INTRODUCTION

Sleep accounts for one-third of our lives and is a crucial determinant of human performance. Lack of sleep is a threat to the nation's public health as it is linked to numerous chronic conditions, including type 2 diabetes, heart disease, obesity and depression (Fernandez-Mendoza & Vgontzas, 2013). Inadequate sleep is associated with elevated risks of vehicle crashes, workplace accidents and mortality (Cappuccio, D’Elia, Strazzullo, & Miller, 2010; Leger et al., 2014). Moreover, sleep is an important determinant of productivity and economic outcomes; one additional hour of sleep is associated with an increase in wages by 16% (Gibson & Shrader, 2014). Insomnia, a common sleep disorder, is characterized as difficulty with initiating or maintaining sleep, resulting in the disturbance of daytime functioning (Sateia, 2014). From 1993 to 2007, the number of office-based physician visits that involved complaints of sleeplessness and the number of visits that resulted in a diagnosis of insomnia increased 2-fold and 7-fold, respectively (Moloney, Konrad, & Zimmer, 2011). The prevalence of insomnia varies due to inconsistent diagnostic criteria, but the condition generally affects 10% to 34% of the population (Ellis, Perlis, Neale, Espie, &...
Bastien, 2012; Karacan et al., 1976). The economic cost of insomnia is substantial, estimated to be more than $100 billion annually in the USA (Wickwire, Shaya, & Scharf, 2016), due to both direct and indirect costs from healthcare utilization, lost productivity, workplace accidents, non-workplace injuries, and comorbidities related to insomnia.

Risk factors for insomnia have been well documented in the literature, including female gender, old age (among non-Hispanic Whites), psychological distress, poor physical health, comorbidities, ethnic/racial minorities and low socioeconomic status (Grandner et al., 2010; Kaufmann et al., 2016; Smagula, Stone, Fabio, & Cauley, 2016). Despite efforts to document various risk factors, little is known about the implications of using medications with insomnia side effects for insomnia symptoms among community-dwelling adults. This is a potentially important omission given the growing medication use across the country. Almost 60% of US adults report frequent use of prescription medications, a prevalence that is higher than ever before (Kantor et al., 2015). Although medications are lifesaving when used properly, they can produce adverse side effects, ranging from minor problems such as dizziness to severe events such as an increased risk of cancer. Polypharmacy – a phenomenon typically defined as the concurrent use of at least five medications to treat one or more conditions – may present unique risks for medication side effects, amplifying the effects of each of the medications in a set. Between 1999 and 2012, while the prevalence of US adults using any prescription medication increased by 16%, the prevalence of consuming at least five prescription medications simultaneously increased by 82.9% (Kantor et al., 2015). Although medication use is critical for disease management, a growing literature suggests that many commonly used medications have adverse psychiatric and neurologic side effects, especially under the condition of polypharmacy. Qato, Ozenberger, and Olfson (2018) used a nationally representative sample of US adults from the National Health and Nutrition Examination Survey (NHANES) and found that respondents who simultaneously consumed at least three medications with depression side effects were 10.7 percentage points more likely to report depressive symptoms compared to non-users. Using the same survey, Do and Schnittker (2020) reported that the concurrent use of three or more medications with cognitive impairment side effects among US older adults increased 3-fold between 1999 and 2016. In addition, individuals who used three or more such medications experienced increased risks of cognitive deficits compared to non-users. Despite growing concerns about sleep disorders (Moloney et al., 2011), no prior studies have systematically documented trends in the use of medications with insomnia side effects and the implication of their use for insomnia symptoms among community-dwelling adults.

A handful of studies have identified medications with insomnia side effects, including medications frequently prescribed for conditions such as cardiovascular disease, asthma, psychiatric disorders, cancer or over-the-counter medications for cold or flu symptoms (Ciríaco et al., 2013; Efron, Jarman, & Barker, 1997; Wernicke, 1985). Yet, many studies have been clinical in nature, exploring the effects of a single medication or a class of medications on insomnia, or using small or non-representative samples of the population. It is possible that insomnia side effects of medications are much more pronounced in naturalistic settings. However, little is known about how frequently the adult population consumes medications with insomnia side effects or about how the use of these medications has changed over time. Moreover, little is known about how many adults simultaneously consume several of such medications, the relationship between these combinations and sleep quality at the population level, and whether the relationship varies across subgroups.

Understanding trends in the use of medications with insomnia side effects and their implications for sleep quality can improve the health of the population by promoting physicians’ proper prescribing practices. This study uses a nationally representative survey and a comprehensive database of medications that have been linked to insomnia side effects to investigate the following questions.

1. The prevalence of using medications with insomnia side effects from 1999 to 2016 among US adults.
2. The relationship between concurrent use of these medications and insomnia-related outcomes.
3. Whether the relationship varies across subgroups.

1.1 | Methods

Data came from the National Health and Nutrition Examination Survey (NHANES), a publicly available and nationally representative survey of the civilian non-institutionalized US population. The National Center for Health Statistics Research Ethics Review Board has approved all cycles of the NHANES (https://www.cdc.gov/nchs/nhanes/irba98.htm). The NHANES used a multistage probability sampling design to represent the general population but it oversampled Black, Hispanic and older adults. The average non-response rate was 22%. All analyses used survey weight to produce nationally representative estimates and to avoid non-response bias. Data from the nine most recent 2-year cycles (1999–2000 to 2015–2016) were used to examine trends in the use of medications with insomnia side effects for adults aged 20 years and older (n = 49,512). To investigate the relationship between medications with insomnia side effects and insomnia, this study used a sample of 10,798 adults in 2005–2008 who completed the sleep disorder questionnaires. Information on insomnia was only available in these years. The rate of non-response for the sleep disorder questionnaires was less than 0.1%. This study removed 536 respondents who used medications for treatment of insomnia1 in the last month and 666 respondents who were ever told by a medical professional that they had a sleep disorder. These individuals possibly already had insomnia or another sleep disorder prior to the survey. Finally, 1,848 respondents who had missing information on control variables were excluded. Missing

1These medications included armodafinil, butabarbital, dextroamphetamine, diphenhydramine, doxepin, estazolam, eszopiclone, flurazepam, lorazepam, modafinil, montelukast, oxazepam, pentobarbital, phenobarbital, ramelteon, suvorexant, temazepam, trazodone, triazolam, zaleplon, zolpidem, doxylamine, quazepam, secobarbital, amobarbital, and lemborexant.
data for control variables were imputed using multiple imputation with chained equations, but the results were not significantly different from when not using imputation. This study used a final sample of 7,748 respondents without missing data.

