

Comorbidities in an asthma population 8-29 years old -a study from the Norwegian Prescription Database

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Comorbidities in an asthma population 8-29 years old

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This is the peer reviewed version of the following article:

Karlstad, Ø., Nafstad, P., Tverdal, A., Skurtveit, S. and Furu, K. (2012), Comorbidities in an asthma population 8–29 years old: a study from the Norwegian Prescription Database. *Pharmacoepidemiology & Drug Safety*, 21:1045–1052, which has been published in final form at <http://dx.doi.org/10.1002/pds.2233>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

Keywords:

Asthma, comorbidity, epidemiology, prescription database,

Key points:

- Comorbidities in asthmatics may influence asthma outcomes and have implications for disease management.
- Diagnostic codes on reimbursed drugs are available in NorPD from 2009 and may be used as surrogate measures of diseases in the population.
- An excess occurrence of nine chronic diseases was observed in the young population of asthmatics, compared to the general population of Norway of the same age.
- A majority of the asthma population had one of the comorbidities measured and few had more than one.

Sponsors: The Research Council of Norway funded this work, grant number 175314/V50.

Conflict of interest statement: The authors declare no conflict of interest.

ABSTRACT

Purpose:

To examine occurrence of chronic diseases and antimicrobial treatment in an asthma population 8-29 years old, compared to the general population.

Methods:

In this cross-sectional study, the asthma population was identified from the general population (retrieved from a census covering the entire Norwegian population) by using filled prescriptions on asthma drugs as a proxy measure of current asthma. The outcome was excess occurrence of specific diseases (comorbidity) among asthmatics, compared to the age-specific general population. Diseases were defined by filled prescriptions with specific diagnostic codes with asthma, compared with the age-specific general population. Diseases were defined by filled prescriptions with specific diagnostic codes (International Classification of Primary Care 2nd edition [ICPC-2] or International Classification of Diseases 10th revision [ICD-10]) during a 1-year period in the Norwegian Prescription Database. Nine chronic diseases were examined: ADHD, epilepsy, migraine, mental illness, cardiovascular disease, diabetes, autoimmune disorders, gastro-oesophageal reflux disease (GORD), allergy. Additionally, antibacterials recommended for respiratory tract infections and antivirals were examined (defined by ATC codes). Standardized Morbidity Ratios (SMR) for each disease was calculated.

Results:

59% of the population had at least one of nine chronic diseases examined, compared to 18% in the general population. Few individuals had more than one additional chronic disease (6% of males, 8% of females). SMRs were increased for all diseases except diabetes, implying higher than expected occurrence of the specific diseases in asthmatics. This pattern was observed in both age groups (8-19 and 20-29 years) and genders. Allergy and GORD had highest SMR (range 3.2-4.8) while the other diseases were in the range 1.2-2.5.

Conclusions:

An excess occurrence of comorbidities was found in the population with asthma. A majority of asthmatics had one additional chronic disease, and few had more than one.

INTRODUCTION

There is increasing recognition that co-occurrence of multiple chronic diseases is common also in children and has a significant impact on the overall health of patients.¹⁻³ The extent and impact of comorbidities in asthmatics has received little attention compared to other chronic diseases like cardiovascular diseases and diabetes, possibly because multimorbidity increases with age¹ while asthma is most prevalent in young populations.

From the societal point of view, health service use is higher in asthmatics with comorbidities and places an extra burden on the healthcare system.^{4,5} At the patient level, comorbidities influence several aspects of asthma, such as detection, diagnosis, severity and the control of asthma symptoms.⁶⁻⁸ Identification and treatment of comorbidities is part of the core management of asthma, especially for more severe cases.⁹ Associations between asthma and allergy, gastro-oesophageal reflux disease (GORD) and infections are well-established⁹⁻¹² while several other diseases have also been associated with asthma in population-based studies.^{7,13-15} However, few studies include children and adolescents.

