Supplemental Online Content

Paljarvi T, Forton J, Luciano S, Herttua K, Fazel S. Analysis of neuropsychiatric diagnoses after montelukast initiation. *JAMA Netw Open*. 2022;5(5):e2213643. doi:10.1001/jamanetworkopen.2022.13643

**eMethods.**

**eReferences.**

**eTable 1.** Medical Codes Used in Defining Cohorts, Propensity Score Matching, and Defining Outcomes

**eFigure 1.** Flow Diagram of Montelukast-Exposed and -Unexposed Asthma Groups

**eFigure 2.** Flow Diagram of Montelukast-Exposed and -Unexposed Allergic Rhinitis Groups

**eTable 2.** Baseline Characteristics of Patients in Asthma Groups Before and After Matching by Exposure to Montelukast

**eTable 3.** Baseline Characteristics of Patients in Allergic Rhinitis Groups Before and After Matching by Exposure to Montelukast

**eTable 4.** 1-Year Incidence of Sleep Outcomes Before Matching

**eTable 5.** 1-Year Incidence of Mental Health Outcomes Before Matching

This supplemental material has been provided by the authors to give readers additional information about their work.
eMethods

Data

The HCOs included in the TriNetX Network are typically large academic medical centres that provide a range of healthcare services, including emergency, outpatient, and inpatient care. A single HCO typically has more than one facility, and EHR data from all these facilities are available on the TriNetX platform. Patients are included regardless of insurance status. The quality of TriNetX data is ensured by and evaluated against pre-specified quality standards. The TriNetX data has been used for epidemiological research on various neuropsychiatric outcomes.

TriNetX is compliant with the Health Insurance Portability and Accountability Act (HIPAA), the US federal law which protects the privacy and security of healthcare data, and any additional data privacy regulations applicable to the contributing HCO. TriNetX is certified to the ISO 27001:2013 standard and maintains an Information Security Management System (ISMS) to ensure the protection of the healthcare data it has access to and to meet the requirements of the HIPAA Security Rule. Any data displayed on the TriNetX Platform in aggregate form only contains de-identified data as per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process by which the data is de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule.

Data for this study were accessed via the TriNetX platform and analysed in June 2021 by using the TriNetX built-in query builder. All data processing was conducted using the TriNetX built-in proprietary algorithms. All diagnoses were identified using the International Classification of Diseases, tenth revision, clinical modification (ICD10-CM) codes, while dispensed prescription medicines were identified using the RxNorm codes (eTable 1).

Design

To partially control for potential unmeasured confounding by cohort and period effects in montelukast prescribing and associated factors, we divided the five-year study period, from 1 January 2015 to 31 December 2019, into five separate consecutive one-year blocks based on calendar time. Eligible patients were identified independently within each calendar year, and cohorts were defined and propensity score-matched separately for each calendar year block.

Cohort definitions

In our data, 34% of the patients with dispensed montelukast were prescribed Singulair and 66% generic form montelukast. Patients with missing information were excluded from the analyses. To control for the confounding effect of recent exposure to LTMA, we excluded patients who had dispensed prescriptions for montelukast, zafirlukast, or zileuton six months before the index prescription. We also excluded patients who had dispensed prescriptions for zafirlukast or zileuton during the follow-up; and additionally, from the control cohorts, those who had dispensed prescriptions for montelukast.

Outcome measurement

Primary outcome measures were 12-month incident neuropsychiatric diagnoses identified by the ICD10-CM codes, including psychotic disorders (F20 – F29); mood disorders (F30 – F39); anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (F40 – F48); adult personality and behaviour disorders (F60 – F69); sleep disorders (G47, F51); and non-fatal self-harm, which also included events of undetermined intent (T14.91, X71 – X83, Y21 – Y33). Within these broader diagnostic groups we also looked at more specific incident diagnoses, including manic episode or bipolar disorder (F30, F31); major depression, single episode (F32); phobic anxiety (F40); generalized anxiety (F41.1); other anxiety disorders (F41.0, F41.3, F41.8, F41.9); OCD (F42, F60.5, R46.81); insomnia and sleep deprivation (G47.0, F51.0); nightmare disorder (G47.5, F51.3, F51.4, F51.5); sleep related movement disorders and restless legs syndrome (G47.6, F51.8, F51.9); circadian rhythm disorders (G47.2); parasomnias, including sleepwalking, sleep terrors and nightmare disorder (G47.5, F51.3, F51.4, F51.5); sleeplated movement disorders and restless legs syndrome (G47.6, G25.81); and other or unspecified sleep disorders (G47.8, G47.9, F51.8, F51.9). By using group-level outcomes and the global outcome, we control for the potential effect of multiple testing, i.e., by testing that the observed associations retain statistical significance at group-level.

For each given primary and secondary outcome, we included patients who did not have a recorded history of the given outcome in their EHR, ie, we modelled incident outcomes. We used a 14-day washout period after the index prescription for measuring outcomes to reduce bias from conditions already present at the time of the index prescription. The EHR data included information on whether the patient had died while in hospital but did not include information on the cause of death. Those who died as inpatients were excluded from the analyses. Due to the lack of cause of death information we were unable to establish whether these deaths could be attributable to montelukast treatment.

