Effectiveness and safety of medicines used in COPD patients

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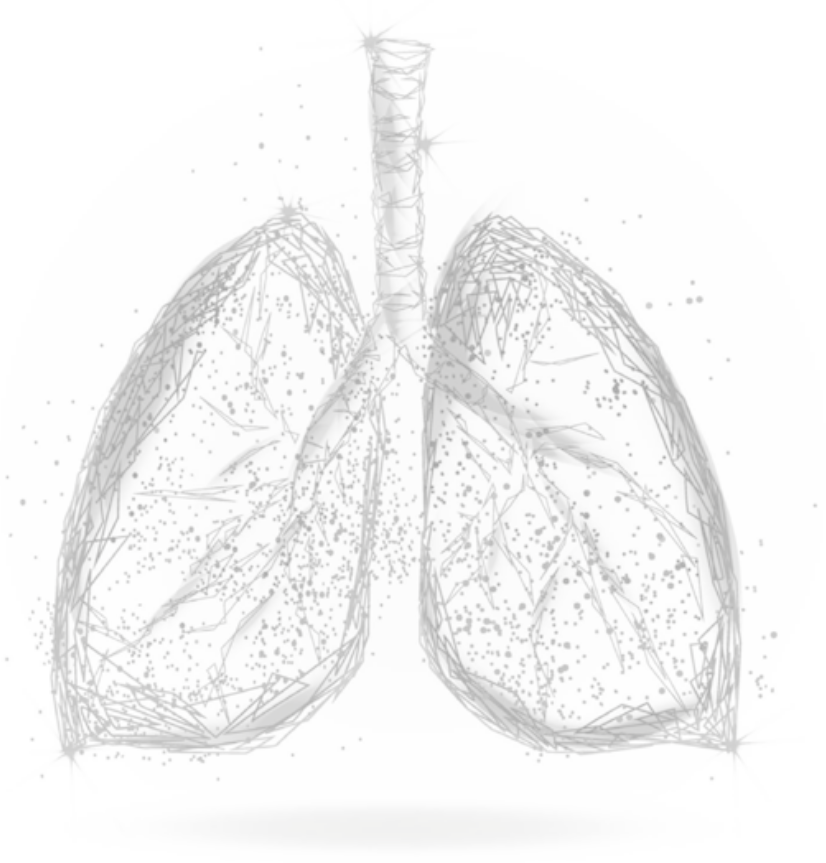
DOI:
10.33612/diss.123921981

CHAPTER 6



Neuropsychiatric safety of varenicline in the general and COPD population with and without psychiatric disorders: a retrospective inception cohort study in a real-world setting

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Submitted for publication.

ABSTRACT

Background

Although varenicline is an effective treatment for smoking cessation, evidence on its real-world neuropsychiatric safety is inconsistent, notably for high-risk populations.

Objectives

To evaluate the association between varenicline use and major neuropsychiatric adverse events (NPAEs) in the general and COPD population with and without psychiatric disorders compared with nicotine replacement therapy (NRT) in a real-world setting.

Methods

A retrospective inception cohort study was conducted among new users of varenicline or NRT using the University of Groningen pharmacy database IADB.nl. The primary outcome was the incidence of any drug-treated NPAEs including depression, anxiety and insomnia within 24 weeks after treatment initiation. Subgroup and sensitivity analyses were also conducted.

Results

In the general population without psychiatric disorders, the incidence of total NPAEs in varenicline and NRT groups was 13.7% and 18.3%, respectively (adjusted OR [aOR] 0.78, 95% confidence interval [CI]: 0.67 to 0.90). In the general population with psychiatric disorders, the incidence of total NPAEs was much higher, 81.3% and 84.3% for varenicline and NRT groups, respectively (aOR 0.81, 95% CI: 0.65 to 0.99). In the COPD population, there were no differences in the incidence of NPAEs between comparison groups in both the psychiatric cohort (aOR 1.01, 95% CI [0.65, 1.58]) and the non-psychiatric cohort (aOR 0.75, 95% CI [0.53, 1.05]). Results from subgroup or sensitivity analyses did not reveal increased risks of varenicline compared to NRT.

Conclusion

Varenicline does not increase the risk for NPAEs in both general and COPD populations compared with NRT, irrespective of the presence of psychiatric disorders. Our results provide reassurance for the patients and physicians and may be of help to enhance the use of varenicline for smoking cessation by weighing its risks and benefits.

INTRODUCTION

Tobacco smoking is the leading preventable risk factor for a range of physical and mental illnesses[1-4] which poses enormous threats to global public health.[5] Although average global smoking rates have declined since 1990 through tobacco control policies,[6] the actual number of smokers and disease burden related to smoking continues to increase owing to population growth.[7] More than 8 million people are killed by tobacco use each year.[8] Therefore, more intensified efforts are needed to fight this deadly epidemic. Smoking cessation strategies as key interventions to prevent smoking-related diseases are therefore urgently needed.[9] Varenicline was the first non-nicotine pharmacotherapy for smoking cessation and has greater efficacy than single bupropion, nicotine replacement therapy (NRT) or placebo.[10,11] However, substantial concerns regarding its neuropsychiatric safety (e.g. suicidal thoughts, aggressive behavior) have been raised since its approval in the United States in 2006.[12] Therefore, after the first safety communication and public health advisory in 2008, the FDA released a black box warning on July 1, 2009.[13] Of note, these reports could not establish the causality because of a lack of control or comparator. Afterwards, many randomized controlled trials (RCTs) were conducted to evaluate the possible risk of neuropsychiatric adverse events (NPAEs). Notably, pooled evidence of these RCTs did not indicate an association between varenicline and NPAEs.[14] Neither did the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) show a significant increase in NPAEs with varenicline relative to NRT or placebo.[10]

Although the FDA warning was removed in 2016, concerns regarding the external validity of the RCT evidence remained. Indeed, due to the strict inclusion and exclusion criteria of RCTs, trial participants were generally healthy. Special risk populations with increased smoking prevalence, such as those with COPD and psychiatric disorders, were usually excluded.[15] Importantly, COPD patients are older and suffer from many comorbidities making these patients more susceptible to drug-drug interactions potentially leading to related adverse drug events (ADEs).[16] Similarly, it has been reported that individuals with psychiatric disorders are prone to experience relapse of psychiatric symptoms.[17,18] Varenicline safety in these specific populations is not well explored. Only few studies assessed the neuropsychiatric safety of varenicline in patients with COPD or psychiatric disorders,[10,19,20] yet results were inconsistent and related evidence from real-world setting is still lacking.