There is currently no systematic recording of diagnostic information in the Norwegian home-dwelling population. Thus, opportunities to study the occurrence of diseases in the population have been limited. However, a change in the reimbursement system for drugs may enable us to assess occurrence of diseases in the entire population. From March 2009, it became mandatory to provide the diagnostic code (International Classification of Primary Care 2nd edition [ICPC-2] or International Classification of Diseases 10th revision [ICD-10]) of the treated medical condition on all reimbursed prescriptions. The Norwegian Prescription Database (NorPD)¹⁶ is one of the first nationwide prescription databases to record this information. These codes may serve as surrogate measures of the diseases present among individuals in ambulatory care. The diseases studied in the present paper have been associated with asthma in previous population-based studies^{7,13-15}, are expected to be of some magnitude in this young population. Furthermore, drug treatment is central to the management of the disease, and drugs are reimbursable.

The aim of the present study was to examine the occurrence of specific types of chronic diseases and antimicrobial treatment in an actively treated asthma population of children, adolescents and young adults, compared to the occurrence in the Norwegian general population of the same age.

MATERIALS AND METHODS

Data sources and study design

We conducted a cross-sectional study utilizing data from three datasets covering the entire Norwegian population. The datasets were linked by using the unique, encrypted 11-digit person identity number (PIN), assigned to all individuals residing in Norway.¹⁶

The latest *Population and Housing Census (PHC)* included all persons resident in Norway on 3rd November 2001 according to the Central Population Register (CPR).¹⁷ The PHC provided

a closed cohort of all Norwegians residents and variables used were the PIN, gender and birth year.

The *Central Population Register (CPR)* contains continuously updated data on every person residing in Norway.¹⁸ The CPR provided information on date of death and emigration between the PHC in 2001 and the end of the study period.

The *Norwegian Prescription Database (NorPD)* stores electronic data on all filled prescriptions from Norwegian pharmacies since January 2004. Pharmacies are obliged to send the data, irrespective of reimbursement status of the dispensed drugs and the prescribers' specialty and occupation.¹⁶ Thus, NorPD has complete coverage of drugs dispensed to the home-dwelling population. Variables from NorPD used in the present study were the PIN, date of dispensing drug, reimbursement code (diagnostic code from March 2009) and the Anatomical Therapeutic Chemical (ATC)¹⁹ classification code of drugs.

Measure of comorbidities

Diagnostic codes from reimbursed drug prescriptions registered in NorPD were used to define the outcome (comorbidities).

Reimbursement scheme with diagnostic codes: Reimbursement of drug costs is a part of the national, tax-supported public health service which all Norwegians have unrestricted access to.²⁰ The drug reimbursement scheme is based on a list of conditions for which specified drugs can be reimbursed. Reimbursement should only be granted if the patient has a chronic condition where long term treatment is needed (at least 3 months of regular or intermittent treatment during a year). From March 2009, physicians were obliged to provide the diagnostic code of the condition being treated on prescriptions deemed eligible for reimbursement. Codes from either the International Classification of Diseases version 10 (ICD-10) or the International Classification of Primary Care version 2 (ICPC-2) can be used. The Norwegian Medicines Agency (NoMA) has defined about 20 additional codes for conditions that have no appropriate ICD-10 and/or ICPC-2 code, some of which has been included in our study (see comments in Table 1).

Occurrence of a comorbid disease: The presence of a comorbid chronic disease in an individual was defined as filling at least one reimbursed prescription with a diagnostic code during a 1-year period. These diagnostic codes were used as a surrogate measure of disease. The following nine chronic diseases were examined: Attention Deficit Hyperactivity Disorder (ADHD, denoted "hyperkinetic disorder" in ICD-10 and ICPC-2), epilepsy, migraine, mental illness, cardiovascular disease, diabetes (type 1 and 2), autoimmune disorders, gastro-oesophageal reflux disease (GORD) and allergy (Table 1).

To study occurrence of antimicrobial treatment (normally not reimbursed), ATC codes on drugs dispensed were used instead of diagnostic codes (Table 1). Antibacterials recommended in Norwegian guidelines²¹ for use in upper and lower respiratory tract infections were included, as well as antivirals used for influenza virus infections.