Insomnia-related outcomes were measured using a series of objective questions about respondents' sleeping habits in the past month and their daytime functional status. Respondents reported the frequency of the following insomnia symptoms in the past month: (a) had trouble falling asleep, (b) woke up during the night and had trouble getting back to sleep, (c) woke up too early in the morning and was/were unable to get back to sleep, and (d) felt unrested during the day. Respondents also reported the frequency of the following daytime sleepiness symptoms in the past month: (e) felt overly sleepy during the day and (f) did not have enough sleep. Acceptable responses included “never,” “rarely” (one time per month), “sometimes” (two to four times per month), “often” (five to 15 times per month) and “almost always” (16–30 times per month). Respondents were asked whether they had any difficulty with the following eight daytime activities due to sleeplessness or tiredness: concentrating, remembering, eating, hobby activities, getting things done, doing finances, working and phone conversations. Interviewers explained to respondents that the terms “sleeplessness” and “tiredness” described the feelings when respondents couldn’t keep their eyes open, when their heads were droopy, when they wanted to nod off, or when they felt the urge to take a nap. Interviewers also clarified that these terms did not refer to the tired or fatigued feelings that respondents might experience after their exercise. Prior studies have demonstrated the reliability (alpha = 0.86) of these questions about daytime activities and that they are acceptable for research and clinical evaluation of functional status outcomes for persons with disorders of excessive sleepiness (Weaver et al., 1997). Respondents were classified as having insomnia symptoms with interference if they “often” or “almost always” had at least one out of four insomnia symptoms in the last month in addition to having difficulty with at least two daytime activities. This approach has been used in other NHANES studies and is consistent with the definition of insomnia in the Diagnostic and Statistical Manual of Mental Disorders Fourth edition (Cepeda, Stang, Blacketer, Kent, & Wittenberg, 2016; Chen, Redline, Shields, Williams, & Williams, 2014; Ohayon, 2005; Roth, 2007). This study also assessed the relationship between medications with insomnia side effects and whether a person had at least one of the four insomnia symptoms, whether they had at least one of the two daytime sleepiness symptoms, and whether they had difficulty with at least two out of eight daytime activities due to sleepiness or tiredness.

Medications were recorded during the in-person prescription medication interviews. Interviewers asked if respondents had taken any prescription medications in the past 30 days. Respondents who gave an affirmative answer were asked to show the containers of all prescription medications they had taken in the last month. Respondents who could not show the medication container were asked to verbally report the name of the medication. Interviewers then entered the medication names into a computer. More than 95% of entries in 2015–2016 resulted in exact or similar matches with an existing drug selected from a database (81% exact matches and 14% similar matches). The NHANES obtained the drug database from Lexicon Plus, a proprietary database of Cerner Multum that provided, on an annual basis, a comprehensive list of all prescription and some non-prescription medications available in the US market.

Medications with insomnia side effects were identified using Micromedex. The database is based on several sources: the US Food and Drug Administration's (FDA's) black box warnings, the FDA's labelled adverse effects, the FDA's Safety Information and Adverse Event Reporting Program (MedWatch), post-marketing surveillance, and a comprehensive review of clinical trials. Previous studies have independently established the accuracy and reliability of Micromedex's coverage of the FDA's black box warnings and drug-drug interactions (Barrons, 2004; Cheng, Guglielmo, Maselli, & Auerbach, 2010). In addition, a growing number of studies have used Micromedex to identify medication side effects and to assess the association between medication side effects and the health of the population (Do & Schnittker, 2020; Qato et al., 2018; Schnittker & Do 2020). This study identified 239 medications with insomnia side effects. This number of medications does not include all medications with insomnia side effects in the US market, but rather the number of medications with insomnia side effects consumed by respondents in this study. From these 239 medications, 118 medications were selected for the analysis in this present paper, including 101 medications that were indicated by Micromedex as having common or serious insomnia side effects and 17 medications that were not indicated as having common or serious insomnia side effects by Micromedex but had an insomnia incidence rate of 10% or higher (Appendix Table S1). Micromedex's indication of common or serious side effects was based on the FDA's drug labels, the insomnia incidence rate, the strength of the evidence, or whether the incidence of insomnia side effects was significantly greater among treated patients versus among placebo patients in clinical studies. This decision excluded medications with insomnia side effects documented based on post-marketing surveillance that lacked a well-defined incidence rate for insomnia and medications with a low incidence rate for insomnia side effects. Respondents were categorized into three groups based on their reported use of medications with insomnia side effects: none (reference category), one medication, and at least two medications. A similar variable was created for the use of medications without known insomnia side effects.

Other covariates include sociodemographic characteristics and risk factors associated with insomnia and/or the use of medications: age groups (20–34, 35–49, 50–64 and 65+ years); race (non-Hispanic Whites, Hispanic, non-Hispanic Blacks and non-Hispanic others); sex (male or female); marital status (married or living with a partner, widowed/divorced/separated, and never married); educational attainment (less than high school, high school graduate, some college, and college or above); household poverty thresholds (<100% of federal poverty threshold, 100%–199%, 200%–299%, 300%–399%, 400%–499%, and 500% or above); whether the person was employed; citizenship status (citizens born in the USA, citizens born abroad, and foreigners); whether the person had any health insurance; the number of chronic conditions (none, one or two, and three
or more) based on self-reported diagnoses of arthritis, cancer, cardiovascular disease (congestive heart failure, coronary heart disease or angina), pulmonary disease (emphysema, chronic bronchitis or asthma), stroke, heart attack, diabetes and hypertension; whether the person was depressed (Patient Health Questionnaire-9 score of 10 or higher) (Kroenke, 2001); BMI categories (underweight, normal weight, overweight and obese); smoking status (non-smokers, smoked at least 100 cigarettes in their lifetime but did not currently smoke [former smokers], and smoked at least 100 cigarettes in their lifetime and currently smoked [current smokers]); drinking status (non-drinkers, moderate drinkers [1 drink/day for women and 1–2 drinks/day for men], and heavy drinkers [≥1 drink/day for women and ≥2 drinks/day for men]); self-rated health status (excellent, very good, good, fair and poor); and whether a person reported any limitations caused by a long-term physical, mental or emotional problem that kept them from working at a job or business, limited the type or amount of work that they could do, or limited in any way any activity. All analyses controlled for year fixed-effects to account for secular trends.

