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PHENOTYPING OF OBSTRUCTIVE AIRWAY DISEASES BASED ON FINNISH HEALTH REGISTRIES

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TIIVISTELMÄ

Jaakko Vuori: Obstruktiivisten hengitystiesairauksien fenotyypittäminen perustuen suomalaisiin terveysrekistereihin
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Obstruktiiviset krooniset hengitystiesairaudet, astma ja keuhkoahtaumatauti, ovat merkittäviä kansansairauksia Suomessa. Astman ja keuhkoahtaumataudin lääkkeiden käyttö ja liitännäissairastavuus on huomattavaa. Vaikka astman ja keuhkoahtaumataudin kliiniset fenotyypit ovat ominaisuuksiltaan samankaltaisia, eroavat ne kuitenkin merkittävästi etiologialtaan. Astman ja keuhkoahtaumataudin sekamuoto (ACO) on tärkeä tunnistaa kliinisessä työssä ja tutkimuksia varten.

Aiemmin astman ajateltiin olevan lapsuusiässä alkava kortikosteroideilla hoidettava tauti. Kuitenkin viime vuosikymmeninä on löydetty useita erilaisia astman alatyyppejä. Aikuisiän astman lisäksi tutkimuksien kohteina ovat olleet allerginen astma, ei-allerginen astma, eosinofiilinen astma, lapsuusiän astma ja lihavuuteen sekä uniapneaan liittyvä astma.

Aineistona käytetään FinnGen-tutkimushankkeen potilasväestöä sekä suomalaisista terveysrekistereistä saatuja tietoja. Tässä tutkimuksessa tarkastellaan kolmea pääryhmää, jotka ovat astmaryhmä (N = 49 406), keuhkoahtaumatautiryhmä (N = 12 935) ja ACO-ryhmä (N = 9 263). Verrokkiryhmässä on 188 627 tapausta, joilla ei ole astma- tai keuhkoahtaumatautidiagnoosia eikä obstruktiivisten keuhkosairauksien lääkeaineostoja. Lisäksi tutkimuksessa tarkastellaan kuutta astman alatyyppiä.

Pääryhmistä ACO-ryhmässä todetaan suurin käyttöaste pitkävaikutteisten beeta-2-agonistien ja inhaloitavien kortikosteroidien yhdistelmälääkeryhmässä (83 %), pitkävaikutteisten beeta-2-agonistien lääkeryhmässä (31 %), pitkävaikutteisten muskariiniantagonistien lääkeryhmässä (31 %) sekä ksantiinilääkeryhmässä (23 %) ($P < 0.001$). Inhaloitavia kortikosteroideja käytetään eniten astmaryhmässä (88 %) ($P < 0.001$). Riski sydän- ja verisuonisairauksiin on merkitsevästi kasvanut keuhkoahtaumaryhmässä (OR: 7,1, $p < 0.001$) sekä ACO-ryhmässä (OR 4,9, $p < 0.001$). Lihavuuteen ja uniapneaan liittyvässä astmassa löydettiin erityinen riski tyypin 2 diabetekseen (OR 3,2, $p < 0.001$) ja verenpainetautiin (OR 3,0, $p < 0.001$).

Tutkimuksen pitkä seuranta-aika auttaa ymmärtämään sairauksien kehitystä. Tutkimuksen tulokset ovat yhtenäisiä odotettujen tulosten kanssa, ja ryhmien muodostus näyttäytyy luotettavana.

Tutkimuksesta voidaan todeta, että käyttämällä suomalaisia terveysrekistereitä voidaan tunnistaa erilaisia obstruktiivisia keuhkosairauksia, astman eri alatyyppejä sekä määrittää obstruktiivisista hengitystiesairauksista terve verrokkiryhmä geneettisiä tutkimuksia varten.

Avainsanat: asthma, COPD, ICS, LABA

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Background, challenges, and aims of the study

Diseases studied

Asthma and chronic obstructive pulmonary disease (COPD) are both obstructive airway diseases. Asthma causes reversible bronchial obstruction spontaneously or due to exposure to allergens or infectious agents. COPD is a disease mainly caused by exposure to smoke, in developed countries usually cigarette smoking. Contrary to asthma, COPD causes irreversible airway obstruction, emphysema and fibrosis of the lung parenchyma. Pulmonary functions are harmed permanently ultimately leading to respiratory failure and death of the patient. Both diseases are common. There are of estimate between 300 000 - 500 000 asthma patients and 200 000 COPD patients in Finland [1]

Even though smoking in Finland has generally decreased, still a significant number of asthma-patients smoke. Approximately 21% of adult asthmatics are current smokers, and 20% ex-smokers [2]. Differentiation of asthma and COPD among middle aged and elderly population can be sometimes challenging as they share features.