Comorbidity may be defined as the occurrence of one or more additional diseases in individuals who have an index disease.²² For brevity, the term "comorbidity" will be used in the present paper for the occurrence of any of the diseases also in the general population who do not necessarily have the index disease (asthma).

Index date and study period: From 3 March 2009, physicians were obliged to write diagnostic codes on all reimbursed prescriptions, and this date was therefore set as the index date. NorPD data on the outcome (comorbidity) for a 1-year period after the index date was retrieved for the Norwegian general population and for the study population with asthma.

Standard population: Norwegian general population

The standard population included all persons who participated in the PHC in 2001 and were under 30 years in 2009 (653,386 males, 620,453 females). Individuals who according to CPR data died or emigrated before the end of the study period (2 March 2010) were excluded (16,282 males, 18,024 females). Thus, 637,104 male and 602,429 female residents in Norway aged 8-29 years in 2009 comprised the standard population. Because the PHC was conducted in 2001, the lowest age class that could be studied was 8 years old.

Study population: Individuals with current asthma in the general population

The study population was patients with asthma currently receiving drug treatment that could be identified in the standard population (20,207 males, 16,853 females). A proxy measure based on dispensed asthma drugs was used to identify this population, a measure described in previous NorPD studies.^{23,24} Included were those who had filled prescription for an asthma drug at least once in the year before and at least once in the year after the index date. Only prescriptions with reimbursement codes for asthma were included. Asthma drugs were defined as inhaled β 2-agonists (ATC code R03AC), inhaled glucocorticoids (R03BA), combination inhalers with β 2-agonists and glucocorticoids (R03AK), and leukotriene receptor antagonists (R03DC).

Statistical methods

The number of comorbidities occurring in the asthma population and in the general population was examined as the proportion of the populations having respectively 0, 1, 2, 3, and 4 or more comorbidities (Table 2).

Associations of asthma with specific comorbidities were examined by calculating Standardized Morbidity Ratios (SMR) (Table 3). The occurrence of each disease (prevalence proportion) was calculated for 1-year age-specific groups in the general population and separately for males and females. From these prevalence proportions, Expected counts (E) in the asthma population were calculated, while Observed counts (O) were retrieved in the same manner as for the general population. The O/E ratio (SMR) was calculated with 95% CIs from the Poisson distribution. Results were stratified by gender and age (8-19 years and 20-29 years). Note that the magnitude of the SMRs is not directly comparable between the different genders and age groups, because they are based on different standard populations.

The study was approved by the Norwegian Data Inspectorate, and the Regional Committee for Medical Research Ethics evaluated it.

RESULTS

Occurrence of nine chronic comorbidities was studied. 59% of male and female asthmatics had at least one of the comorbidities, compared to 18% of males and females in the general population (Table 2). Relatively few in the asthma population had more than one of these comorbidities (6% of males, 8% of females). When antimicrobial treatment was included, 69% of male and 71% of female asthmatics had at least one comorbidity, compared to 30% and 34% in the general population.

The occurrence of specific comorbidities in the asthma population is presented in Table 3. The prevalence proportion (O/n) of the asthma population having allergy was above 50% for all groups, and antibacterial treatment was also relatively prevalent (14-32%). The prevalence was higher in the oldest age group for all comorbidities except allergy in males, ADHD and antivirals. The largest percentage point difference in prevalence between the low and high age group were observed for migraine in females and for mental illness, as well as for the highly prevalent comorbidities (allergy, antimicrobials).

The SMR estimates generally showed an increased occurrence for all diseases, except diabetes (Table 3). This pattern was consistent in all gender and age groups and implies a higher than expected occurrence of the specific diseases in the asthma population compared to the gender- and age-specific general population. GORD and allergy had high SMRs (range 3.2-4.8). The other diseases were in the range 1.3-2.1, except for diabetes and ADHD which showed inconsistent patterns.