Weighted annual prevalence of using medications with insomnia side effects was calculated to adjust for the complex survey sampling. Logistic regression was used to quantify the statistical significance of trends in using medications with insomnia side effects from 1999 to 2016. Multivariate ordinary least squared and logistic models were used to assess the association between insomnia-related outcomes and the use of medications with insomnia side effects. To address the issue of unobserved heterogeneity in health and other factors, all analyses controlled for the use of medications without insomnia side effects (Do & Schnittker, 2020; Qato et al., 2018; Schnittker & Do, 2020). If the relationship between medications with insomnia side effects and insomnia was driven by unobserved heterogeneity in health and other factors, the relationship between medications without known insomnia side effects and insomnia should be equally significant as that between medications with insomnia side effects and insomnia. A two-sided p-value of less than 0.05 was considered statistically significant.

2 | RESULTS

Figure 1 demonstrates the unadjusted (Panel a) and age/gender-adjusted (Panel b) prevalence of using medication with insomnia side effects among US adults. In Panel (a), the prevalence of adults taking one medication with insomnia side effects increased from 10.5% to 17.4% between 1999 and 2016, or a relative increase of 65.7% (p < .001). The use of two or more of these medications increased even more compared to the baseline: from 2.8% in 1999 to 7.4% in 2016, or a relative increase of 164% (p < .001). A similar pattern was observed even after controlling for age and gender (Panel b), suggesting that the increase in consumption of medications with insomnia side effects was unlikely to have been driven by demographic changes. Further investigation revealed that most of the increase in using medications with insomnia side effects was due to growth in consumption of medications that treated/controlled certain medical conditions, including cancer, hypothyroidism, psychiatric disorders, neurologic disorders, pain, smoking cessation, and asthma (Appendix Table S2).

Table 1 presents descriptive statistics of insomnia-related outcomes and covariates for the full analytic sample and by the number of medications with insomnia side effects. Overall, 39.4% of US adults reported having at least one insomnia symptom, 28.8% had at least one daytime sleepiness symptom, and 21% reported difficulty with two or more daytime activities due to sleeplessness or tiredness. About 13.9% of respondents reported at least one insomnia symptom and difficulty with at least two daytime activities (“insomnia with interference” hereafter). In addition, 13.9% of adults

Figure 1 Unadjusted and age/gender-adjusted weighted prevalence of US adults aged 20+ years taking medications with insomnia side effects, with 95% confidence intervals. Data source: NHANES 1999 to 2016
|                         | All respondents | Number of medications with insomnia side effects taken by respondents |
|-------------------------|-----------------|-----------------------------------------------------------------------|
|                         | N = 7,748       | N = 6,547 N = 989 N = 212                                            | p-value<sup>a</sup> |
| Unweighted frequency (weighted %) unless otherwise indicated |                 |                                                                      |                   |
| Main outcomes (binary)  |                 |                                                                      |                   |
| Whether had any insomnia symptoms and difficulty with ≥2 daytime activities | 1,012 (13.9) | 760 (12.3) 187 (18.9) 65 (30.4) | <.001 |
| Whether had any insomnia symptoms | 2,849 (39.4) | 2,261 (37.1) 456 (47.8) 132 (62.3) | <.001 |
| Whether had any daytime sleepiness symptoms | 2,086 (28.8) | 1,656 (27.0) 332 (35.8) 98 (45.2) | <.001 |
| Whether had any difficulty with ≥2 daytime activities | 1,575 (21.0) | 1,226 (19.4) 263 (26.3) 86 (37.9) | <.001 |
| Main outcomes (continuous), weighted mean (standard error) |                 |                                                                      |                   |
| Number of insomnia symptoms | 0.7 (0.02) | 0.7 (0.01) 0.9 (0.05) 1.3 (0.11) | .016 |
| Number of daytime sleepiness symptoms | 0.4 (0.01) | 0.4 (0.01) 0.5 (0.03) 0.7 (0.06) | .010 |
| Number of daytime activities with difficulty | 0.9 (0.03) | 0.8 (0.03) 1.0 (0.06) 1.7 (0.16) | .014 |
| Questions about frequency of insomnia symptoms last month |                 |                                                                      |                   |
| Whether had trouble falling asleep ≥5 times | 1,113 (15.1) | 861 (13.7) 184 (19.7) 68 (31.8) | <.001 |
| Whether woke up during the night ≥5 times | 1,407 (18.8) | 1,096 (17.3) 242 (26.4) 69 (28.9) | <.001 |
| Whether woke up too early in the morning ≥5 times | 1,229 (15.6) | 978 (14.8) 197 (18.9) 54 (22.2) | .002 |
| Whether felt unrested during the day ≥5 times | 1,697 (24.6) | 1,317 (22.5) 285 (31.7) 95 (46.6) | <.001 |
| Questions about frequency of daytime sleepiness symptoms last month |                 |                                                                      |                   |
| Whether felt overly sleepy during the day ≥5 times | 1,194 (16.0) | 919 (14.4) 208 (21.1) 67 (31.7) | <.001 |
| Whether did not have enough sleep ≥5 times | 1,683 (23.9) | 1,354 (22.6) 254 (28.7) 75 (35.5) | <.001 |
| Questions about difficulty with daytime activities because the person was tired or sleepy |                 |                                                                      |                   |
| Any difficulty with concentrating on things | 1,543 (20.7) | 1,200 (19.2) 253 (24.9) 90 (40.9) | <.001 |
| Any difficulty with remembering things | 1,298 (16.4) | 1,004 (14.9) 219 (21.5) 75 (31.2) | <.001 |
| Any difficulty with eating | 237 (2.6) | 184 (2.4) 37 (2.8) 16 (6.0) | .043 |
| Any difficulty with working on a hobby | 889 (12.2) | 678 (11.0) 151 (15.8) 60 (25.5) | <.001 |
| Any difficulty with getting things done | 792 (10.2) | 632 (9.7) 117 (11.5) 43 (18.5) | .012 |
| Any difficulty with taking care of financial affairs | 667 (9.2) | 523 (8.8) 99 (9.1) 45 (19.8) | <.001 |