We therefore conducted this cohort study based on real-life data to assess the risk of NPAEs in starters with varenicline versus NRT starters in both the general and the COPD population with and without psychiatric disorders.

METHODS

Study design and setting

We conducted a retrospective inception cohort study based on the University of Groningen pharmacy dispensing database IADB.nl (http://www.iadb.nl/) which has been widely used for various drug utilization studies.[21] IADB.nl contains information of prescribed medications from 70 community pharmacies covering a representative population of approximately 700,000 persons of the Netherlands, regardless of insurance type. It provides both patient information (e.g. date of birth, gender) and complete prescription records including the date of dispensing, quantity dispensed, dose regimen, the number of days the drug will be used, and the related Anatomical Therapeutic Chemical (ATC) codes.

Study population

We included adult patients (>18 years) who started with varenicline or NRT. The individuals only prescribed varenicline (ATC code: N07BA03) or NRT (N07BA01) were included as anti-smoking drug users from the general population. Individuals that were prescribed drugs for obstructive airway disease (R03) at least 3 times within 1 year since 1st prescription after the age of 40 years were defined as COPD patients. COPD patients who were prescribed varenicline or NRT were included as COPD anti-smoking drug users.

For both the general and COPD population with anti-smoking drug use, the first prescription date of varenicline and NRT was set as entry date (index date) of participants for exposure and control groups, respectively. Those who were prescribed other smoking cessation drugs including bupropion (N06AX12), nortriptyline (N06AA10) and cytisine (N07BA04) rather than the studied drugs (varenicline, NRT) within 180 days before or 180 days after index date were excluded. Those who were registered in IADB.nl less than 24 weeks before or after index date were also excluded. For individuals who were prescribed both varenicline and NRT and met criteria of both groups (see Figure 1), we allocated the study subject to the group with the first index date according to the intention-to-treat principle.

In both the general and the COPD population, we classified the individuals into a psychiatric cohort and non-psychiatric cohort according to the presence of psychiatric disorders defined by the prescription of two or more drugs from the neurological ATC group, i.e. N02, N03, N04, N05, N06 within 6 months before index date. In all, our study population covered four separate cohorts (1. General population with psychiatric disorders, 2. General population without psychiatric disorders, 3. COPD population with psychiatric disorders and 4. COPD population without psychiatric disorders) in which the association between exposure and outcomes were assessed (Figure 1).

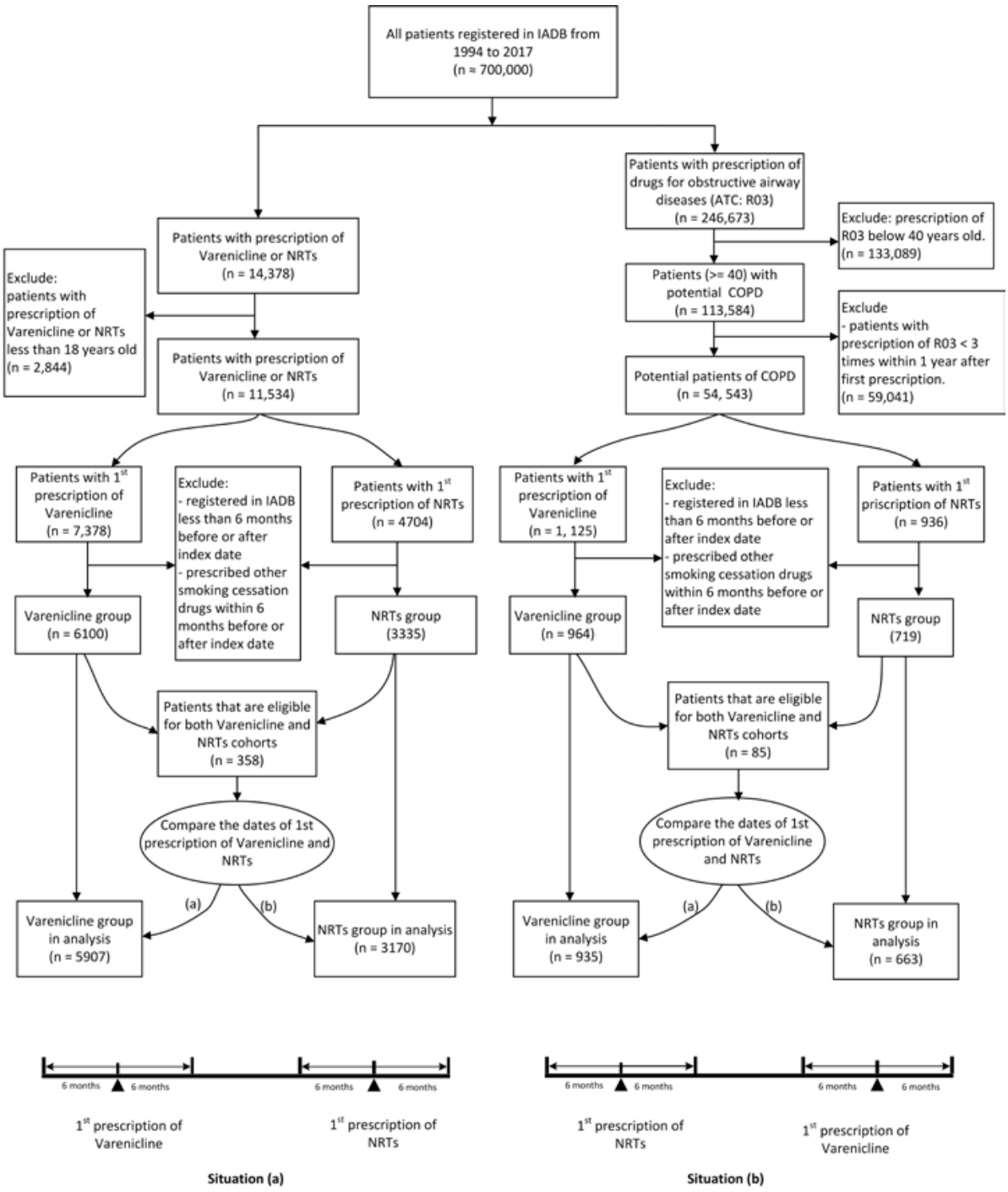

Figure 1. Flow chart of population selection. NRT: nicotine replacement therapies; ATC: anatomical therapeutic chemical.