The overlap – or comorbidity – of asthma and COPD is clinically important to define. 'Asthma-COPD-overlap syndrome' (ACOS or ACO) is often defined as persistent airflow limitation with features of asthma [3, 4]. People diagnosed with ACO typically have exacerbations and experience symptoms such as dyspnea more frequently than people with COPD alone [3]. They have a true reduction as well as a functional reduction in lung capacity. ACO, according to Dey et al. [5], includes "several overlapping clinical phenotypes of chronic airways diseases and does not define a single disease" [5]. Patients with ACO express traits from the Th1 (COPD) and Th2 (asthma) characteristics, and their drug profile and health care utilization as a systematically defined patient group are a matter of interest to determine as well as the relation between genotypes and phenotypes.

Even though the clinical phenotypes of asthma and COPD share similar features the etiology of those diseases is known to differ significantly. In COPD the immune response is mediated mainly through T helper type 1 (Th1) cells and in asthma through Th2 response.

Asthma, COPD and ACOS share clinical features, but they differ in prognosis, age and gender range, co-morbidity profile, and recently more and in treatment recommendations. Co-morbidities for asthma include upper-airway diseases such as chronic sinusitis, nasal polyposis, allergic rhinoconjuctivitis, vasomotor rhinitis, and potentially other atopic manifestations and eosinophilic diseases such eosinophilic pneumonia and eosinophilic granulomatosis with polyangiitis (EGPA) [6]. Among elderly asthma patients also gastroesophageal reflux disease, type 2 diabetes, obesity, metabolic syndrome, depression and anxiety are common, which often complicate the treatment of asthma. Childhood asthma is associated with increased risk of type 1 diabetes [7].

Co-morbidities in COPD are smoking related and include cardiovascular disorders, type II diabetes, osteoporosis, stroke, peripheral arterial disease, and cognitive decline [8].

Therapies between asthma and COPD are overlapping but during the last years, some changes have become obvious. The first preferred approach in medicating asthma is inhaled corticosteroids (ICS) in GINA guidelines (Global initiative for asthma) [3]. Treatment options in addition to ICSs include long-acting beta2-agonist (LABA) and in the case of medication needing enhancement long-acting muscarine antagonists (LAMA). For all asthma patients a fast symptom relieving short-acting beta2-agonist (SABA) inhalation medication is also added.

COPD is often an underdiagnosed disease and in the early stages of the disease. Patients may use short acting symptom relieving medication such as SAMA or SABA (short-acting muscarine antagonist) for a long time, until stepping up to regular medication with ICS and LAMA/LABA combinations. According to current care guidelines, in COPD the recommended ICS dosing is smaller compared with that in asthma. In addition, the recommendation is to start with LAMA and/or LAMA and then add ICS if desired results have not been accomplished [9].