(Continues)
### TABLE 1 (Continued)

|                          | All respondents | Number of medications with insomnia side effects taken by respondents | p-value<sup>a</sup> |
|--------------------------|----------------|---------------------------------------------------------------------|---------------------|
|                          |                | None | 1 medication | 2+ medications |                |                |
| N = 7,748                |                | N = 6,547 | N = 989 | N = 212 |                |                |
| Any difficulty at work   | 510 (7.5)      | 401 (6.8) | 81 (9.9) | 28 (13.9) | .001          |                |
| Any difficulty with maintaining a phone conversation | 561 (6.8) | 444 (6.2) | 78 (7.8) | 39 (16.6) | <.001         |                |
| Whether used medications with insomnia side effects last month |                |                |                |                |                |                |
| None                    | 6,510 (82.5)   |                |                |                |                |                |
| 1 medication            | 1,006 (13.9)   |                |                |                |                |                |
| 2+ medications          | 232 (3.5)      |                |                |                |                |                |
| Whether used medications without insomnia side effects last month |                |                |                |                |                |                |
| None                    | 3,890 (51.2)   | 3,676 (57.5) | 186 (22.6) | 28 (16.0) | <.001         |                |
| 1 medication            | 1,254 (17.9)   | 1,037 (17.5) | 190 (21.5) | 27 (13.5) | .022          |                |
| 2+ medications          | 2,604 (30.9)   | 1,797 (25.0) | 630 (55.8) | 177 (70.5) | <.001         |                |
| Race and ethnicity      |                |                |                |                |                |                |
| Non-Hispanic White      | 3,766 (71.3)   | 2,936 (68.4) | 657 (83.6) | 173 (90.7) | <.001         |                |
| Hispanic                | 2,009 (12.2)   | 1,811 (13.5) | 173 (6.4) | 25 (3.2) | <.001         |                |
| Non-Hispanic Black      | 1,683 (11.3)   | 1,505 (12.4) | 147 (6.0) | 31 (5.2) | <.001         |                |
| Non-Hispanic others     | 290 (5.2)      | 258 (5.6) | 29 (3.9) | 3 (0.8) | <.001         |                |
| Gender                  |                |                |                |                |                |                |
| Women                   | 3,966 (51.5)   | 3,152 (47.5) | 658 (69.6) | 156 (73.7) | <.001         |                |
| Men                     | 3,782 (48.5)   | 3,358 (52.5) | 348 (30.4) | 76 (26.3) |                |                |
| Age groups (years)      |                |                |                |                |                |                |
| 20–34                   | 2,229 (29.7)   | 2,083 (33.0) | 124 (14.6) | 22 (11.7) | <.001         |                |
| 35–49                   | 1,984 (31.5)   | 1,720 (31.9) | 208 (29.0) | 56 (32.3) | .223          |                |
| 50–64                   | 1,769 (23.5)   | 1,424 (22.1) | 272 (29.2) | 73 (34.6) | <.001         |                |
| 65+                     | 1,766 (15.2)   | 1,283 (12.9) | 402 (27.2) | 81 (21.3) | <.001         |                |
| Marital status          |                |                |                |                |                |                |
| Married or partnered    | 4,825 (65.8)   | 4,096 (66.3) | 602 (64.8) | 127 (59.0) | .192          |                |
| Widowed/divorced/separated | 1,676 (17.7) | 1,287 (16.1) | 305 (24.0) | 84 (30.0) | <.001         |                |
| Never married           | 1,247 (16.5)   | 1,127 (17.6) | 99 (11.1) | 21 (11.0) | <.001         |                |
| Education               |                |                |                |                |                |                |
| Less than high school   | 2,200 (18.3)   | 1,885 (18.7) | 259 (16.7) | 56 (14.3) | .291          |                |

<sup>a</sup> Number of post-hoc tests: 14,454.
TABLE 1 (Continued)

|                              | All respondents | Number of medications with insomnia side effects taken by respondents |
|------------------------------|-----------------|-----------------------------------------------------------------------|
|                              |                 | None                                                                 |
|                              |                 | 1 medication                                                          |
|                              |                 | 2+ medications                                                        |
| N = 7,748                    |                 | N = 6,547                                                             |
|                              |                 | N = 989                                                               |
|                              |                 | N = 212                                                               |
|                              |                 | p-value<sup>a</sup>                                                   |
| High school graduate         | 1,662 (24.7)    | 1,553 (24.7)                                                          |
|                              | 251 (24.6)      | 58 (24.4)                                                             |
| Some college                 | 2,132 (30.7)    | 1,792 (30.4)                                                          |
|                              | 266 (30.8)      | 74 (37.9)                                                             |
| College graduate or above    | 1,554 (26.3)    | 1,280 (26.2)                                                          |
|                              | 230 (28.0)      | 44 (23.3)                                                             |
| Poverty                      |                 |                                                                      |
| <100% poverty threshold      | 1,421 (11.8)    | 1,221 (12.3)                                                          |
|                              | 148 (8.5)       | 52 (13.5)                                                             |
| 100%-199%                    | 2,029 (19.9)    | 1,701 (20.1)                                                          |
|                              | 268 (18.6)      | 60 (20.7)                                                             |
| 200%-299%                    | 1,257 (15.9)    | 1,052 (15.7)                                                          |
|                              | 175 (18.1)      | 30 (11.3)                                                             |
| 300%-399%                    | 983 (15.1)      | 823 (15.0)                                                            |
|                              | 130 (16.1)      | 30 (15.4)                                                             |
| 400%-499%                    | 629 (10.8)      | 531 (10.9)                                                            |
|                              | 82 (10.6)       | 16 (11.2)                                                             |
| 500%+                        | 1,429 (26.4)    | 1,182 (26.1)                                                          |
|                              | 203 (28.1)      | 44 (27.8)                                                             |
| Employment status            |                 |                                                                      |
| Not employed or not in the labour force | 3,107 (31.0) | 2,381 (27.9)                                                          |
|                              | 568 (43.8)      | 158 (52.3)                                                             |
| Employed                     | 4,641 (69.0)    | 4,129 (72.1)                                                          |
|                              | 438 (56.2)      | 74 (47.7)                                                             |
| US citizenship               |                 |                                                                      |
| Citizens born in the US or its territories | 5,995 (85.2) | 4,903 (83.5)                                                          |
|                              | 876 (92.3)      | 216 (96.4)                                                             |
| Citizens born abroad         | 721 (6.6)       | 627 (7.0)                                                              |
|                              | 80 (5.0)        | 14 (3.1)                                                              |
| Foreigners                   | 1,032 (8.2)     | 980 (9.5)                                                              |
|                              | 50 (2.6)        | 2 (0.5)                                                               |
| Had any health insurance     |                 |                                                                      |
| Yes                          | 5,901 (80.7)    | 4,784 (78.3)                                                          |
|                              | 907 (92.4)      | 210 (89.7)                                                             |
| No                           | 1,847 (19.3)    | 1,726 (21.7)                                                          |
|                              | 99 (7.6)        | 22 (10.3)                                                              |
| Health conditions            |                 |                                                                      |
| Arthritis                    | 1,895 (22.4)    | 1,334 (18.8)                                                          |
|                              | 439 (37.9)      | 122 (46.5)                                                             |
| Cancer                       | 649 (7.8)       | 444 (6.4)                                                              |
|                              | 154 (12.6)      | 51 (20.5)                                                              |
| Cardiovascular disease       | 448 (4.3)       | 312 (3.7)                                                              |
| (congestive heart failure, coronary heart disease or angina) |            | 99 (6.9)                                                              |
|                              | 37 (9.6)        |                                                                      |
| Pulmonary disease            | 1,205 (16.2)    | 917 (14.6)                                                             |
| (emphysema, chronic bronchitis or asthma) |            | 226 (23.4)                                                             |
|                              | 62 (25.3)       |                                                                      |
| Stroke                       | 238 (2.3)       | 153 (1.6)                                                              |
|                              | 66 (5.0)        | 19 (6.7)                                                               |
| Heart attack                 | 277 (2.7)       | 197 (2.4)                                                              |
|                              | 61 (4.1)        | 19 (4.6)                                                               |
| Diabetes                     | 749 (6.7)       | 535 (5.4)                                                              |
|                              | 166 (12.4)      | 48 (15.0)                                                              |