Propensity score-matching

We used standardized (mean) differences as a balance metric between the exposed and unexposed cohorts before and after propensity score matching. Montelukast-exposed and -unexposed cohorts of asthma and allergic rhinitis patients were matched for the following covariates: age at index prescription; sex; race; type 2 diabetes mellitus; overweight and obesity; mental and behavioural disorders due to psychoactive substance use; any psychotic disorder; any mood disorder; manic episode; bipolar disorder; major depression, single episode; any anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorder; phobic anxiety; generalized anxiety; other anxiety; obsessive-compulsive disorder and
behaviour (OCD); disorders of adult personality and behaviour; any sleep disorder; ischemic heart disease; vasomotor rhinitis; allergic rhinitis due to pollen; other seasonal allergic rhinitis; other allergic rhinitis; unspecified allergic rhinitis; chronic rhinitis; chronic sinusitis; reflux disease; dermatitis and eczema; cough; snoring; self-harm, including undetermined intent; history of dispensed prescriptions for: antihistamines (nasal, oral); sedating antihistamines (promethazine, diphenhydramine, hydroxyzine); non-sedating antihistamines (cetirizine, fexofenadine, loratadine); opioid analgesics; sedatives and hypnotics; antidepressants; antipsychotics; calcium channel blockers; antilipemic agents; ace inhibitors; gastric medications (including medicines used to treat reflux disease); glucocorticoids; antirheumatics; muscle relaxants; decongestants (nasal, systemic); anti-inflammatories (inhalation, nasal, topical); bronchodilators (inhalation, oral, xanthine-derivative, anticholinergic); leukotriene-modifying agents (montelukast, zafirlukast, zileuton); viantarol; metformin; levothyroxine; antitussives and expectorants; and six most prescribed medications commonly used to treat insomnia (eszopiclone, doxepin, melatonin, temazeepam, trazodone, zolpidem). These covariates were included to improve comparability of the montelukast-exposed and control (montelukast-unexposed) cohorts in relation to comorbidities and use of various other prescription medicines that could bias the comparison.

Within the asthma cohort, 76% (n=36245/47772) of montelukast-exposed patients were successfully matched with an unexposed patient. Within the allergic rhinitis cohort, 67% (n=41228/61186) of montelukast-exposed patients were successfully matched with an unexposed patient. The number of excluded patients reflects the fact that in the real-world context, the montelukast exposed and unexposed cohorts, even when these patient groups had the same underlying indication (asthma or allergic rhinitis), had differences in the distribution of potential confounding factors at baseline. This highlights the need to control for these baseline differences as potential confounders.
1. Topaloglu U, Palchuk MB. Using a Federated Network of Real-World Data to Optimize Clinical Trials Operations. JCO Clin Cancer Inform. 2018. 2:1-10. doi:10.1200/CCL17.00067.

2. Paljarvi T, Strang J, Quinn PD, Luciano S, Fazel S. Abuse-deterrent extended-release oxycodone and risk of opioid-related harm. Addiction. 2021. 116(9):2409-2415. doi: 10.1111/add.15392.

3. Harrison PJ, Luciano S. Incidence of Parkinson’s disease, dementia, cerebrovascular disease and stroke in bipolar disorder compared to other psychiatric disorders: An electronic health records network study of 66 million people. Bipolar Disord. 2021. 23(5):454-462. doi: 10.1111/bdi.13022.

4. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry. 2021. 8(5):416-427. doi: 10.1016/S2215-0366(21)00084-5.

5. Colbourne L, Luciano S, Harrison PJ. Onset and recurrence of psychiatric disorders associated with anti-hypertensive drug classes. Transl Psychiatry. 2021. 11(1):319. doi: 10.1038/s41398-021-01444-1.

6. Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry. 2021. 8(2):130-140. doi: 10.1016/S2215-0366(20)30462-4.

7. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011. 46(3):399-424. doi:10.1080/00273171.2011.568786.
### eTable 1. Medical Codes Used in Defining Cohorts, Propensity Score Matching, and Defining Outcomes

| Coding system and codes | Description |
|-------------------------|-------------|
| ICD-10-CM               | Diagnoses   |
| C00-D49                 | Neoplasms   |
| E11                     | Type 2 diabetes mellitus |
| E66                     | Overweight/obesity |
| F10-F19                 | Mental and behavioral disorders due to psychoactive substance use |
| F20-F29                 | Psychotic disorders |
| F30-F39                 | Mood disorders (any) |
| F30, F31                | Manic episode (F30) and bipolar disorder (F31) |
| F32                     | Major depression, single episode |
| F40-F48                 | Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (any) |
| F40                     | Phobic anxiety |
| F41                     | Generalized (F41.1) and other anxiety |
| F42, F60.5, R46.81      | Obsessive-compulsive disorder and behaviour |
| F60-F69                 | Disorders of adult personality and behavior |
| G47, F51                | Sleep disorders (any) |
| G47.0, F51.0            | Insomnia |
| G47.1, F51.1            | Hypersonnia |
| G47.2                   | Circadian rhythm disorders |
| G47.3                   | Sleep apnea |
| G47.5, F51.3-F51.4      | Parasomnias |
| G47.6, G25.81           | Movement disorders, restless legs syndrome |
| I20-I25                 | Ischemic heart disease |
| J30                     | Vasomotor and allergic rhinitis |
| J30.0                   | Vasomotor rhinitis |
| J30.1                   | Allergic rhinitis due to pollen |
| J30.2                   | Other seasonal allergic rhinitis |
| J30.8                   | Other allergic rhinitis |
| J30.9                   | Allergic rhinitis, unspecified |
| J31                     | Chronic rhinitis |
| J32                     | Chronic sinusitis |
| J44                     | Chronic obstructive pulmonary disease (COPD) |
| J45                     | Asthma |
| J45.2                   | Mild intermittent asthma |
| J45.3                   | Mild persistent asthma |
| J45.4                   | Moderate persistent asthma |
| J45.5                   | Severe persistent asthma |
| J45.9                   | Other/unspecified asthma |
| K21                     | Reflux disease |
| L20-L30                 | Dermatitis/eczema |
| O00-O9A, Z33            | Pregnancy |
| R05                     | Cough |
| R06.0                   | Dyspnea |
| R06.83                  | Snoring |
| T14.91, X71-X83, Y21-Y33| Self-harm (including undetermined intent) |