Exposure and outcomes

We defined individuals using varenicline as the exposure group and those using NRT as the reference group. The primary outcome was incidence of any drug-treated neuropsychiatric adverse event (NPAE) including depression (drugs with ATC-codes N06A, N06CA), anxiety (N05B) and insomnia (N05C), defined as one or more prescriptions of the specified drugs within 24 weeks after the first prescription of varenicline or NRT.

Covariates

The following covariates were included as possible confounders: age, gender, social economic status (SES) based on postal codes, previous psychiatric disorders and other comorbidities including heart failure, ischemic heart disease, hypertension, cancer, diabetes, osteoporosis, peptic ulcer and gastroesophageal reflux disease (GERD), rheumatic arthritis, thyroid disorder, anemia, glaucoma, gout, and allergic rhinitis. All the comorbidities were defined by at least two prescriptions of related drugs within 6 months prior to index date (see detailed ATC codes in supplementary Table S1), The ATC codes used to define the comorbidities in this study were consistent with those in previous published papers.[22-26]

Statistical methods

The continuous and categorical variables are presented as means with standard deviations (SD) and numbers with percentages, respectively. The differences of characteristics between two groups were compared using student's t-tests and chi-square tests for continuous and categorical variables, respectively. Binary logistic regression modeling was used to obtain the odds ratio (OR) and corresponding 95% confidence interval (CI) after adjustment for the potential confounders. A two-sided $p \leq 0.05$ was considered to be statistically significant for all tests. All analyses were performed using IBM SPSS statistics 25 (IBM Corporation, Armonk, NY, USA) for Windows.

Subgroup and sensitivity analyses

Considering the possible influence of age and gender on the association between NPAEs and varenicline use, we further analyzed the primary outcome in the four cohorts (general and COPD populations with or without psychiatric disease, separately) by stratifying the results by age groups and gender. To further test the robustness of the results, we performed several sensitivity analyses. First, because the common treatment duration of varenicline is 12 weeks, we explored the outcome occurring within 12 weeks after treatment initiation. Second, to exclude an active psychiatric status, we further selected subjects who were not prescribed any drugs for psychiatric disorders within 30 days before index date. Finally, considering the influence of policy changes about reimbursement of smoking cessation treatment on the use of anti-smoking drugs,[27] we also performed a sensitivity analysis by excluding the patients whose prescription date of varenicline or NRT may be in the period of Dutch smoking policy changes (i.e. from July 1st 2011 to June 30, 2013).

RESULTS

Baseline characteristics

In total, we included 9077 subjects who initiated varenicline or NRT from the general population, of which 2627 had psychiatric disorders. For the COPD population, we

included 1598 individuals, of which 649 had psychiatric disorders. In both the general and COPD population, individuals treated with varenicline were younger than those treated with NRT (Table 1). Drug use for heart failure and ischemic heart disease was lower in the varenicline-treated than the NRT-treated group. In patients without psychiatric disorders, drug use for other comorbidities (e.g. diabetes and osteoporosis) was also less in individuals treated with varenicline than in those with NRT.

Primary outcome in the general and COPD population

In the general population with psychiatric disorders, the incidence of overall NPAEs within 24 weeks was lower in the varenicline group than the NRT group (81.3% vs 84.3%, OR 0.81 [0.66, 0.99], Table 2). After adjusting for potential confounders, the association did not substantially change (adjusted OR (aOR) 0.81, 95% CI [0.65, 0.99]). All the specific NPAEs were also less in the varenicline group than the NRT group, although the difference between the two comparison groups for depression and insomnia events did not reach statistical significance.

In the general population without psychiatric disorders, the incidence rates of NPAEs were lower than among those with psychiatric disorders. The incidence of overall NPAEs within 24-weeks in the varenicline group was lower than those in the NRT group (13.7% and 18.3%, respectively; aOR 0.78, 95% CI [0.67, 0.90]). No difference was observed between the two treatment groups for depression and anxiety, however, less insomnia was seen for varenicline than NRT (aOR was 0.63, 95% CI [0.49, 0.82]).

In the COPD population, we did not see a statistical significant difference for incidence of overall NPAEs between the varenicline and NRT groups for both the psychiatric cohort (OR 1.01, 95% CI [0.65, 1.58], Table 3) and the non-psychiatric cohort (OR 0.75, 95% CI [0.53, 1.05]). There were also no differences for specific NPAEs between treatment groups in these two cohorts except for anxiety, which was observed significantly less in the varenicline group compared with the NRT group (aOR 0.68, 95% CI [0.49, 0.94] for the psychiatric cohort and aOR 0.69, 95% CI [0.50, 0.96] for the non- psychiatric cohort, respectively).

Subgroup analysis

In the general population with psychiatric disorders, the risk of overall NPAEs was even lower among varenicline than NRT users for younger patients (aOR 0.54, 95% CI [0.28, 1.04] for age < 40, aOR 0.78, 95% CI [0.63, 0.98] for age 40-65, Table S2) and females (aOR 0.74, 95% CI [0.57, 0.97]). However, in the general population without psychiatric disorders, a lower risk of overall NPAE by varenicline treatment compared with NRT was seen in older patients (aOR 0.52, 95% CI [0.33, 0.82]) and male subjects (aOR 0.78, 95% CI [0.61, 0.99]).

Table 1. Baseline characteristics of general and COPD population with and without psychiatric disorders by treatment groups.