(Continues)
|                              | All respondents | Number of medications with insomnia side effects taken by respondents |
|------------------------------|-----------------|---------------------------------------------------------------------|
|                              | N = 7,748       | None        | 1 medication | 2+ medications |
| Hypertension                 |                 | N = 6,547  | N = 989      | N = 212        | p-value^a  |
|                              |                 | 2,438 (28.0) | 1,851 (25.1) | 476 (41.8)     | 111 (41.7)  | <.001      |
| Depression (PHQ−9 score >= 10) |                 | Yes        | No           |                |                |            |
|                              |                 | 499 (5.2)   | 7,249 (94.8) |                |                | <.001      |
| BMI categories               |                 | Underweight | Normal weight | Overweight     | Obese         |            |
|                              |                 | 132 (1.7)   | 2,216 (31.6) | 2,763 (34.7)   | 2,637 (32.1)  | .282       |
|                              |                 | 115 (1.7)   | 1,881 (32.1) | 2,361 (35.2)   | 2,153 (31.0)  | .110       |
|                              |                 | 16 (1.7)    | 284 (30.5)   | 319 (30.7)     | 387 (37.1)    | .017       |
|                              |                 | 1 (0.3)     | 51 (23.8)    | 83 (38.0)      | 97 (37.8)     |            |
| Smoking status               |                 | Never smoked | Former smoker | Current smoker |                |            |
|                              |                 | 4,133 (52.7) | 1,912 (24.0) | 1,703 (23.3)   |                | .073       |
|                              |                 | 3,509 (52.8) | 1,531 (23.1) | 1,470 (24.1)   |                | .028       |
|                              |                 | 530 (54.3)  | 301 (26.6)   | 175 (19.0)     | 58 (23.0)     |            |
|                              |                 | 94 (42.6)   | 80 (34.5)    | 58 (23.0)      |                |            |
| Drinking status              |                 | Non-drinkers | Moderate drinkers | Heavy drinkers |                | .021       |
|                              |                 | 2,648 (27.2) | 2,368 (34.5) | 2,732 (38.3)   |                | .120       |
|                              |                 | 2,143 (26.0) | 1,952 (34.0) | 2,415 (40.0)   |                |            |
|                              |                 | 399 (32.8)  | 346 (37.9)   | 261 (29.3)     | 56 (34.8)     | <.001      |
|                              |                 | 106 (32.8)  | 70 (32.5)    | 56 (34.8)      |                |            |
| Self-rated health status     |                 | Excellent   | Very good    | Good          | Fair           | Poor        |            |
|                              |                 | 803 (12.2)  | 2,327 (36.4) | 3,065 (37.7)   | 1,338 (11.9)   | 215 (1.9)   | <.001      |
|                              |                 | 728 (13.3)  | 1,973 (36.7) | 2,579 (37.4)   | 1,095 (11.3)   | 135 (1.3)   |            |
|                              |                 | 64 (7.3)    | 306 (37.3)   | 397 (38.4)     | 187 (13.5)     | 52 (3.4)    |            |
|                              |                 | 11 (6.0)    | 48 (26.0)    | 89 (41.5)      | 56 (18.0)      | 28 (8.5)    |            |
| Any physical, mental or emotional limitations |     | Yes | No |                |                |                |            |
|                              |                 | 1,542 (16.9) | 6,206 (83.1) |                |                | <.001      |
|                              |                 | 1,077 (14.1) | 5,433 (85.9) |                |                |            |
|                              |                 | 339 (27.3)  | 667 (72.7)   | 126 (42.6)     |                |            |
|                              |                 | 126 (42.6)  | 106 (57.4)   |                |                |            |

Note: Data Source: NHANES 2005–2006 and 2007–2008.

^a p-value indicates if means are significantly different across respondents who took none, one or at least two medications with insomnia side effects, based on logistics regression (for binary variables) or OLS regression (for continuous variables). BMI, body mass index.
| Outcome:                      | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
|------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
|                              |             | β (95% CI)  |             | β (95% CI)  |             | β (95% CI)  |             | β (95% CI)  |
| **Medications with insomnia side effects** |             |             |             |             |             |             |             |             |
| None (ref.)                  |             |             |             |             |             |             |             |             |
| One                          | 1.55        | 1.28        | 0.12        | 1.49        | 0.26        | 1.48        | 0.24        |
|                             | (1.28, 1.89)| (1.05, 1.58)| (−0.00, 0.25)| (1.22, 1.82)| (0.12, 0.40)| (1.21, 1.81)| (0.09, 0.38)|
| Two or more                  | 2.10        | 1.78        | 0.17        | 1.96        | 0.50        | 1.73        | 0.32        |
|                             | (1.28, 3.44)| (1.22, 2.60)| (0.00, 0.35)| (1.28, 3.00)| (0.26, 0.73)| (1.16, 2.60)| (0.11, 0.52)|
| **Medications without insomnia side effects** |             |             |             |             |             |             |             |             |
| None (ref.)                  |             |             |             |             |             |             |             |             |
| One                          | 0.95        | 1.18        | 0.08        | 0.87        | −0.10       | 1.14        | 0.07        |
|                             | (0.72, 1.26)| (0.98, 1.42)| (−0.06, 0.22)| (0.70, 1.09)| (−0.26, 0.05)| (0.90, 1.44)| (−0.10, 0.23)|
| Two or more                  | 0.90        | 1.04        | 0.07        | 0.90        | −0.04       | 0.95        | −0.06       |
|                             | (0.69, 1.16)| (0.89, 1.22)| (−0.05, 0.18)| (0.72, 1.14)| (−0.20, 0.12)| (0.76, 1.19)| (−0.22, 0.10)|
| No. observations            | 7,748       | 7,748       | 7,748       | 7,748       | 7,748       | 7,748       | 7,748       | 7,748       |