**ICD-10-PCS**

| 10 | Pregnancy |
| RxNorm/RxCUI |

| 3498 | Diphenhydramine |
| 3638 | Doxepin |
| 4077 | Estazolam |
| 4501 | Flurazepam |
| 5553 | Hydroxyzine |
| 6711 | Melatonin |
| 6809 | Metformin |
| 8745 | Promethazine |
| 10355 | Temazepam |
| 10582 | Levothyroxine |

(continued)
| Coding system and codes | Description                                |
|-------------------------|--------------------------------------------|
| 10737                   | Trazodone                                  |
| 10767                   | Triazolam                                  |
| 20610                   | Cetirizine                                  |
| 28889                   | Loratadine                                  |
| 39993                   | Zolpidem                                   |
| 40575                   | Zaleplon                                    |
| 74667                   | Fexofenadine                                |
| 87636                   | Montelukast                                 |
| 114970                  | Zafirlukast                                 |
| 461016                  | Eszopiclone                                 |
| 596205                  | Ramelteon                                   |
| 1424884                 | Vilanterol                                  |
| 1547099                 | Suvorexant                                  |
| AH000                   | Antihistamines                              |
| CN101                   | Opioid analgesics                           |
| CN300                   | Sedatives/hypnotics                         |
| CN600                   | Antidepressants                             |
| CN700                   | Antipsychotics                              |
| CV200                   | Calcium channel blockers                    |
| CV350                   | Antilipemic agents                          |
| CV800                   | Ace inhibitors                              |
| DE200                   | Anti-inflammatories, topical                |
| GA900                   | Gastric medications, other (including medicines used to treat reflux disease) |
| HS051                   | Glucocorticoids                             |
| MS100                   | Antirheumatics                              |
| MS200                   | Muscle relaxants                            |
| NT100                   | Decongestants, nasal                        |
| NT200                   | Anti-inflammatories, nasal                  |
| NT400                   | Antihistamines, nasal                       |
| RE101                   | Anti-inflammatories, inhalation             |
| RE102                   | Bronchodilators, inhalation                 |
| RE103                   | Bronchodilators, oral                       |
| RE104                   | Bronchodilators, xanthine-derivative        |
| RE105                   | Bronchodilators, anticholinergic            |
| RE200                   | Decongestants, systemic                     |
| RE300                   | Antitussives/expectorants                   |
Asthma patients aged 15–64 years at index prescription and alive for the subsequent 12 months
- Montelukast-exposed patients, n=322505
- Control cohort patients, n=1344631

Excluded patients exposed to LTMAs six months before index prescription or during follow-up (other than montelukast for the montelukast-exposed cohort)
- Montelukast-exposed patients, n=52909
- Control cohort patients, n=299209

Asthma patients with eligible index prescription
- Montelukast-exposed patients with a new montelukast prescription, n=269596
- Control cohort patients not exposed to LTMAs, n=1045422

Excluded patients with history of COPD, OSA, or neoplasms, and patients who were pregnant or were prescribed with oral glucocorticoids at baseline or during follow-up.
- Montelukast-exposed cohort, n=221824
- Control cohort, n=816781

Asthma patients fulfilling all eligibility criteria before matching
- Montelukast-exposed patients, n=47772
- Control cohort patients, n=228641

Excluded patients not matched at baseline (1:1 propensity score-matching)
- Montelukast-exposed cohort, n=11527
- Control cohort, n=192396

Asthma patients matched and analysed for outcomes
- Montelukast-exposed patients, n=36245
- Control cohort patients, n=36245

**eFigure 1. Flow Diagram of Montelukast-Exposed and -Unexposed Asthma Groups**
Allergic rhinitis patients without comorbid asthma, aged 15–64 years at index prescription, and alive for the subsequent 12 months
- Montelukast-exposed patients, n=127573
- Control cohort patients, n=293037

Excluded patients exposed to LTMAs six months before index prescription or during follow-up (other than montelukast for the montelukast-exposed cohort)
- Montelukast-exposed patients, n=14522
- Control cohort patients, n=36278

Allergic rhinitis patients with eligible index prescription
- Montelukast-exposed patients with a new montelukast prescription, n=113051
- Control cohort patients not exposed to LTMAs, n=256759

Excluded patients with history of COPD, OSA, neoplasms, or dyspnoea, and patients who were pregnant at baseline or during follow-up.
- Montelukast-exposed cohort, n=51865
- Control cohort, n=118489

Allergic rhinitis patients fulfilling all eligibility criteria before matching
- Montelukast-exposed patients, n=61186
- Control cohort patients, n=138270

Excluded patients not matched at baseline (1:1 propensity score-matching)
- Montelukast-exposed cohort, n=19958
- Control cohort, n=97042

Allergic rhinitis patients matched and analysed for outcomes
- Montelukast-exposed patients, n=41228
- Control cohort patients, n=41228

eFigure 2. Flow Diagram of Montelukast-Exposed and -Unexposed Allergic Rhinitis Groups