	General population (n = 9077)				COPD population (1598)			
	Psychiatric cohort (n = 2627)		Non-psychiatric cohort (n = 6450)		Psychiatric cohort (n = 649)		Non-psychiatric cohort (n = 949)	
Characteristics	Varenicline (N=1427)	NRT (N=1200)	Varenicline (N=4480)	NRT (N= 1970)	Varenicline (N=327)	NRT (N=322)	Varenicline (N=608)	NRT (N= 341)
Age (years)								
Mean (SD)	54.5 (9.6)*	55.8 (12.3)	52.1 (9.7)*	53.4 (12.5)	59.2 (8.6)*	62.4 (10.2)	58.9 (8.9)*	62.7 (9.8)
Age range	32 - 87	25 - 92	32 - 102	22 - 90	41 - 87	41 - 92	40 - 102	42 -89
Gender (n, %)								
Men	541 (37.9)*	523 (43.6)	2406 (53.7)	1100 (55.8)	111 (33.9)	126 (39.1)	310 (51.0)	184 (54.0)
Female	886 (62.1)	677 (56.4)	2074 (46.3)	870 (44.2)	216 (66.1)	196 (60.9)	298 (49.0)	157 (46.0)
Year of index date (n, %)								
1994-2010	519 (36.4)*	492 (41.0)	1497 (33.4)*	895 (45.4)	135 (41.3)	135 (41.9)	211 (34.7)	124 (36.4)
2011-2017	908 (63.6)	708 (59.0)	2983 (66.6)	1075 (54.6)	192 (58.7)	187 (58.1)	397 (65.3)	217 (63.6)
Social economic status (n, %)								
Low	714 (50.0)*	655 (54.6)	2117 (47.3)*	1080 (54.8)	170 (52.0)	172 (53.4)	287 (47.2)	175 (51.3)
High	713 (50.0)	545 (45.4)	2363 (52.7)	890 (45.2)	157 (48.0)	150 (46.6)	321 (52.8)	166 (48.7)
Comorbidities (n, %)								
Heart failure	41 (2.9)*	82 (6.8)	47 (1.0)*	53 (2.7)	23 (7.0)*	42 (13.0)	20 (3.3)*	27 (7.9)
Ischemic heart disease	25 (1.8)*	39 (3.3)	36 (0.8)*	31 (1.6)	9 (2.8)*	20 (6.2)	9 (1.5)*	12 (3.5)
Hypertension	508 (35.6)	465 (38.8)	1039 (23.2)*	547 (27.8)	146 (44.6)	167 (51.9)	234 (38.5)	145 (42.5)
Cancers	9 (0.6)*	0 (0.0)	9 (0.2)	9 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Diabetes mellitus	162 (11.4)	129 (10.8)	260 (5.8)*	146 (7.4)	53 (16.2)	40 (12.4)	47 (7.7)*	43 (12.6)
Osteoporosis	39 (2.7)	32 (2.7)	25 (0.6)*	26 (1.3)	17 (5.2)	20 (6.2)	6 (1.0)*	14 (4.1)
Peptic ulcer and GERD	436 (30.6)	407 (33.9)	474 (10.6)*	253 (12.8)	134 (41.0)	142 (44.1)	123 (20.2)	82 (24.0)
Rheumatic arthritis	170 (11.9)	172 (14.3)	204 (4.6)*	123 (6.2)	45 (13.8)	41 (12.7)	40(6.6)	21 (6.2)

Table 1. (continued)

Characteristics	General population (n = 9077)				COPD population (1598)			
	Psychiatric cohort (n = 2627)		Non-psychiatric cohort (n = 6450)		Psychiatric cohort (n = 649)		Non-psychiatric cohort (n = 949)	
	Varenicline (N=1427)	NRT (N=1200)	Varenicline (N=4480)	NRT (N= 1970)	Varenicline (N=327)	NRT (N=322)	Varenicline (N=608)	NRT (N= 341)
Thyroid disorder	55 (3.9)	40 (3.3)	96 (2.1)	49 (2.5)	18 (5.5)	13 (4.0)	18 (3.0)	5 (1.5)
Anemia	49 (3.4)	52 (4.3)	49 (1.1)*	38 (1.9)	11 (3.4)	20 (6.2)	4 (0.7)*	12 (3.5)
Glaucoma	13 (0.9)	12 (1.0)	17 (0.4)*	23 (1.2)	4 (1.2)	4 (1.2)	3 (0.5)*	7 (2.1)
Gout	4 (0.3)	9 (0.8)	16 (0.4)*	24 (1.2)	1 (0.3)	3 (0.9)	3 (0.5)*	10 (2.9)
Allergic rhinitis	76 (5.3)	47 (3.9)	104 (2.3)	34 (1.7)	28 (8.6)	24 (7.5)	33 (5.4)	15 (4.4)

*p<0.05; GERD: Gastroesophageal Reflux Disease. NRT: Nicotine replacement therapy.

Table 2. Incidence of neuropsychiatric adverse events (NPAEs) and association with varenicline compared with NRT in general population with and without psychiatric disorders with follow up of 24 weeks.

	Psychiatric cohort Varenicline vs NRT (1427 vs 1200)			Non-psychiatric cohort Varenicline vs NRT (4480 vs 1970)		
NPAEs	**Events (n, %)**	**Crude OR (95% CI)**	**Adjusted OR* (95% CI)**	**Events (n, %)**	**Crude OR (95% CI)**	**Adjusted OR** (95% CI)**
Overall	1160 (81.3): 1012 (84.3)	0.81 [0.66, 0.99]	0.81 [0.65, 0.99]	612 (13.7): 360 (18.3)	0.71 [0.61, 0.82]	0.78 [0.67, 0.90]
Depression	629 (44.1): 548 (45.7)	0.94 [0.80, 1.09]	0.90 [0.77, 1.05]	148 (3.3): 57 (2.9)	1.15 [0.84, 1.56]	1.15 [0.84, 1.57]
Anxiety	456 (32.0): 472 (39.3)	0.72 [0.62, 0.85]	0.71 [0.61, 0.84]	215 (4.8): 110 (5..6)	0.85 [0.67, 1.08]	0.90 [0.71, 1.15]
Insomnia	372 (26.1): 352 (29.3)	0.85 [0.72, 1.01]	0.89 [0.75, 1.06]	147 (3.3): 105 (5.3)	0.60 [0.47, 0.78]	0.63 [0.49, 0.82]

NPAEs: neuropsychiatric adverse events; NRT: nicotine replacement therapy; OR: odds ratio; CI: confidence interval; *Adjusted for age, gender, socioeconomic status, heart failure, ischemic heart disease and cancer;. **Adjusted for age, socioeconomic status, heart failure, ischemic heart disease, hypertension, diabetes, osteoporosis, peptic ulcer and GERD, Rheumatic arthritis, anemia, glaucoma and gout;

Table 3. Incidence of neuropsychiatric adverse events (NPAEs) and association with varenicline compared with NRT in COPD population with and without psychiatric disorders with follow up of 24 weeks.