Note: All analyses controlled for age groups (20–34, 35–49, 50–64 and 65+ years), race (non-Hispanic Whites, Hispanic, non-Hispanic Blacks and non-Hispanic others), gender, marital status (married or living with partner, widowed/divorced/separated, and never married), educational attainment (less than high school, high school graduate, some college, and college or above), household poverty thresholds (<100% of federal poverty threshold, 100%–199%, 200%–299%, 300%–399%, 400%–499% and 500% or above), whether the person was employed, citizenship status (citizens born in the US, citizens born abroad, and foreigners), whether the person had any health insurance, number of chronic conditions (none, one or two, and three or more), whether the person was depressed (PHQ-9 score >= 10), body mass index categories (underweight, normal weight, overweight and obese), smoking status (non-smokers, former smokers and current smokers), drinking status (non-drinkers, moderate drinkers and heavy drinkers), self-rated health status (excellent, very good, good, fair and poor), whether the person reported any physical, mental or emotional limitations, and year fixed-effect.

CI, confidence interval; β, beta coefficient; OR, odds ratio.

Data Source: NHANES 2005–2006 and 2007–2008.
TABLE 3 Adjusted logistic regressions of individual insomnia and daytime sleepiness symptoms on use of medications with insomnia side effects for adults aged 20+ years

| Medications with insomnia side effects | Had trouble falling asleep | Woke up during the night | Woke up early in the morning | Felt unrested during the day | Felt sleepy during the day | Did not have enough sleep |
|--------------------------------------|---------------------------|--------------------------|-----------------------------|-----------------------------|---------------------------|--------------------------|
| None (ref.)                          | 1.16 (0.92, 1.47)         | 1.08 (0.85, 1.36)         | 1.04 (0.84, 1.28)           | 1.45 (1.18, 1.78)           | 1.38 (1.06, 1.79)         | 1.38 (1.13, 1.70)         |
| One                                  | 1.57 (1.02, 2.40)         | 0.92 (0.61, 1.38)         | 0.89 (0.58, 1.35)           | 2.06 (1.52, 2.78)           | 1.79 (1.22, 2.63)         | 1.50 (1.00, 2.24)         |
| Two or more                          |                           |                          |                             |                             |                           |                          |
| Medications without insomnia side effects |                        |                          |                             |                             |                           |                          |
| None (ref.)                          | 0.97 (0.76, 1.26)         | 1.19 (0.88, 1.61)         | 1.10 (0.83, 1.46)           | 1.05 (0.86, 1.27)           | 1.10 (0.85, 1.43)         | 1.09 (0.84, 1.40)         |
| Two or more                          | 0.98 (0.79, 1.22)         | 1.29 (0.98, 1.70)         | 1.08 (0.82, 1.43)           | 1.01 (0.83, 1.21)           | 0.93 (0.74, 1.15)         | 0.95 (0.74, 1.22)         |
| No. observations                     | 7,748                     | 7,748                    | 7,748                       | 7,748                       | 7,748                     | 7,748                    |

Note: All analyses controlled for age groups (20–34, 35–49, 50–64 and 65+ years), race (non-Hispanic Whites, Hispanic, non-Hispanic Blacks and non-Hispanic others), gender, marital status (married or living with partner, widowed/divorced/separated, and never married), educational attainment (less than high school, high school graduate, some college, and college or above), household poverty thresholds (<100% of federal poverty threshold, 100%–199%, 200%–299%, 300%–399%, 400%–499%, and 500% or above), whether the person was employed, citizenship status (citizens born in the US, citizens born abroad, and foreigners), whether the person had any health insurance, number of chronic conditions (none, one or two, and three or more), whether the person was depressed (PHQ-9 score >= 10), body mass index categories (underweight, normal weight, overweight and obese), smoking status (non-smokers, former smokers and current smokers), drinking status (non-drinkers, moderate drinkers and heavy drinkers), self-rated health status (excellent, very good, good, fair and poor), whether the person reported any physical, mental or emotional limitations, and year fixed-effect.

Abbreviations: CI, confidence interval; OR, odds ratio.
Data Source: NHANES 2005–2006 and 2007–2008.

consumed one medication with insomnia side effects in the last month, whereas 3.5% consumed two or more. Individuals who took more medications with insomnia side effects were more likely to report insomnia-related symptoms. Compared to non-users, those who used two or more medications with insomnia side effects were more likely to report insomnia-related symptoms, daytime sleepiness symptoms, and difficulty with at least two daytime activities, respectively.

Sociodemographic and health status also varied by the number of medications with insomnia side effects. Compared to non-users, respondents who took at least two medications with insomnia side effects were more likely: to also consume medications without known insomnia side effects; to be non-Hispanic White, female, aged 50 years or older, widowed, divorced or separated, unemployed, US citizens, insured, depressed, obese and former smokers; to rate their health fair or poor; to report physical, mental or emotional limitations; and to report chronic conditions.

Table 2 reports the association between medications with insomnia side effects and insomnia-related outcomes (see Appendix Table S3 for the full results). Relative to non-users, using one and using two or more medications with insomnia side effects were associated with an increase in the odds of insomnia with interference by 1.55 times (95% confidence interval [CI], 1.28 to 1.89) and 2.10 times (95% CI, 1.28 to 3.40), respectively. In addition, respondents who used two or more medications with insomnia side effects were more likely to report at least one insomnia symptom (odds ratio [OR], 1.78; 95% CI, 1.22 to 2.60), difficulty with at least two daytime activities (OR, 1.96; 95% CI, 1.28 to 3.00), and at least one daytime sleepiness symptom (OR, 1.73; 95% CI, 1.16 to 2.60). The use of two or more medications with insomnia side effects was also associated with an increase in the number of insomnia symptoms (coefficient, 0.17; 95% CI, 0.002 to 0.35), the number of daytime activities with which the person had difficulty (coefficient, 0.50; 95% CI, 0.26 to 0.73), and the number of daytime sleepiness symptoms (coefficient, 0.32; 95% CI, 0.11 to 0.52). This study also documented a dose-response relationship such that the association between medications with insomnia side effects and insomnia increased over each category of additional medication. In contrast, the use of medications without known insomnia side effects was not associated with all outcomes. These results imply that polypharmacy played a critical role.
### TABLE 4  Adjusted logistic regressions of daytime impairments on use of medications with insomnia side effects for adults aged 20+ years