© 2022 Paljarvi T et al. JAMA Network Open.
### Table 2. Baseline Characteristics of Patients in Asthma Groups Before and After Matching by Exposure to Montelukast

| Percent                      | Before matching | After matching | Standard difference | Before matching | After matching | Standard difference |
|------------------------------|-----------------|----------------|---------------------|-----------------|----------------|---------------------|
| Number of patients           | 47772           | 228641         |                     | 36245           | 36245         |                     |
| Mean age (SD)                | 35.9 (15.4)     | 34.8 (14.9)    | 0.076               | 35.1 (15.2)     | 34.9 (15.2)   | 0.011               |
| Female                       | 63.0            | 59.7           | 0.064               | 61.6            | 61.8           | 0.006               |
| Race, white                  | 70.6            | 65.6           | 0.111               | 68.7            | 68.4           | 0.011               |
| Race, black                  | 10.3            | 21.2           | 0.129               | 18.2            | 18.2           | 0.009               |
| Montelukast                  | 55.8            | 7.1            | 1.225               | 41.7            | 41.7           | 0.001               |
| Zafirlukast                  | 0.1             | <0.1           | 0.025               | 0.2             | 0.2            | <0.001              |
| Zileuton                     | 0.1             | <0.1           | 0.033               | 0.1             | 0.1            | <0.001              |
| Asthma                       |                 |                |                     |                 |                |                     |
| Mild intermittent            | 25.7            | 22.5           | 0.079               | 25.6            | 25.8           | 0.006               |
| Mild persistent              | 11.9            | 7.8            | 0.120               | 11.5            | 11.6           | 0.010               |
| Moderate persistent          | 10.3            | 5.2            | 0.169               | 9.4             | 9.5            | 0.012               |
| Severe persistent            | 1.5             | 0.5            | 0.081               | 1.3             | 1.3            | 0.006               |
| Other/unspecified asthma     | 55.8            | 50.8           | 0.106               | 55.8            | 56.0           | 0.006               |
| Vasomotor and allergic rinitis|                 |                |                     |                 |                |                     |
| Vasomotor rhinitis           | 21.1            | 13.3           | 0.222               | 21.1            | 21.4           | 0.009               |
| Allergic rhinitis due to pollen| 10.4           | 5.1            | 0.191               | 8.9             | 8.9            | 0.006               |
| Other seasonal allergic rhinitis| 11.0           | 6.6            | 0.152               | 10.2            | 10.2           | 0.009               |
| Other allergic rhinitis      | 10.1            | 4.8            | 0.194               | 8.6             | 8.7            | 0.009               |
| Unspecified allergic rhinitis| 29.6            | 18.1           | 0.277               | 28.0            | 28.3           | 0.006               |
| Chronic rhinitis, nasopharyngitis and pharyngitis | 5.0 | 2.9 | 0.108 | 4.8 | 4.9 | 0.006 |
| Chronic sinusitis            | 9.8             | 7.2            | 0.088               | 9.5             | 9.6            | 0.008               |
| Type 2 diabetes mellitus     | 6.2             | 6.5            | 0.018               | 6.0             | 5.8            | 0.013               |
| Overweight and obesity       | 14.1            | 13.8           | 0.010               | 14.3            | 14.1           | 0.005               |
| Mental and behavioural disorders due to psychoactive substance use | 7.6 | 13.5 | 0.192 | 8.9 | 8.8 | 0.007 |
| Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders | 1.0 | 1.9 | 0.080 | 1.1 | 1.1 | 0.008 |
| Mood (affective) disorders   | 16.3            | 18.5           | 0.060               | 16.9            | 16.5           | 0.013               |
| Manic episode                | 0.1             | 0.2            | 0.015               | 0.2             | 0.2            | 0.008               |
| Bipolar disorder             | 2.4             | 3.2            | 0.049               | 2.5             | 2.5            | 0.011               |
| Major depressive disorder, single episode | 12.5 | 14.3 | 0.053 | 13.2 | 12.8 | 0.013 |
| Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders | 20.1 | 21.9 | 0.047 | 20.9 | 20.7 | 0.009 |
| Other anxiety disorders      | 17.1            | 18.4           | 0.038               | 17.6            | 17.6           | 0.008               |
| Obsessive-compulsive disorder| 0.7             | 0.6            | 0.010               | 0.6             | 0.6            | 0.010               |
| Sleep disorders not due to a substance or known physiological condition | 1.6 | 1.6 | 0.011 | 1.6 | 1.6 | 0.012 |
| Disorders of adult personality and behaviour | 1.5 | 2.0 | 0.037 | 1.7 | 1.7 | 0.009 |