	Psychiatric cohort Varenicline vs NRT (327 vs 322)			Non-psychiatric cohort Varenicline vs NRT (608 vs 341)		
NPAEs	Events (n, %)	Crude OR (95% CI)	Adjusted OR* (95% CI)	Events (n, %)	Crude OR (95% CI)	Adjusted OR** (95% CI)
Overall	276 (84.4): 278 (86.3)	0.86 [0.55, 1.33]	1.01 [0.65, 1.58]	104 (17.1): 79 (23.2)	0.68 [0.49, 0.95]	0.75 [0.53,1.05]
Depression	146 (44.6): 145 (45.0)	0.99 [0.72, 1.34]	0.90 [0.65, 1.24]	22 (3.6): 10 (2.9)	1.24 [0.58, 2.66]	1.37 [0.62, 3.03]
Anxiety	110 (33.6): 136 (42.2)	0.69 [0.50, 0.95]	0.68 [0.49, 0.94]	38 (6.3): 25 (7.3)	0.84 [0.50, 1.42]	0.69 [0.50, 0.96]
Insomnia	102 (31.2): 124 (38.5)	0.72 [0.52, 1.00]	0.84 [0.60, 1.18]	25 (4.1): 21 (6.2)	0.65 [0.36, 1.19]	0.83 [0.59, 1.16]

NPAEs: neuropsychiatric adverse events; NRT: nicotine replacement therapy; OR: odds ratio; CI: confidence interval; *Adjusted for age, heart failure, ischemic heart disease; **Adjusted for age, heart failure, ischemic heart disease, diabetes, osteoporosis, anemia, glaucoma and gout;

In the COPD population, in both the psychiatric and non-psychiatric cohorts, there was no difference for overall NPAEs between the varenicline and NRT groups in each age group and gender group (aOR 0.99, 95% CI [0.53,1.87]; aOR 0.76, 95% CI [0.44, 1.31]; respectively for men and women, Table S2).

Sensitivity analysis

In the general population, considering a follow-up of 12 weeks, the risk of overall NPAEs was less for varenicline compared with NRT in both the psychiatric and non-psychiatric cohorts (aOR 0.78, 95% CI: 0.64 to 0.94; aOR 0.74, 95% CI: 0.62 to 0.89; respectively, Table S3). After limiting the study population to those who were not prescribed drugs for any psychiatric disorder or those who were not prescribed drugs for depression, anxiety and insomnia within 1 month before index date, there was no statistical significant difference for overall NPAEs, irrespective of presence of psychiatric disorders in the previous year (Table S4). The result was similar when we limited our cohort to individuals whose study period was not in the period of Dutch smoking policy change; the aOR for varenicline compared with NRT was 0.86, 95% CI [0.69, 1.07] in the psychiatric cohort and 0.86, 95% CI [0.71, 1.03] in non-psychiatric cohort.

In the COPD population, there were no statistical significant differences for overall and subgroup NPAEs within follow-up of 12 weeks between the two treatments except for anxiety in the psychiatric cohort (aOR 0.64, 95% CI [0.46, 0.90], Table S5). After limiting the study population to those who were not prescribed drugs for any psychiatric disorder or those who were not prescribed drugs for depression, anxiety and insomnia within 1 month before index date, there was no statistical significant difference for overall NPAEs, irrespective of presence of psychiatric disorders (Table S6). Similar results were seen when limiting individuals to those whose study period was not in the period of Dutch smoking policy change (OR 0.97, 95% CI: 0.62 to 1.51; OR 1.00, 95% CI: 0.64 to 1.58; respectively for the psychiatric and non-psychiatric cohorts, Table S6)

DISCUSSION

Main findings and interpretation

Within 24 weeks following initiation of varenicline treatment, we found no significantly increased risk of NPAEs in both the general and COPD population compared with those using NRT, irrespective of the presence of psychiatric disorders. These findings are consistent with the results of previous RCTs and large observational studies,[10,28,29] Considering the fact that the smoking cessation treatment may last for only 12 weeks without further treatment,[30] we also explored the NPAEs in this shorter time period and observed no increased risk in overall and specific NPAEs for varenicline compared with NRT.

In contrast to the concerns about a possible increased risk of NPAEs among varenicline users, we found a 19% and 22% relative decrease in NPAEs in varenicline users of the general population with and without psychiatric disorders, respectively, compared with NRT. Regarding the safety of varenicline for specific NPAEs, we recorded a 29% reduced risk of anxiety by varenicline (vs NRT) in the psychiatric cohort, and a 37% reduced risk of insomnia in the non-psychiatric cohort. Rates of depression events were comparable between the two groups in both psychiatric and non-psychiatric cohorts among the general population. These results were consistent with the pooled results of 39 RCTs in a meta-analysis,[14] which indicated that less anxiety (hazard ratio (HR) 0.75, 95% CI: 0.61, 0.93) was also observed in the varenicline group (vs NRT), and depression episodes were also evenly distributed among two treatments (HR 0.96, 95% CI: 0.75, 1.22). Compared with our study, the difference is that in this review an increased risk of insomnia was observed in the varenicline group (HR 1.56, 95% CI: 1.36, 1.78).[14] Of note, the aforementioned review did not explore the risk of varenicline on NPAEs separately in those with and without psychiatric disorders, which may contribute to the observed differences in this review compared to our results. Of note, our result is consistent with another cohort study based data from the general practice that no increased depression were observed to be associated with varenicline (HR 0.88 [0.77-1.00]). [31]

COPD patients are considered a high-risk population with high prevalence of smoking and relatively older age, making these persons more susceptible for possible adverse drug reactions (ADEs).[16,32] Of note, in our study we did not observe an increased risk of overall NPAEs among COPD patients using varenicline in both the psychiatric and non-psychiatric cohorts. Of note, regarding the occurrence of specific NPAEs, less anxiety was seen in the varenicline group than in the NRT group in both cohorts. The safety of varenicline was not fully explored among COPD patients in previous studies. To the best of our knowledge, only two studies (one RCT and one cohort study) were previously conducted.[19,33] Similar to our results, both of these two studies did not find an increased risk of NPAEs for varenicline. Notably, in the cohort study even a reduced risk of depression was observed in varenicline users compared with users of NRT among COPD patients.[19] This may be misled by unmeasured confounders, however, after modelling the effects of possible unmeasured confounders, the author concluded that an increased risk of these adverse events was very unlikely.[19]

It is notable that there is a large heterogeneity in the definition of NPAEs across studies. In some studies, the investigators focused on moderate to serious adverse events like depression, suicide or mental disorders that require hospitalization or an emergency department visit.[19,29,34,35] While other studies included all adverse symptoms (e.g. angry, nervousness) or adverse events such as traffic offences.[10,30] In this study, we used prescriptions to define neuropsychiatric outcomes for the most commonly reported NPAEs including depression, anxiety and insomnia during the study period.