Diabetes was the only disease that did not have a consistent increased SMR for the asthma population, and was even below 1.0 for the youngest females. In an additional analysis, we only included the diagnostic codes that are more specific for diabetes type 1 (ICPC “T89 Insulin-dependent diabetes mellitus”, and ICD “E10 Diabetes mellitus type I”). This gave SMR of 1.3 [1.0-1.6] for the youngest males and 1.1 [0.8-1.5] for the oldest males. For females, the numbers were respectively 0.8 [0.5-1.1] and 0.9 [0.6-1.3].

DISCUSSION

In this study of children, adolescents and young adults, we found that chronic diseases were present more often in asthmatics than in the general population. Likewise, use of specific antimicrobial treatments occurred more frequently among individuals with asthma. The present study is the first to examine asthma and comorbid diseases in the entire Norwegian population by using the diagnostic codes from NorPD. Our results obtained from diagnostic codes on prescriptions are essentially in line with studies that obtained diagnostic information from administrative data or self-reports.^{7,13-15} However, most studies are in adults and few have reported age-stratified results.

Adams et al.¹⁴ found associations of asthma and diabetes but not arthritis in adults 18-34 years old, but an association was present in older age groups. Cazzola et al.¹³ reported hypertension, allergic rhinitis, diabetes, dyslipidemia, depression and GORD to be associated with asthma. Associations were generally weaker in 15-34 year olds compared to older adults except for allergic rhinitis, depression and diabetes. Prosser et al.¹⁵ found asthma to be associated with a wide range of diseases in adults, including infections in the lower and upper respiratory tract, depression, hypertension, diabetes and certain autoimmune disorders. Zhang et al.⁷ found

associations with allergy, arthritis/rheumatism, hypertension, diabetes and mental illness in an adult population. Most chronic conditions were more prevalent in adults but allergies and mental illness were more frequent in 18-34 year olds.

In studies of specific diseases, anxiety and depression has been associated with asthma²⁵⁻²⁷ and a bidirectional relationship has been suggested.²⁵ The association may be dependent on how asthma is defined.^{28,29} Asthma has been found to be associated with migraine in adults.^{30,31} In studies comparing epileptics to non-epileptics, an association with asthma has been reported.^{32,33} ADHD and asthma are most prevalent in children and adolescents, and this is reflected in our data by ADHD being one of the more prevalent comorbidities of asthma. Associations with ADHD have been reported in the literature, including a NorPD study that used ATC codes as proxy measures for diagnosis of both diseases.^{34,35} Associations between diabetes and asthma has been found in several studies in adults.^{7,13-15} Our data had relatively few diabetes cases in the asthma population and did not show a consistent association. Of note is that a high proportion of participants in our young study population are expected to be type 1 diabetics, while studies among adults will be predominated by type 2 diabetics. For GORD, the absolute numbers (prevalence) is lower in asthmatics in our study than reported in the literature among children¹¹ and adults¹², possibly because it has not been diagnosed and subsequently treated with prescription drugs (over-the-counter drugs are also available). However, the strong relative association (SMR) is reported in other studies as well.^{11,12} Links between asthma and allergies and respiratory infections are well known and receive much attention in asthma guidelines.^{9,10} An association between asthma and antibacterials is difficult to disentangle from associations of asthma and infections themselves, and the present study was not designed for this purpose.

Our measure of comorbidity will capture chronic diseases diagnosed by a physician, where the physician and the patient have chosen to treat with drugs in the ambulatory setting. The study is cross-sectional and the temporal sequence events can not be determined. The associations observed may have several explanations and we will discuss three possibilities.

First, there may be a genuinely increased co-occurrence of other diseases in individuals with asthma. This may be due to a pathway where one problem is central to development of the other. For example, the comorbidity may be a risk factor for development of asthma, or for triggering asthma symptoms or increasing severity. The causal link may be reversed, in that asthma contributes to development of other diseases. Alternatively, asthma and comorbidities may be indirectly linked via common genetic and environmental factors for development of disease.