© 2022 Paljarvi T et al. JAMA Network Open.
| Percent | Before matching | Standard difference | After matching | Standard difference |
|---------|----------------|---------------------|---------------|---------------------|
|         | Exposed        | Unexposed           |               | Exposed             | Unexposed           |               |
| Obsessive-compulsive personality disorder | 0.1 | <0.1 | 0.032 | 0.1 | 0.1 | 0.010 |
| Sleep disorders | 7.1 | 7.4 | 0.013 | 7.5 | 7.4 | 0.004 |
| Ischemic heart diseases | 1.7 | 1.9 | 0.016 | 1.7 | 1.7 | 0.009 |
| Gastro-esophageal reflux disease | 16.5 | 13.7 | 0.078 | 15.8 | 15.4 | 0.011 |
| Dermatitis and eczema | 12.2 | 11.7 | 0.016 | 13.2 | 13.4 | 0.005 |
| Cough | 19.3 | 18.2 | 0.025 | 20.1 | 20.6 | 0.012 |
| Snoring | 5.1 | 4.4 | 0.037 | 5.4 | 5.5 | 0.005 |
| Obsessive-compulsive behaviour | 0.1 | <0.1 | 0.023 | 0.1 | 0.1 | 0.011 |
| Intentional self-harm | 0.2 | 0.3 | 0.036 | 0.2 | 0.2 | 0.007 |
| Antihistamines | 39.1 | 32.3 | 0.139 | 37.3 | 37.6 | 0.006 |
| Diphenhydramine | 7.7 | 9.3 | 0.060 | 8.5 | 8.7 | 0.009 |
| Hydroxyzine | 5.3 | 6.0 | 0.029 | 5.8 | 5.8 | 0.003 |
| Promethazine | 7.7 | 8.2 | 0.022 | 7.9 | 7.9 | 0.005 |
| Cetirizine | 16.5 | 9.9 | 0.195 | 15.4 | 15.4 | 0.004 |
| Loratadine | 10.5 | 8.3 | 0.077 | 10.7 | 10.8 | 0.007 |
| Fexofenadine | 5.6 | 3.2 | 0.115 | 5.2 | 5.3 | 0.005 |
| Opioid analgesics | 27.9 | 31.5 | 0.084 | 29.3 | 29.1 | 0.006 |
| Sedatives and hypnotics | 19.9 | 21.3 | 0.039 | 20.0 | 19.8 | 0.010 |
| Temazepam | 0.5 | 0.4 | 0.013 | 0.4 | 0.5 | 0.007 |
| Zolpidem | 3.5 | 3.6 | 0.010 | 3.4 | 3.5 | 0.008 |
| Eszopiclone | 0.3 | 0.3 | 0.012 | 0.3 | 0.3 | 0.005 |
| Antidepressants | 24.1 | 23.8 | 0.018 | 23.4 | 22.7 | 0.017 |
| Doxepin | 0.4 | 0.4 | 0.010 | 0.4 | 0.4 | 0.006 |
| Trazodone | 4.3 | 5.1 | 0.040 | 4.4 | 4.3 | 0.004 |
| Antipsychotics | 4.6 | 6.0 | 0.063 | 4.8 | 4.7 | 0.006 |
| Calcium channel blockers | 5.4 | 5.3 | 0.006 | 5.1 | 4.9 | 0.017 |
| Ace inhibitors | 10.2 | 8.7 | 0.048 | 8.8 | 8.3 | 0.019 |
| Topical anti-inflammatories | 53.5 | 43.4 | 0.203 | 50.7 | 50.9 | 0.006 |
| Gastric medications (other) | 20.1 | 18.9 | 0.029 | 19.4 | 19.3 | 0.005 |
| Glucocorticoids | 36.1 | 31.9 | 0.085 | 37.0 | 37.7 | 0.013 |
| Melatonin | 1.7 | 1.9 | 0.019 | 1.8 | 1.7 | 0.008 |
| Metformin | 4.9 | 4.5 | 0.017 | 4.4 | 4.2 | 0.010 |
| Levothyroxine | 5.8 | 4.7 | 0.048 | 5.0 | 4.8 | 0.011 |
| Antirheumatics | 29.3 | 33.7 | 0.096 | 31.3 | 31.0 | 0.008 |
| Skeletal muscle relaxants | 12.0 | 12.8 | 0.029 | 12.2 | 12.0 | 0.010 |
| Nasal decongestants | 3.6 | 3.9 | 0.015 | 4.0 | 4.0 | 0.007 |
| Nasal anti-inflammatories | 54.3 | 42.1 | 0.246 | 51.1 | 51.3 | 0.008 |
| Nasal antihistamines | 8.3 | 4.1 | 0.169 | 7.2 | 7.3 | 0.008 |
| Inhalant anti-inflammatories | 52.4 | 39.8 | 0.254 | 49.2 | 49.4 | 0.009 |
| Inhalant bronchodilators | 66.8 | 62.5 | 0.089 | 63.6 | 63.3 | 0.008 |
| Oral bronchodilators | 62.3 | 58.9 | 0.070 | 59.8 | 59.7 | 0.008 |
| Xanthine-derivative bronchodilators | 0.3 | 0.2 | 0.016 | 0.4 | 0.3 | 0.009 |
| Anticholinergic bronchodilators | 11.5 | 10.4 | 0.033 | 12.1 | 12.4 | 0.010 |
| Vilaanterol | 1.8 | 0.9 | 0.064 | 1.5 | 1.4 | 0.009 |
| Systemic decongestants | 7.2 | 6.6 | 0.026 | 7.3 | 7.4 | 0.005 |
| Antitussives and expectorants | 13.5 | 12.9 | 0.017 | 14.0 | 13.9 | 0.011 |
| Emergency visit | 23.4 | 29.2 | 0.131 | 26.0 | 25.9 | 0.004 |
| Inpatient visit | 14.9 | 16.4 | 0.046 | 15.4 | 15.3 | 0.005 |
**Table 3.** Baseline Characteristics of Patients in Allergic Rhinitis Groups Before and After Matching by Exposure to Montelukast