Despite differences in clinical definitions, the observed 24-week event rates of specific NPAEs (3%-9%) for depression, anxiety or insomnia in our general population without psychiatric disorders were similar to previous studies.[14] However, the rate of NPAEs was substantially higher in participants with psychiatric disorders than those without such illness, which was also consistent with findings from previous studies.[35-37] When we further limited our study population to those who did not experience any psychiatric disorder or not experienced any depression, anxiety and insomnia within 1 month of enrollment, we found that both the overall NPAEs and specific NPAE reduced substantially.

Although the rates of NPAEs are different between psychiatric and non-psychiatric cohorts in this study, the presence of psychiatric disorders did not influence the risk of NPAEs by varenicline compared with NRT which was also consistent with previous studies.[10,38] In a prospective longitudinal study among psychiatric patients, there was no exacerbation of psychiatric symptoms detected except gastrointestinal adverse events.[39] However, although it is not within the scope of this study, what need to be mentioned is that an increased rate of outpatient visits for schizophrenia was previously reported to be present only in patients with a pre-existing mental health disorder.[34] This may be explained by mediation through individual genetic liability.[40]

In interpreting the absence of increased risks by varenicline (vs NRT) observed in the general population, we can only speculate that the positive effect from varenicline may result from its effect of consistently reducing withdrawal-related symptoms of negative affect and raised levels of positive affect.[41] It has been reported that varenicline yields higher abstinence rates than NRT,[10,11] irrespective of smoker characteristics.[42] The successful quitting of smoking by varenicline may offer more benefits to the psychiatric status compared with NRT. Moreover, there is evidence that quitting smoking is associated with recovery in stress, anxiety and depression in smokers.[43,44] A significant and progressive improvement of anxiety and depression was also reported in an observational study, and the protective effect was observed regardless of the presence of psychiatric pathology.[38]

Many studies demonstrated gender differences in varenicline efficacy for smoking cessation,[45,46] some studies also found a difference in neuropsychiatric events between genders.[47] In this study, we found less risk of NPAEs by varenicline for females in the psychiatric cohort compared with NRT. This may be explained by the better therapeutic response to varenicline in women compared with men. [45] However, in the non-psychiatric cohort, we observed less risk of NPAEs in males by varenicline (vs NRT) which we cannot explain and more research needs to be done on gender disparities. Similarly, there are some indications for age group-dependent NPAEs risk by varenicline (vs NRT) in two cohorts of this study. In the psychiatric cohort, there were

lower event rates in the varenicline group than the NRT group in younger age groups. Contrary, in the non-psychiatric cohort, lower event rates were seen in older users of varenicline than NRT. The age-specific effectiveness of varenicline relative to NRT patch or gum were also reported that only younger smokers achieved greater likelihood of abstinence than NRTs.[48]As such, age disparities also need to be studied more closely.

Strengths and limitations

A major strength of this study is that we evaluated the safety of varenicline in both the general and COPD population with and without psychiatric disorders based on large real-life population data making the results representative and more applicable to daily clinical practice. Both short- (12 weeks) and long-term (24 weeks) NPAEs after treatment initiation were explored in this study. Besides the influence of current or previous psychiatric disorders, we also evaluated the influence of age and gender on the NPAEs between treatment groups. Additionally, to test the robustness of our study results, several sensitivity analyses were conducted.

There are several potential limitations in our study that need to be discussed. First, as no diagnostic information was available in this study, outcome events and comorbidities were defined by prescriptions of related drugs as proxies. Although we used similar ATC codes as in previous studies and it's reported that pharmacy data can be used to provide reliable prevalence estimates of several chronic conditions,[26] it may still have led to some misclassification. Second, the prescription of medication may not always lead to intake of the drugs (non-adherence) and such misclassification, if random, may have caused associations to be biased towards the null value. Third, some serious behavioral changes like self-harm or suicide could not be evaluated in this study due to the limitation of the prescription database, although we included the most frequently reported NPAEs that are commonly drug treated. Similarly, some minor symptoms like fatigue could not be evaluated. Fourth, although we tried our best to exclude the influence of baseline differences between exposure groups by adjusting for potential confounders, possible unmeasured confounding may still exist. From the baseline characteristics, we could see that the prevalence of comorbidity in varenicline users was lower than in NRT users which may have been the result of the reluctance of prescribing varenicline by clinicians considering its possible risk of related adverse events for high-risk populations. Such potential channeling bias may have caused a relatively better profile of varenicline. However, this kind of bias may not be large, as most associations (OR) between varenicline and specific NPAEs observed in this study were still below 1 and such bias should be large enough to contradict our conclusion. Additionally, the difference in characteristics could also be attributable to a disparity in the cumulative cigarette exposure between treatment groups,[49] however, it's pity that smoking history was not available in this study.

CONCLUSION

From this population-based real-life inception cohort study, we conclude that varenicline is not associated with a significant increased risk of NPAEs in both general and COPD patients with or without psychiatric disorders following its initiation compared with NRT. These results provide further support for the safety of varenicline to quit smoking in both the general and COPD populations.

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SUPPLEMENTARY MATERIALS

Table S1. List of ATC codes used for identification of related diseases and outcome events.

Variables	ATC codes
COPD	R03
General psychiatric disorders	N02, N03, N04, N05, N06
Depression	N06A, N06CA,
Anxiety	N05B
Insomnia	N05C
Heart failure	C01AA, C03C
Ischemic heart disease	C01DA
Hypertension	C02, C03 (except C03C), C07, C08, C09
Cancers	L01
Diabetes mellitus	A10
Osteoporosis	M05B
Peptic ulcer and GERD	A02B
Rheumatic arthritis	M01, M02
Thyroid disorders	H03
Anemia	B03
Glaucoma	S01E
Gout	M04
Allergic rhinitis	R01AD

ATC: anatomical therapeutic chemical; GERD: gastroesophageal reflux disease;

Table S2. Subgroup analysis: incidence of neuropsychiatric adverse events (NPAEs) and association with varenicline compared with NRT within follow up of 24 weeks stratified by age and gender.