Second, there may be a higher detection rate of comorbidities in individuals with asthma, i.e. detection bias occurs.³⁶ This may be an issue in any epidemiologic study where health care service use is measured. Asthmatics do more often than their healthy peers visit physicians for monitoring of the disease and prescription renewals. Any additional health problems more easily come to the attention of physicians and a prescription for a drug may ensue. This may also go the opposite direction in that asthma is more easily detected in individuals who have other reasons for visiting a physician. This kind of bias is probably most pertinent in milder, intermittent cases of asthma, and for comorbidities with a high proportion of subclinical cases that are not usually detected. An increased detection rate of diabetes and epilepsy seems less likely due to the severity of these diseases. Furthermore, our definition of the asthma population will have excluded some milder cases of asthma and individuals who tried asthma drugs only once as part of diagnosing respiratory complaints.

Third, some individuals may have a lower threshold for seeking healthcare services including drug treatment, and/or some physicians have a lower threshold for setting a diagnosis and prescribing drugs. Use of healthcare services may be a learned behavior where individuals with asthma who often are in contact with their physician will likely be more aware of their illnesses and may have learned to use, and possibly overuse, healthcare services. In support of the latter explanation are studies reporting a higher occurrence of a broad range of different conditions in asthmatics.^{5,7,13-15} It would be interesting to find a “reference disease” that is not linked to asthma and study if there is an excess occurrence of this “reference disease”.

The asthma drugs used to identify our asthma population are the mainstay of asthma pharmacotherapy⁹ and are quite specifically used for asthma at this age. Largely all patients on anti-asthma treatment in Norway receive at least one of the included drugs²³ and a high validity of this measure was found in 7-year olds.²⁴ In the present study, we used a stricter criterion for defining the asthma population in that individuals with asthma had to fill at least two prescriptions and at least 1 year apart. Thus, the inception of asthma complaints took place before the 1-year study period and lasted for at least one year (persistently or episodes of asthma at least one year apart).

A limitation of the study is the cross-sectional design which unable us to determine a causal relationship between comorbidities and the occurrence of asthma. The recording of diagnostic codes has only recently been implemented but when more years of data are accumulated, long-term studies can be done to confirm our findings and to disentangle the sequence of events. The time period of one year may be too short to capture some comorbidities, e.g. individuals with infrequent episodes of migraine may have long gaps between prescription refills. The length of study period is especially pertinent when studying a time-varying disease such as asthma where disease activity and the use of asthma drugs²³ is variable over shorter and longer time periods. A possible detection bias was discussed above. A further limitation is that for allergy and GORD, over-the-counter drugs without reimbursement are available. Some individuals may also have used non-reimbursed prescription drugs. This is probably most relevant for migraine and mental illnesses, if the physician deems the disease as not chronic or not properly diagnosed yet. Patients have economic incentives for receiving their drugs on reimbursement but acquiring a prescription may be more convenient for patients due to higher physician visit frequency.

One of the strengths of our study is that we use individual level data from three complete, nationwide datasets. NorPD captures all individuals receiving prescription drugs in the ambulatory care setting, including drugs prescribed by specialists in secondary and tertiary care. The universal healthcare system should ensure access to necessary healthcare services for all residents. Thus, we could examine the occurrence of a broad range of diseases in the Norwegian general population of the entire age range. The method for identifying chronic diseases is consistent between diseases and does not rest on subjective judgment by patients about their disease as in self-report studies, while recall bias is eliminated. However, the choice by patients and physicians to use drugs for a medical condition may be influenced by subjective judgments, as discussed above.

Comorbidities may influence and complicate several aspects of asthma, such as detection, diagnosis, severity and the control of asthma symptoms.⁶⁻⁸ Furthermore, the response to asthma therapy may be altered (e.g., obesity alter response to corticosteroids³⁷) or adherence

to asthma therapy decreases (e.g., depression^{28,38}). The drugs used for the treatment of comorbid diseases can have detrimental effects on asthma (e.g., NSAIDs⁹).

In summary, by using a nationwide prescription database with diagnostic codes we have shown an excess occurrence of several chronic diseases in the young population with asthma, compared with the age-specific general population of Norway. Fifty-nine percent of the asthma population had at least one additional chronic disease, while relatively few had more than one additional disease.

Table 1: Comorbidities and corresponding diagnostic codes (ICPC-2 and ICD-10 codes) examined in the Norwegian Prescription Database (NorPD).