| Percent                           | Before matching | After matching | Standard difference | Before matching | After matching | Standard difference |
|-----------------------------------|-----------------|----------------|---------------------|-----------------|----------------|---------------------|
| Number of patients                | 61186           | 138270         |                     | 41228           | 41228          |                     |
| Mean age (SD)                     | 40.7 (14.0)     | 7.8 (14.9)     | 0.203               | 40.0 (14.0)     | 40.3 (14.5)    | 0.016               |
| Female                            | 66.1            | 62.6           | 0.074               | 65.7            | 65.7           | 0.004               |
| Race, white                       | 72.1            | 58.8           | 0.287               | 69.8            | 70.1           | 0.008               |
| Race, black                       | 14.3            | 24.2           | 0.253               | 15.4            | 14.8           | 0.018               |
| Montelukast                       | 38.5            | 2.9            | 0.968               | 10.1            | 9.6            | 0.017               |
| Zafirlukast                       | 0.1             | <0.1           | 0.020               | 0.1             | 0.1            | <0.001              |
| Zileuton                          | <0.1            | <0.1           | 0.021               | <0.1            | <0.1           | 0.019               |
| Vasomotor and allergic rhinitis   |                 |                |                     |                 |                |                     |
| Vasomotor rhinitis                | 25.5            | 21.9           | 0.109               | 20.9            | 20.4           | 0.012               |
| Allergic rhinitis due to pollen   | 12.6            | 7.9            | 0.142               | 9.6             | 9.5            | 0.011               |
| Other seasonal allergic rhinitis  | 15.2            | 14.3           | 0.034               | 12.3            | 12.0           | 0.010               |
| Other allergic rhinitis           | 11.5            | 6.9            | 0.145               | 8.4             | 8.4            | 0.006               |
| Unspecified allergic rhinitis     | 38.5            | 31.7           | 0.157               | 32.8            | 32.5           | 0.012               |
| Chronic rhinitis, nasal pharyngitis and pharyngitis | 5.3 | 3.7 | 0.081 | 4.0 | 4.0 | 0.005 |
| Chronic sinusitis                 | 17.8            | 16.6           | 0.214               | 14.3            | 14.6           | 0.010               |
| Type 2 diabetes mellitus          | 6.7             | 7.1            | 0.015               | 6.4             | 6.3            | 0.008               |
| Overweight and obesity            | 14.1            | 15.4           | 0.045               | 13.3            | 13.2           | 0.006               |
| Mental and behavioural disorders due to psychoactive substance use | 6.4 | 10.4 | 0.145 | 6.5 | 6.3 | 0.009 |
| Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders | 0.5 | 1.5 | 0.103 | 0.5 | 0.5 | 0.004 |
| Mood (affective) disorders        | 15.4            | 17.3           | 0.055               | 14.5            | 14.2           | 0.009               |
| Manic episode                     | 0.1             | 0.1            | 0.017               | 0.1             | 0.1            | <0.001              |
| Bipolar disorder                  | 1.3             | 2.2            | 0.065               | 1.3             | 1.3            | 0.008               |
| Major depressive disorder, single episode | 12.1 | 13.5 | 0.046 | 11.3 | 11.1 | 0.006 |
| Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders | 21.3 | 20.8 | 0.006 | 19.8 | 19.1 | 0.015 |
| Other anxiety disorders           | 18.5            | 17.2           | 0.025               | 17.1            | 16.7           | 0.010               |
| Obsessive-compulsive disorder     | 0.5             | 0.7            | 0.019               | 0.5             | 0.5            | 0.008               |
| Sleep disorders not due to a substance or known physiological condition | 2.4 | 1.8 | 0.031 | 1.9 | 1.9 | 0.004 |
| Disorders of adult personality and behaviour | 0.8 | 1.8 | 0.088 | 0.8 | 0.8 | 0.015 |
| Obsessive-compulsive personality disorder | 0.1 | <0.1 | 0.018 | 0.1 | 0.1 | 0.012 |
| Sleep disorders                   | 8.6             | 8.3            | 0.013               | 7.7             | 7.6            | 0.007               |
| Ischemic heart diseases           | 1.5             | 1.5            | 0.008               | 1.5             | 1.4            | 0.009               |
| Gastro-esophageal reflux disease  | 16.7            | 16.2           | 0.012               | 14.9            | 14.7           | 0.007               |
| Dermatitis and eczema             | 12.2            | 15.1           | 0.088               | 11.3            | 11.3           | 0.009               |
| Cough                             | 18.2            | 15.7           | 0.063               | 15.7            | 15.3           | 0.009               |