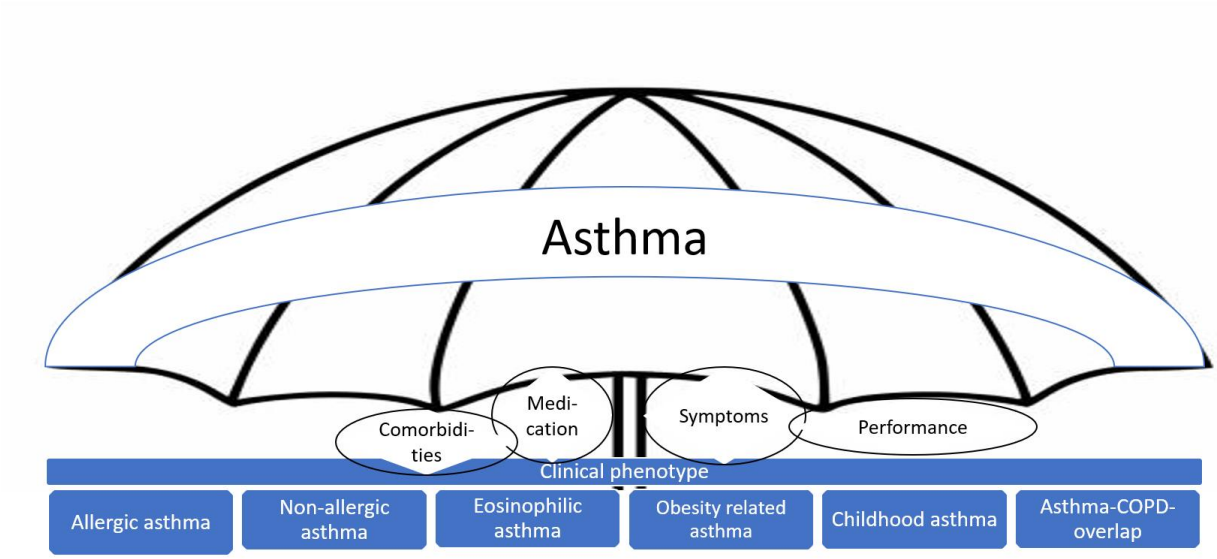

Figure 1

Presentation of asthma subphenotypes under the umbrella term *asthma.* Scheme modified from a publication by Rebecca Howard et al. [10]

In asthma, several clinical subphenotypes such as allergic asthma, non-allergic-asthma, eosinophilic asthma, childhood and adulthood onset asthma, obesity related asthma, occupational asthma, severe and frequently exacerbating asthma have been described [11]. Genetic studies in 'true' asthma patients with different phenotypic profiles might help us to better understand the etiological differences and potentially also different therapeutical needs.

The overlap and comorbidity with similar diseases such as COPD is important to distinguish. With chronic respiratory diseases sharing symptoms, medicines, Kela's reimbursement code, harmonized multiregistry approach could prove valuable in differentiating the diseases. Moreover, differentiating clinically important asthma sub-phenotypes, which have a different respond to medication, is important.

So far inhaled corticosteroids have been the number one choice for asthma, ACO and moderate/severe COPD regardless of what phenotype patient has. However, especially oral corticosteroids in severe/frequently exacerbating asthma have several adverse effects, such as weight gain, cataract, opportunistic infections, impaired glucose balance and development of type 2 diabetes, impaired GER and GI-ulcers, insomnia and even psychosis. While we begin to gain a better understanding of the endotypes of these diseases the development of precision medications has started. Biological medications, such as anti-IL-5 monoclonal antibody therapies have been approved for the treatment of asthma and other anti-IL-4/IL-13 medications have indications for comorbidities related to asthma [12].

FinnGen study design

FinnGen study is a multinational research project aiming to improve personalized medicine via genetic research. Through collaboration with Finnish biobanks and national health registries, the study combines genomic information with digital health care data (Figure 2). FinnGen study was launched in 2017 and is ongoing with upcoming data freezes, that further increase the study population. The study is the largest research project in the Finnish history utilizing biobank samples, aiming to include samples from 500 000 Finnish individuals and finish genotyping by August 2023 (Figure 4). There are multiple research groups within FinnGen, that study the genetic background of numerous diseases, including asthma and COPD.

The DNA samples are gathered from seven regional and three national biobanks from collections available for all researchers under the internationally unique Finnish Biobank Act. The samples include Finnish population cohorts such as FINRISK (FINRISK1-9), Health2000 & 2011 study, and Northern birth cohort [13, 14, 15] (legacy samples in Figure 3). In addition, there are samples from 6 Finnish public hospitals (representing secondary and

tertiary care), private health care (representing mainly occupational health care) and the Finnish Blood Transfusion Service (representing healthy blood doners) (new samples in Figure 3).