| Outcomes          | Difficulty with concentrating | Difficulty with remembering | Difficulty with eating | Difficulty with hobbies | Difficulty getting things done | Difficulty with finance | Difficulty at work | Difficulty on the phone |
|-------------------|--------------------------------|------------------------------|------------------------|-------------------------|-------------------------------|------------------------|---------------------|-------------------------|
|                   | OR (95% CI)                    | OR (95% CI)                  | OR (95% CI)            | OR (95% CI)             | OR (95% CI)                   | OR (95% CI)            | OR (95% CI)         | OR (95% CI)            |
| Medications with insomnia side effects |                   |                              |                        |                        |                               |                        |                     |                          |
| None (ref.)       | None (ref.)                    |                              |                        |                        |                               |                        |                     |                          |
| One               | 1.32 (1.10, 1.59)              | 1.45 (1.15, 1.83)            | 1.21 (0.73, 2.01)      | 1.30 (1.01, 1.69)       | 1.15 (0.90, 1.46)             | 1.04 (0.78, 1.40)     | 1.61 (1.19, 2.16)    | 1.59 (1.07, 2.38)     |
| Two or more       | 2.21 (1.40, 3.48)              | 1.88 (1.18, 3.00)            | 1.88 (0.74, 4.75)      | 1.80 (1.14, 2.83)       | 1.45 (0.88, 2.40)             | 1.95 (1.13, 3.35)     | 1.66 (0.96, 2.89)    | 3.19 (2.03, 4.99)     |
| Medications without insomnia side effects |                   |                              |                        |                        |                               |                        |                     |                          |
| None (ref.)       | 0.99 (0.79, 1.24)              | 0.83 (0.66, 1.04)            | 0.63 (0.38, 1.03)      | 1.04 (0.80, 1.37)       | 0.85 (0.64, 1.12)             | 0.83 (0.59, 1.15)     | 1.01 (0.68, 1.51)    | 0.81 (0.57, 1.16)     |
| One               | 0.88 (0.71, 1.08)              | 1.01 (0.78, 1.32)            | 1.09 (0.65, 1.84)      | 1.12 (0.84, 1.49)       | 0.90 (0.66, 1.24)             | 0.99 (0.68, 1.44)     | 0.95 (0.64, 1.41)    | 1.01 (0.67, 1.52)     |
| Two or more       | 1.0 (0.71, 1.32)               | 1.09 (0.65, 1.84)            | 1.12 (0.84, 1.49)      | 0.90 (0.66, 1.24)       | 0.99 (0.68, 1.44)             | 0.95 (0.64, 1.41)     | 1.01 (0.67, 1.52)    |                          |
| No. observations  | 7,748                          | 7,748                        | 7,748                  | 7,748                   | 7,748                        | 7,748                  | 7,748               | 7,748                   |

Note: All analyses controlled for age groups (20–34, 35–49, 50–64 and 65+ years), race (non-Hispanic Whites, Hispanic, non-Hispanic Blacks and non-Hispanic others), gender, marital status (married or living with partner, widowed/divorced/separated, and never married), educational attainment (less than high school, high school graduate, some college, and college or above), household poverty thresholds (<100% of federal poverty threshold), 100%–199%, 200%–299%, 300%–399%, 400%–499%, and 500% or above), whether the person was employed, citizenship status (citizens born in the US, citizens born abroad, and foreigners), whether the person had any health insurance, number of chronic conditions (none, one or two, and three or more), whether the person was depressed (PHQ-9 score >= 10), body mass index categories (underweight, normal weight, overweight and obese), smoking status (non-smokers, former smokers and current smokers), drinking status (non-drinkers, moderate drinkers and heavy drinkers), self-rated health status (excellent, very good, good, fair and poor), whether the person reported any physical, mental or emotional limitations, and year fixed-effect.

Abbreviations: CI, confidence interval; OR, odds ratio.

Data Source: NHANES 2005–2006 and 2007–2008
in the relationship between medications with insomnia side effects and insomnia-related outcomes, and that the relationship was unlikely to have been driven by unobservable heterogeneity in health or other factors.

Table 3 quantifies the relationship between medications with insomnia side effects and each of the six symptoms for insomnia and daytime sleepiness. The positive association between medications with insomnia side effects and insomnia was mainly driven by the relationship between the use of these medications and the odds of "having trouble falling asleep" and "feeling unrested during the day." The use of these medications was also associated with both symptoms of daytime sleepiness, including "feeling sleepy during the day" and "not having enough sleep." Table 4 illustrates that the use of medications with insomnia side effects was associated with difficulty performing five out of eight daytime activities. In contrast, the use of medications without known insomnia side effects shown in Tables 3 and 4 was not associated with insomnia symptoms, daytime sleepiness symptoms and difficulty with daytime activities.

Appendix Figures S1-S16 report the relationship between medications with insomnia side effects and insomnia with interference by sociodemographic and health characteristics. The use of medications with insomnia side effects was associated with insomnia with interference for the following groups: older adults, non-Hispanic Whites; women; married, widowed, divorced, separated and never-married adults; non-college-graduated respondents; both employed and unemployed respondents; both low-income and high-income respondents; US-born respondents; respondents with any type of health insurance; current smokers; and moderate drinkers. This study also documented a statistically significant and positive association between medications with insomnia side effects and insomnia with interference for healthy adults – including those who reported excellent/very good/good health, adults without depression, and adults who had at most one chronic condition. These results suggest that the relationship between medications with insomnia side effects and insomnia with interference was unlikely to have been driven by poor health or comorbidities.

3 | DISCUSSION

This study is the first to use a nationally representative sample of US adults to investigate trends in the use of medications with insomnia side effects and the relationship between these medications and insomnia at the population level. The use of one and at least two medications with insomnia side effects increased substantially by 66% and 164% in the past two decades, respectively. In addition, concurrent use of these medications was associated with increased risks of insomnia-related outcomes. In contrast, the use of medications without known insomnia side effects was not associated with increased risks of insomnia.