	General populations				COPD populations			
	Psychiatric cohort		Non-psychiatric cohort		Psychiatric cohort		Non-psychiatric cohort	
Subgroups	Crude OR (95% CI)	aOR (95% CI)	Crude OR (95% CI)	aOR (95% CI)	Crude OR (95% CI)	aOR (95% CI)	Crude OR (95% CI)	aOR (95% CI)
Age **								
Age < 40	0.58 [0.32, 1.05]	0.54 [0.28, 1.04]	1.01 [0.61, 1.66]	0.93 [0.54, 1.64]	---	---	---	---
40-65	0.81 [0.65, 1.01]	0.78 [0.63, 0.98]	0.86 [0.71, 1.04]	0.87 [0.72, 1.07]	0.88 [0.56, 1.38]	0.89 [0.55, 1.43]	0.91 [0.57, 1.46]	0.93 [0.57, 1.52]
>65	1.02 [0.66, 1.59]	1.12 [0.69, 1.81]	0.50 [0.33, 0.78]	0.53 [0.34, 0.83]	1.08 [0.50, 2.35]	1.03 [0.44, 2.41]	0.51 [0.25, 1.05]	0.51 [0.24, 1.11]
Gender (n, %)**								
Men	0.87 [0.67, 1.13]	0.89 [0.68, 1.17]	0.71 [0.56, 0.91]	0.78 [0.61, 0.99]	0.95 [0.54, 1.69]	1.24 [0.66, 2.34]	0.81 [0.46, 1.43]	0.99 [0.53, 1.87]
Female	0.73 [0.56, 0.95]	0.74 [0.57, 0.97]	0.89 [0.71, 1.11]	0.91 [0.72, 1.14]	0.78 [0.46, 1.33]	0.78 [0044, 1.36]	0.73 [0.44, 1.22]	0.76 [0.44, 1.31]

NPAEs: neuropsychiatric adverse events; NRTs: nicotine replacement therapy; aOR: adjusted odds ratio; *adjusted gender, social economic status and comorbidities; **adjusted age, social economic status, comorbidities.

Table S3. Sensitivity analysis: incidence of neuropsychiatric adverse events (NPAEs) and association with varenicline compared with NRT in general population with and without psychiatric disorders within follow up of 12 weeks.

	Psychiatric cohort Varenicline vs NRTs (1427 vs 1200)			Non-psychiatric cohort Varenicline vs NRTs (4480 vs 1970)		
NPAEs	**Events (n, %)**	**Crude OR (95% CI)**	**Adjusted OR# (95% CI)**	**Events (n, %)**	**Crude OR (95% CI)**	**Adjusted OR# (95% CI)**
Follow-up of 12 weeks						
Overall	1062 (74.4): 948 (79.0)	0.77 [0.64, 0.93]	0.78 [0.64, 0.94]	363 (8.1): 223 (11.3)	0.69 [0.58,0.82]	0.74 [0.62, 0.89]
Depression	560 (39.2): 491 (40.9)	0.93[0.80, 1.09]	0.89 [0.76, 1.05]	86 (1.9): 30 (1.5)	1.27 [0.83, 1.92]	1.29 [0.84, 1.97]
Anxiety	367 (25.7): 423 (35.3)	0.64 [0.54, 0.75]	0.63 [0.53, 0.74]	119 (2.7): 61 (3.1)	0.85 (0.62, 1.17)	0.90 [0.65, 1.24]
Insomnia	321 (22.5): 311 (25.9)	0.83 [0.69, 0.99]	0.88 [0.73, 1.05]	82 (1.8): 61 (3.1)	0.58 [0.42, 0.82]	0.62 [0.44, 0.88]

NPAE: neuropsychiatric adverse events; OR: odds ratio; NRTs: nicotine replacement therapy; # adjusted for age, gender, social economic status and related comorbidities.

Table S4. Sensitivity analysis: incidence of neuropsychiatric adverse events (NPAEs) and association with compared with NRT in general population within follow up of 24 weeks.

	General populations					
	Psychiatric cohort (varenicline vs NRTs)			Non-psychiatric cohort (varenicline vs NRTs)		
Limitations	**Events**	**OR (95% CI)**	**aOR (95% CI)***	**Events**	**OR (95% CI)**	**aOR (95% CI)***
Exclude participants prescribed drugs for any NSP within 1 month before index date						
Overall	254 (57.6): 157 (60.4)	0.89 [0.65, 1.22]	0.87 [0.63, 1.21]	418 (9.6): 192 (10.4)	0.91 [0.76, 1.10]	0.93 [0.78, 1.12]
Depression	158 (35.8): 82 (31.5)	1.21 [0.88, 1.68]	1.18 [0.84, 1.67]	139 (3.2): 50 (2.7)	1.18 [0.85, 1.64]	1.16 [0.84, 1.62]
Anxiety	78 (17.7): 62 (23.8)	0.69 [0.47, 0.10]	0.68 [0.46, 1.01]	197 (4.5): 85 (4.6)	0.98 [0.76, 1.27]	1.02 [0.78, 1.33]
Insomina	75 (17.0): 48 (18.5)	0.94 [0.74, 1.20]	0.94 [0.62, 1.43]	131 (3.0): 91 (4.9)	0.60 [0.46, 0.79]	0.61 [0.46, 0.80]
Exclude participants prescribed drugs for depression, anxiety and insomnia within 1 month before index date						
Overall	314 (48.9): 201 (46.1)	1.12 [0.88, 1.43]	1.05 [0.82, 1.36]	424 (9.6): 203 (10.6)	0.90 [0.75, 1.07]	0.92 [0.77, 1.11]
Depression	191 (29.8): 104 (23.9)	1.35 [1.02, 1.79]	1.25 [0.93, 1.66]	143 (3.3): 52 (2.7)	1.20 [0.87, 1.66]	1.19 [0.86, 1.65]
Anxiety	99 (15.4): 81 (18.6)	0.80 [0.58, 1.10]	0.75 [0.54, 1.05]	199 (4.5): 92 (4.8)	0.94 [0.73, 1.21]	0.98 [0.75, 1.26]
Insomnia	92 (14.3): 63 (14.4)	0.99 [0.70, 1.40]	1.03 [0.72, 1.47]	132 (3.0): 94 (4.9)	0.60 [0.46, 0.78]	0.61 [0.47, 0.81]
Exclude participants whose study period includes policies changes						
Overall	797 (76.0): 733 (77.7)	0.91 [0.74, 1.12]	0.86 [0.69, 1.07]	352 (11.1): 205 (12.9)	0.85 [0.70, 1.02]	0.86 [0.71, 1.03]
Depression	468 (44.7): 411 (43.6)	1.04 [0.88, 1.25]	0.98 [0.82, 1.18]	115 (3.6): 45 (2.8)	1.30 [0.91, 1.84]	1.28 [0.90, 1.82]
Anxiety	343 (32.7): 372 (39.4)	0.75 [0.62, 0.90]	0.72 [0.60, 0.87]	169 (5.3): 95 (6.0)	0.89 [0.69, 1.15]	0.91 [0.70, 1.19]
Insomnia	273 (26.0): 280 (29.7)	0.83 [0.69, 1.02]	0.87 [0.71, 1.07]	109 (3.4): 83 (5.2)	0.65 [0.48, 0.87]	0.66 [0.49, 0.88]

NPAEs: neuropsychiatric adverse events; NRTs: nicotine replacement therapy; aOR: adjusted odds ratio; *adjusted age, gender, social economic status and comorbidities. We set the indexdate was within period between July 1st, 2011 and June 30, 2013; Policy change: In the Netherlands, pharmacologic Smoking Cessation Treatments (pSCTs) were reimbursed in 2011. In 2012 the reimbursement was discontinued. As of 2013, pSCTs were again reimbursed, provided they are accompanied by behavioral counseling.