	Comorbidity	ICPC-2	ICD-10	Comment
Chronic diseases	Attention Deficit Hyperactivity Disorder (ADHD) ^a	P81	F90	a) Denoted as hyperkinetic disorder in ICPC and ICD coding systems.
	Epilepsy	N88	G40	
	Migraine	N89	G43	
	Mental distress (depression, anxiety)	-74 ^b ; P74; P76	-74 ^b ; F41; F32	b) Reimbursement code for anxiety disorders, defined by NoMA (replaces ICPC and ICD codes).
	Cardiovascular disease (hypercholesterolemia, hypertension)	-26 ^c ; -27 ^c ; K86-87	-26 ^c ; -27 ^c ; I10-13; I15	c) Reimbursement codes for primary and secondary prevention of atherosclerotic disease, defined by NoMA (replaces ICPC and ICD codes).
	Diabetes ^d (Type 1, type 2)	T89-90	E10-11; E13-14	d) ICPC codes do not distinguish between diabetes type 1 and 2.
	Autoimmune disorders (Arthritis-related diseases, systemic connective tissue disorders, ankylosing spondylitis, noninfective enteritis and colitis, psoriasis)	L88; L99; D94; S91	M05-08; M13; M30-35; M45; K50-51; L40	
	Gastro-oesophageal reflux disease (GORD) ^e	D84	K21	e) OTC drugs also on market but are not reimbursed.
	Allergy ^f (Allergic rhinitis, allergic conjunctivitis, atopic dermatitis, urticaria)	R97; F71; S87; S98	J30; H10.1 ^g ; L20; L50	f) OTC drugs also on market but are not reimbursed. g) NoMA specifies that only the 4th level code H10.1 is eligible for reimbursement.
antimicrobial treatment	Antibacterials ^h (upper and lower respiratory tract)		ATC codes: J01AA02; J01CA04; J01CE02; J01FA	h) Drugs (ATC codes) recommended by guidelines [†] for treatment of upper and lower respiratory tract infections.
	Antivirals ⁱ (influenza virus infection)		ATC codes: J05AH01; J05AH02	i) H1N1 influenza during study period. Pharmacists could write prescriptions and dispense drugs according to set regulations, without consulting physicians.

ATC, Anatomical Therapeutic Chemical classification system for drugs; ICD-10, International Statistical Classification of Diseases, 10th revision; ICPC-2, International Classification of Primary Care, 2nd edition; NoMA, Norwegian Medicines Agency; OTC, over-the-counter drugs (drugs sold without prescription);

[†] Norwegian Directorate of Health. [Norwegian national guidelines for treatment with antibiotics in general practice]. 2008. Available from: <http://www.helsebiblioteket.no/microsite/Antibiotikaretningslinjer> (in Norwegian).

Table 2: Number of comorbid diseases occurring in the asthma population and the general population (8-29 years old) during a 1-year period.

Number of comorbidities	Male subjects		Female subjects	
	% of asthma population ^a (n=20,207)	% of general population (n=637,104)	% of asthma population ^a (n=16,853)	% of general population (n=602,429)
Chronic diseases ^b				
0	40.8	82.4	41.4	81.9
1	53.3	16.2	50.4	16.2
2	5.3	1.3	6.9	1.6
3	0.6	0.1	1.0	0.2
4+	0.1	0.0	0.2	0.0
Chronic diseases and antimicrobial treatment ^c				
0	30.7	70.2	29.1	66.4
1	48.2	24.3	44.6	26.3
2	17.3	4.8	20.0	6.1
3	3.3	0.6	5.2	1.0
4+	0.5	0.1	1.1	0.2

a) Not adjusted to the age-distribution of the general population.

b) 9 different comorbidities measured, see Table 1.

c) 11 different comorbidities measured, see Table 1.

Table 3: Standardized Morbidity Ratio (SMR) for occurrence of comorbid diseases in the asthma population (8-29 years old) during a 1-year period (Reference: Occurrence of diseases in the general population by gender and 1-year age specific groups).

