by psychotropic, as well as sedative-hypnotic drugs, but not narcotics and psychodysleptics were generally greater than increases in prescribing for those medications, particularly for adults aged 45-64y (compare Table 5 to [31]), suggesting the potential role of medication misuse in the increases in mortality by poisoning.

We believe that despite those limitations, our study shows significant increases in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics, especially poisoning by psychotropic drugs in different age/racial groups, particularly non-elderly Non-Hispanic Native Americans and whites, both between 2000-2011, and even more so between 2011-2017. Moreover, some of those increases in mortality rates have significantly exceeded the increases in prescription rates for the corresponding medications. Those results, as well as earlier studies showing associations between medication use and health-related, including mortality outcomes (e.g. [19-26]) further support the need for a comprehensive evaluation of the impact of prescribing and misuse of various medications on health and mortality outcomes in different population groups, as well as the related guidance regarding the use of those medications. Additionally, such analyses may help elucidate the role of medication use/misuse in the long-term decline in life expectancy in Non-Hispanic whites compared to other major racial groups (save for Native Americans) in the US [1].

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