Table S5. Sensitivity analysis: incidence of neuropsychiatric adverse events (NPAEs) and association with varenicline compared with NRT in COPD population with and without psychiatric disorders within follow up of 12 weeks.

	Psychiatric cohort Varenicline vs NRTs (327 vs 322)			Non-psychiatric cohort Varenicline vs NRTs (608 vs 341)		
Outcomes	**Events (n, %)**	**Crude OR (95% CI)**	**Adjusted OR# (95% CI)**	**Events (n, %)**	**Crude OR (95% CI)**	**Adjusted OR # (95% CI)**
Follow-up of 12 weeks						
Overall	260 (79.5): 267 (82.9)	0.80 [0.54, 1.19]	0.89 [0.59, 1.36]	63 (10.4): 45 (13.2)	0.76 [0.51, 1.14]	0.84 [0.54, 1.29]
Depression	134 (41.0): 127 (39.4)	1.07 [0.78, 1.46]	0.94 [0.67, 1.32]	13 (2.1): 5 (1.5)	1.47 [0.52, 4.15]	1.95 [0.65, 5.91]
Anxiety	95 (29.1): 123 (38.2)	0.66 [0.48, 0.92]	0.64 [0.45, 0.90]	16 (2.6): 13 (3.8)	0.68 [0.32, 1.44]	0.68 [0.31, 1.52]
Insomnia	88 (26.9): 114 (35.4)	0.67 [0.48, 0.94]	0.72 [0.51, 1.03]	20 (3.3): 11 (3.2)	1.02 [0.48, 2.16]	1.12 [0.51, 2.46]

Table S6. Sensitivity analysis: incidence of neuropsychiatric adverse events (NPAEs) and association with compared with NRT in COPD population within follow up of 24 weeks.

	COPD populations					
	Psychiatric cohort (varenicline vs NRTs)			Non-psychiatric cohort (varenicline vs NRTs)		
Limitations	**Events**	**OR (95% CI)**	**aOR (95% CI)***	**Events**	**OR (95% CI)**	**aOR (95% CI)***
Exclude participants prescribed drugs for any NSP within 1 month before index date						
Overall	54 (60.0): 39 (61.9)	0.92 [0.48, 1.79]	0.85 [0.41, 1.77]	72 (12.1): 40 (12.7)	0.95 [0.63, 1.43]	0.92 [0.60, 1.43]
Depression	29 (32.2): 19 (30.2)	1.10 [0.55, 2.21]	0.88. [0.39, 1.97]	20 (3.4): 10 (3.2)	1.06 [0.49, 2.29]	1.12 [0.50, 2.52]
Anxiety	22 (24.4): 20 (31.7)	0.70 [0.34, 1.42]	0.87 [0.40, 1.90]	38 (6.4): 19 (6.0)	1.06 [0.60, 1.87]	1.10 [0.60, 2.01]
Insomina	15 (16.7): 16 (25.4)	0.59 [0.27, 1.30]	0.60 [0.24, 1.49]	25 (4.2): 16 (5.1)	0.82 [0.43, 1.56]	0.71 [0.36, 1.37]
Exclude participants prescribed drugs for depression, anxiety and insomnia within 1 month before index date						
Overall	68 (51.1): 48 (47.5)	1.16 [0.69, 1.94]	1.29 [0.73, 2.26]	73 (12.1): 43 (13.0)	0.92 [0.62, 1.38]	0.93 [0.61, 1.42]
Depression	35 (26.3): 23 (22.8)	1.21 [0.66, 2.22]	1.08 [0.56, 2.08]	21 (3.5): 10 (3.0)	1.16 [0.54, 2.49]	1.33 [0.60, 2.99]
Anxiety	27 (20.3): 23 (22.8)	0.86 [0.46, 1.62]	0.97 [0.49, 1.91]	38 (6.3): 21 (6.4)	0.99 [0.57, 1.72]	1.00 [0.56, 1.79]
Insomnia	21 (15.8): 20 (19.8)	0.76 [0.39, 1.49]	0.87 [0.42, 1.82]	25 (4.2): 17 (5.2)	0.80 [0.43, 1.50]	0.72 [0.37, 1.39]
Exclude participants whose study period includes policies changes						
Overall	203 (78.1): 211 (80.2)	0.88 [0.58, 1.34]	0.97 [0.62, 1.51]	63 (14.2): 41 (15.1)	0.93 [0.61, 1.43]	1.00 [0.64, 1.58]
Depression	114 (43.8): 110 (41.8)	1.09 [0.77, 1.54]	0.96 [0.66, 1.40]	18 (4.1): 7 (2.6)	1.60 [0.66, 3.89]	1.73 [0.68, 4.42]
Anxiety	89 (34.2): 109 (41.4)	0.74 [0.52, 1.05]	0.72 [0.49, 1.05]	35 (7.9): 20 (7.4)	1.08 [0.61, 1.91]	1.21 [0.66, 2.24]
Insomnia	81 (31.2): 106 (40.3)	0.67 [0.47, 0.96]	0.75 [0.51, 1.10]	19 (4.3): 15 (5.5)	0.77 [0.38, 0.53]	0.71 [0.34, 1.45]

NPAEs: neuropsychiatric adverse events; NRTs: nicotine replacement therapy; *aOR: adjusted odds ratio; adjusted age, gender, social economic status and comorbidities. We set the indexdate was within period between July 1st, 2011 and June 30, 2013; Policy change: In the Netherlands, pharmacologic Smoking Cessation Treatments (pSCTs) were reimbursed in 2011. In 2012 the reimbursement was discontinued. As of 2013, pSCTs were again reimbursed, provided they are accompanied by behavioural counselling.