Comorbidity ^c	Male subjects ^a					Female subjects ^b				
	Occurrence (O/n)	Observed count (O)	Expected count (E)	SMR (O/E)	[95% CI]	Occurrence (O/n)	Observed count (O)	Expected count (E)	SMR (O/E)	[95% CI]
8-19 years										
ADHD	4.0 %	585	469	1.2	[1.1, 1.4]	2.2 %	223	129	1.7	[1.5, 2.0]
Epilepsy	1.0 %	149	84	1.8	[1.5, 2.1]	1.1 %	111	56	2.0	[1.6, 2.4]
Migraine	0.9 %	133	76	1.7	[1.5, 2.1]	2.0 %	203	118	1.7	[1.5, 2.0]
Mental illness	0.4 %	65	39	1.7	[1.3, 2.1]	0.9 %	90	67	1.3	[1.1, 1.7]
Cardiovascular	0.1 %	20	13	1.5	[1.0, 2.3]	0.2 %	21	12	1.8	[1.1, 2.7]
Diabetes	0.6 %	83	62	1.3	[1.1, 1.7]	0.4 %	37	43	0.9	[0.6, 1.2]
Autoimmune	0.7 %	103	66	1.6	[1.3, 1.9]	1.0 %	104	67	1.5	[1.3, 1.9]
GORD	1.6 %	236	52	4.6	[4.0, 5.2]	1.3 %	134	34	4.0	[3.3, 4.7]
Allergy	56.1 %	8258	1,977	4.2	[4.1, 4.3]	51.8 %	5274	1,098	4.8	[4.7, 4.9]
Antibacterials ^d	13.8 %	2024	1,212	1.7	[1.6, 1.7]	19.6 %	1994	1,212	1.6	[1.6, 1.7]
Antivirals ^{d,e}	13.8 %	2033	986	2.1	[2.0, 2.2]	13.1 %	1330	684	1.9	[1.8, 2.1]
20-29 years										
ADHD	1.6 %	89	39	2.3	[1.8, 2.8]	1.6 %	108	42	2.5	[2.1, 3.1]
Epilepsy	1.3 %	69	39	1.8	[1.4, 2.2]	1.4 %	93	49	1.9	[1.6, 2.3]
Migraine	1.1 %	60	37	1.6	[1.3, 2.1]	5.6 %	370	198	1.9	[1.7, 2.1]
Mental illness	4.5 %	249	134	1.9	[1.6, 2.1]	7.7 %	510	266	1.9	[1.8, 2.1]
Cardiovascular	1.3 %	69	39	1.8	[1.4, 2.2]	1.2 %	77	40	1.9	[1.5, 2.4]
Diabetes	0.8 %	45	41	1.1	[0.8, 1.5]	1.0 %	64	46	1.4	[1.1, 1.8]
Autoimmune	1.9 %	104	80	1.3	[1.1, 1.6]	2.8 %	188	121	1.5	[1.3, 1.8]
GORD	3.3 %	179	56	3.2	[2.8, 3.7]	2.7 %	183	52	3.5	[3.0, 4.0]
Allergy	51.5 %	2831	591	4.8	[4.6, 5.0]	55.9 %	3729	903	4.1	[4.0, 4.3]
Antibacterials ^d	22.9 %	1259	777	1.6	[1.5, 1.7]	31.7 %	2113	1,370	1.5	[1.5, 1.6]
Antivirals ^{d,e}	9.7 %	534	251	2.1	[2.0, 2.3]	11.1 %	739	389	1.9	[1.8, 2.0]

ADHD, Attention Deficit Hyperactivity Disorder (hyperkinetic disorder); GORD, Gastro-oesophageal reflux disease; SMR, standardized morbidity ratio.

a) Males n=20,207 (8-19 years n=14,709; 20-29 years n=5,498).

b) Females n=16,853 (8-19 years n=10,187; 20-29 years n=6,666).

c) Individuals that have more than one comorbidity is counted on each comorbidity (sum of observed counts (O) on all comorbidities does not equate to the study population size).

d) From ATC codes on drugs.

e) H1N1 influenza epidemic occurred during the observed 1-year period.

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