© 2022 Paljarvi T et al. *JAMA Network Open.*
| Percent                      | Before matching | Before matching | Standard difference | Before matching | Before matching | Standard difference |
|------------------------------|-----------------|-----------------|---------------------|-----------------|-----------------|---------------------|
|                              | Exposed | Unexposed | Standard difference | Exposed | Unexposed | Standard difference |
| Snoring                      | 0.8     | 0.7      | 0.008               | 0.8     | 0.8      | 0.005               |
| Obsessive-compulsive behavior| 0.1     | <0.1     | 0.018               | 0.1     | <0.1     | 0.031               |
| Intentional self-harm        | 0.1     | 0.1      | 0.016               | 0.1     | 0.1      | <0.001              |
| Antihistamines               | 43.1    | 55.1     | 0.245               | 38.1    | 35.9     | 0.046               |
| Diphenhydramine              | 6.4     | 10.5     | 0.152               | 6.2     | 6.1      | 0.005               |
| Hydroxyzine                  | 5.9     | 7.5      | 0.065               | 5.1     | 5.0      | 0.010               |
| Promethazine                 | 12.5    | 10.5     | 0.061               | 10.6    | 10.2     | 0.014               |
| Cetirizine                   | 14.8    | 24.5     | 0.243               | 13.9    | 13.4     | 0.014               |
| Loratadine                   | 9.4     | 20.9     | 0.326               | 9.7     | 9.9      | 0.009               |
| Fexofenadine                 | 7.0     | 8.7      | 0.060               | 6.2     | 6.1      | 0.006               |
| Opioid analgesics            | 34.9    | 35.8     | 0.022               | 30.7    | 29.7     | 0.021               |
| Sedatives and hypnotics      | 23.0    | 23.0     | 0.008               | 20.0    | 19.4     | 0.014               |
| Temazepam                    | 0.6     | 0.6      | 0.008               | 0.6     | 0.4      | 0.016               |
| Zolpidem                     | 4.5     | 4.1      | 0.019               | 3.6     | 3.6      | 0.004               |
| Eszopiclone                  | 0.6     | 0.4      | 0.018               | 0.5     | 0.4      | 0.007               |
| Antidepressants              | 26.2    | 25.4     | 0.013               | 22.3    | 21.7     | 0.014               |
| Doxepin                      | 0.6     | 0.5      | 0.010               | 0.4     | 0.4      | 0.006               |
| Trazodone                    | 4.7     | 5.5      | 0.039               | 4.0     | 3.9      | 0.007               |
| Antipsychotics               | 3.0     | 5.4      | 0.123               | 2.8     | 2.7      | 0.012               |
| Calcium channel blockers     | 6.4     | 6.8      | 0.018               | 5.6     | 5.4      | 0.009               |
| Antilipemic agents           | 14.1    | 12.7     | 0.036               | 11.4    | 10.9     | 0.016               |
| Ace inhibitors               | 10.1    | 10.0     | 0.015               | 8.9     | 8.6      | 0.010               |
| Topical anti-inflammatories  | 53.2    | 49.7     | 0.072               | 45.0    | 44.5     | 0.012               |
| Gastric medications (other)  | 20.9    | 22.1     | 0.035               | 17.8    | 17.1     | 0.019               |
| Glucocorticoids              | 46.4    | 40.2     | 0.117               | 39.8    | 39.1     | 0.013               |
| Melatonin                    | 1.0     | 2.2      | 0.092               | 1.0     | 1.1      | 0.008               |
| Metformin                    | 5.8     | 5.8      | 0.010               | 5.0     | 4.9      | 0.010               |
| Levotyroxine                 | 7.1     | 5.6      | 0.060               | 5.8     | 5.6      | 0.009               |
| Antirheumatics               | 34.8    | 42.4     | 0.162               | 31.9    | 30.9     | 0.022               |
| Skeletal muscle relaxants    | 17.9    | 17.8     | 0.008               | 15.4    | 14.8     | 0.020               |
| Nasal decongestants          | 4.9     | 6.2      | 0.062               | 4.2     | 4.2      | 0.011               |
| Nasal anti-inflammatories    | 49.1    | 43.5     | 0.115               | 40.4    | 40.0     | 0.010               |
| Nasal antihistamines         | 14.0    | 8.0      | 0.185               | 9.1     | 9.0      | 0.003               |
| Inhalant anti-inflammatories | 43.6    | 37.5     | 0.129               | 35.1    | 34.7     | 0.010               |
| Inhalant bronchodilators     | 20.2    | 17.2     | 0.073               | 15.7    | 15.3     | 0.013               |
| Oral bronchodilators         | 14.5    | 11.9     | 0.077               | 11.2    | 10.9     | 0.013               |
| Xanthine-derivative bronchodilators | 0.1 | 0.1 | 0.009 | 0.1 | 0.1 | <0.001 |
| Anticholinergic bronchodilators | 5.6 | 5.4 | 0.010 | 4.5 | 4.6 | 0.003 |
| Vilanterol                   | 0.2     | 0.1      | 0.038               | 0.1     | 0.1      | 0.005               |
| Systemic decongestants       | 11.0    | 14.0     | 0.098               | 9.6     | 9.4      | 0.010               |
| Antitussives and expectorants| 22.3    | 20.0     | 0.049               | 18.9    | 18.4     | 0.011               |
| Emergency visit              | 20.2    | 28.9     | 0.204               | 20.9    | 20.2     | 0.014               |
| Inpatient visit              | 13.1    | 16.8     | 0.105               | 11.8    | 11.7     | 0.004               |
eTable 4. 1-Year Incidence of Sleep Outcomes Before Matching

| Patients with asthma | Unexposed (n=228641) | OR | 95%CI |
|----------------------|----------------------|----|-------|
| **Exposed (n=47772)** | **Exposed (n=61186)** | **Unexposed (n=138270)** | **OR** | **95%CI** |
| Any sleep problem    | 43275                | 1016 | 23 | 206483 | 4857 | 23 | 1.00 | 0.94, 1.07 |
| Insomnia             | 44312                | 768  | 17 | 211529 | 3721 | 17 | 0.99 | 0.91, 1.07 |
| Hypersomnia          | 47430                | 113  | 2  | 227221 | 477  | 2  | 1.15 | 0.94, 1.42 |
| Circadian rhythm disorders | 47637 | 55  | 1  | 227920 | 227  | 1  | 1.17 | 0.87, 1.57 |
| Parasomnias          | 47655                | 60   | 1  | 228013 | 225  | 1  | 1.29 | 0.97, 1.72 |
| Movement disorders   | 47328                | 110  | 2  | 226509 | 498  | 2  | 1.07 | 0.87, 1.31 |
| Other and undefined sleep disorders | 46782 | 237 | 5  | 223566 | 1248 | 5  | 0.91 | 0.80, 1.05 |