Medical providers may have neglected the side effect of insomnia when prescribing medications for treatment of other physical and mental conditions, despite the well-documented consequences of insomnia for other medical conditions, quality of life, mortality and healthcare costs (Cappuccio et al., 2010; Fernandez-Mendoza & Vgontzas, 2013; Kyle, Morgan, & Espie, 2010; Reynolds & Ebben, 2017; Wickwire et al., 2016). Despite patients’ concerns about the insomnia side effects of medications and the growing prevalence of insomnia (Curtis et al., 2006; Moloney et al., 2011), the use of medications with insomnia side effects, as documented in this study, has increased considerably over the last two decades. Many medications with insomnia side effects are intended for prevention or treatment of physical or mental conditions. Although these medications may be beneficial for controlling diseases for which they are intended, they may induce insomnia and other medical conditions associated with insomnia. The decision to prescribe these medications may in part reflect physicians’ belief that other conditions should be prioritized over insomnia, or that any insomnia side effects related to medications can be treated later after the primary condition is under control. Yet, many adults increasingly report worrisome insomnia symptoms (Moloney et al., 2011), and given the patterns documented in this study, medications may have partly played a role in their experience. Therefore, medical providers may want to conduct screenings for insomnia or other sleep disorders before and during the administration of medications with insomnia side effects to adjust medication doses, especially when patients consume several of these medications.

This study also emphasizes the important role of polypharmacy in intensifying the insomnia side effects of medications. From 1999 to 2012, the prevalence of US adults taking five or more prescription medications simultaneously increased by 83% (Kantor et al., 2015). This present study found that the concurrent use of at least two medications with insomnia side effects increased even more over this baseline increase in polypharmacy, by almost 164% between 1999 and 2016. Prior studies have documented the negative health consequences of polypharmacy, including adverse drug events, drug-drug interactions, medication non-adherence, falls and cognitive impairment (Fulton & Riley Allen, 2005). Polypharmacy may present unique risks for medication side effects, amplifying the effects of each of the medications in a set (Do & Schnittker, 2020). Further, polypharmacy may increase the risk of drug-drug interactions that may result in insomnia symptoms. However, it is possible that the relationship between concurrent use of medications with insomnia side effects and insomnia is driven by the confounding effect of comorbidities associated with polypharmacy, rather than the synergic effects of polypharmacy and the potential drug-drug interactions. If this is the case, then the relationship between concurrent use of medications without insomnia side effects and insomnia should be equally significant as that between the concurrent use of medications with insomnia side effects and insomnia. This present study found that the risks of insomnia, daytime impairment and daytime sleepiness increased with each category of additional medications with insomnia side effects. In contrast, concurrent use of multiple medications without known insomnia side effects was not associated with insomnia-related outcomes. This finding implies that the relationship between concurrent use of
multiple medications with insomnia side effects and insomnia was not driven by unobserved comorbidities related to polypharmacy. It also suggests that consuming multiple medications with insomnia side effects simultaneously may amplify such adverse side effects of medications.

Disparities in the use of medications with insomnia side effects across subgroups may in part help explain disparities in insomnia at the population level. In additional analyses (Appendix Table S4), the use of multiple medications with insomnia side effects was particularly common among non-Hispanic Whites, women, older adults, unemployed respondents, US citizens born in the USA, respondents with health insurance, chronically ill respondents, respondents with depression, respondents who reported poor or fair health, and respondents who reported limitations. The more common use of medications with insomnia side effects among these subgroups was potentially due to their high levels of health insurance coverage and access to prescription medications (i.e. non-Hispanic Whites, older adults, US citizens, and respondents with health insurance) or due to their high prevalence of mental and physical illnesses that require pharmaceutical interventions (i.e., respondents with depression or multiple chronic conditions, respondents who reported fair or poor health, and respondents who reported any type of limitations).

Future research should develop and examine whether and to what degree disparities in the use of medications with insomnia side effects may in part help explain the racial/ethnic, gender, cohort and other sociodemographic disparities in insomnia.

Although this paper has several strengths, such as using a nationally representative survey and a comprehensive database of medications with known insomnia side effects, it faces several limitations. First, it is challenging to estimate the causal impact of medications with insomnia side effects on insomnia due to the cross-sectional nature of the NHANES. It is unclear whether medications with insomnia side effects induce insomnia or whether insomnia leads to the onset of other health conditions that require pharmaceutical interventions. Second, medications with insomnia side effects may also have other side effects that indirectly increase the risk of insomnia. Third, although Micromedex provided a comprehensive list of medications with insomnia side effects, there might be other medications with insomnia side effects that were not included in the database.

This study addressed these issues by controlling for a comprehensive list of comorbidities that were related to insomnia and/or the use of medications, but there might be other unobserved heterogeneity. This study also controlled for the use of medications without known insomnia side effects and found that these medications were not significantly associated with insomnia symptoms. This implies that unobserved heterogeneity in health or other factors associated with medication use was unlikely to affect the results in this study, and that there were few medications with insomnia side effects that had not been identified by Micromedex. Fourth, the NHANES recorded any use of prescription medications in the past month as opposed to regular use. Therefore, the results are likely to have underestimated the association between medications with insomnia side effects and insomnia. Finally, the NHANES lacks information on dosage associated with medications with insomnia side effects. This is an important omission because many medications are dose dependent. This paper attempted to test the effects of treatment intensity in other ways. In Appendix Table S5, the use of medications with and without insomnia side effects was further classified into categories of duration of use (at most 1 year and more than 1 year). Respondents who used multiple medications with/without insomnia side effects were assigned the length of time that corresponded with the length of time for the medication with/without insomnia side effects they had been taking the longest. Among respondents who consumed at least one medication with insomnia side effect, the median duration of use was 1,460 days, suggesting that most respondents used these medications for treatment of chronic conditions or disease prevention. Results in Appendix Table S5 suggest that the use of medications with insomnia side effects was generally associated with increased risks of all insomnia-related outcomes regardless of the duration of use. In many cases, the association between medications with insomnia side effects and insomnia-related outcomes was larger among respondents who used these medications for more than 1 year compared to those who used them for at most 1 year, although the differences were not statistically significant. While the duration of use cannot perfectly substitute information on medication dosage, it does provide information on the long-term amount of medication that a person has been consuming before the survey.

4 | CONCLUSION

This study demonstrated a considerable growth in the concurrent use of medications with insomnia side effects over the past decades. It also presented a relationship between the concurrent use of medications with insomnia side effects and insomnia-related outcomes. The results highlighted the important role of polypharmacy in amplifying medication side effects. Efforts aimed to reduce polypharmacy by promoting proper prescribing practices may alleviate the exposure to medication side effects and improve the health of the population.

CONFLICT OF INTEREST

No conflicts of interest declared.

AUTHOR CONTRIBUTION

DD planned the study, performed all statistical analyses and wrote the paper.

ORCID

Duy Do https://orcid.org/0000-0001-9919-6848

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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