| Any sleep problem    | 53999                | 1574 | 29 | 123704 | 3442 | 28 | 1.05 | 0.99, 1.12 |
| Insomnia             | 55035                | 1274 | 23 | 126579 | 2718 | 21 | **1.08** | 1.01, 1.16 |
| Hypersomnia          | 60649                | 138  | 2  | 137707 | 287  | 2  | 1.10 | 0.90, 1.35 |
| Circadian rhythm disorders | 60740 | 52  | 1  | 137949 | 153  | 1  | 0.82 | 0.53, 1.29 |
| Parasomnias          | 60883                | 50   | 1  | 138173 | 114  | 1  | 1.01 | 0.73, 1.42 |
| Movement disorders   | 60291                | 168  | 3  | 137208 | 314  | 2  | 1.19 | 0.91, 1.56 |
| Other and undefined sleep disorders | 60085 | 338 | 6  | 135828 | 905  | 7  | **0.86** | 0.76, 0.97 |

IR/1000, Incidence rate per 1000 persons; OR, Odds ratio; CI, Confidence interval. Patients aged 15 to 64 years at index prescription in years 2015 – 2019. The same patient can contribute to more than one incident diagnosis from different diagnostic groups during the follow-up.
**eTable 5. 1-Year Incidence of Mental Health Outcomes Before Matching**

| Patients with asthma | Exposed (n=47772) | Unexposed (n=228641) | OR | 95%CI |
|----------------------|------------------|----------------------|----|------|
|                      | Patients in cohort | Patients with outcome | IR/1000 | Patients in cohort | Patients with outcome | IR/1000 |    |      |
| Psychotic disorders  | 47217            | 94                    | 2     | 223404          | 729                  | 3       | **0.61** | 0.49, 0.76 |
| Mood disorders       | 38362            | 1404                  | 36    | 177601          | 7424                 | 42      | **0.87** | 0.82, 0.92 |
| Manic episode/bipolar disorder | 46361 | 197 | 4 | 219493 | 1336 | 6 | **0.70** | 0.60, 0.82 |
| Major depression, single episode | 40500 | 1253 | 31 | 189399 | 6646 | 35 | **0.88** | 0.83, 0.93 |
| Anxiety and related disorders | 36098 | 2202 | 61 | 167993 | 10499 | 62 | **0.98** | 0.93, 1.02 |
| Phobic anxiety       | 47327            | 148                   | 3     | 226055          | 694                  | 3       | **1.02** | 0.86, 1.22 |
| Generalized anxiety  | 45089            | 750                   | 17    | 214419          | 3436                 | 16      | **1.04** | 0.95, 1.15 |
| Other anxiety        | 38821            | 1756                  | 45    | 182180          | 8687                 | 48      | **0.95** | 0.90, 1.00 |
| Obsessive-compulsive disorder and behaviour | 47391 | 80 | 2 | 226946 | 321 | 1 | **1.21** | 0.95, 1.55 |
| Adult personality disorders | 46938 | 127 | 2 | 223395 | 829 | 4 | **0.74** | 0.59, 0.93 |
| Self-harm, non-fatal | 47545            | 56                    | 1     | 226781          | 336                  | 1       | **0.82** | 0.59, 1.14 |

| Patients with allergic rhinitis | Exposed (n=61186) | Unexposed (n=138270) | OR | 95%CI |
|---------------------------------|-------------------|----------------------|----|------|
|                                  | Patients in cohort | Patients with outcome | IR/1000 | Patients in cohort | Patients with outcome | IR/1000 |    |      |
| Psychotic disorders  | 60643            | 61                   | 1     | 136222          | 306                  | 2       | **0.46** | 0.35, 0.61 |
| Mood disorders       | 50194            | 1821                 | 36    | 110993          | 4356                 | 39      | **0.92** | 0.87, 0.98 |
| Manic episode/bipolar disorder | 60009 | 160 | 3 | 135000 | 538 | 4 | **0.68** | 0.57, 0.81 |
| Major depression, single episode | 52543 | 1560 | 30 | 116965 | 3802 | 32 | **0.91** | 0.86, 0.97 |
| Anxiety and related disorders | 45879 | 3013 | 66 | 104986 | 6481 | 62 | **1.07** | 1.00, 1.15 |
| Phobic anxiety       | 60477            | 152                  | 2     | 137066          | 423                  | 3       | **0.82** | 0.68, 0.98 |
| Generalized anxiety  | 57060            | 1074                 | 19    | 130340          | 2267                 | 17      | **1.11** | 0.96, 1.28 |
| Other anxiety        | 49385            | 2348                 | 47    | 113299          | 5159                 | 45      | **1.06** | 0.97, 1.15 |
| Obsessive-compulsive disorder and behaviour | 60590 | 80 | 1 | 137346 | 215 | 1 | **0.86** | 0.66, 1.11 |
| Adult personality disorders | 60420 | 99 | 2 | 135745 | 386 | 3 | **0.59** | 0.47, 0.74 |
| Self-harm, non-fatal | 60808            | 50                   | 1     | 137753          | 108                  | 1       | **1.08** | 0.77, 1.51 |

IR/1000, Incidence rate per 1000 persons; OR, Odds ratio; CI, Confidence interval. Patients aged 15 to 64 years at index visit in years 2015 – 2019. The same patient can contribute to more than one incident diagnosis from different diagnostic groups during the follow-up.