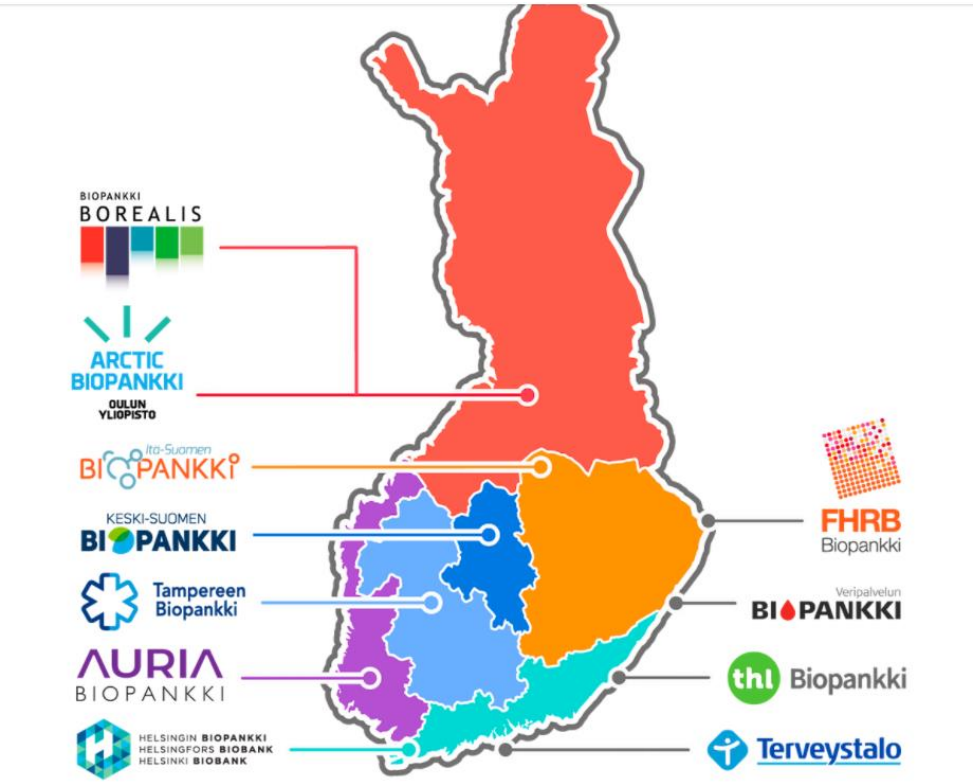

Figure 2. Seven regional (left) and four nationwide (right) biobanks that provided all the DNA samples and health care data to the FinnGen study.

In FinnGen study the genetic data is combined with health data from various sources, using HILMO registry (1987-), AVOHILMO registry (2011-), Kela's drug reimbursement (1987-) and purchase registry (1995-), cancer registry (1953-) and cause of death registry (1988-) (Figure 3).

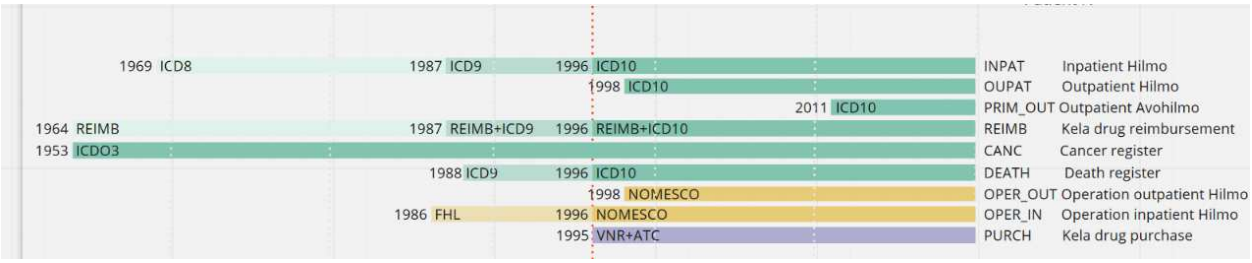

Figure 3. Nine registries with the founding years used in FinnGen to collect health care for the participants are shown.In the present study, ICD8 and ICD9 nomenclatures have been mapped into the ICD10 codes and all the results are given in the ICD10 format.

The founding years of the registries varied beginning from year 1953 to 2011 with every registry being still operational. Register of secondary health care visits (HILMO) includes all the hospital admissions, procedures and specialist visits. The shortest follow-up time was for AVOHILMO registry which provides data of all the visits in primary health care. The data from all registries is conformed and evolving nomenclature is harmonized to be concordant.

Kela (Kansaneläkelaitos) is the National Social Security Institution that grants special reimbursement rights to asthma and COPD medication to those Finnish citizens who fulfill the strict criteria and need regular medication (ref). The criteria include systematic examining of PEF follow-up (morning-even difference before and after bronchodilation), baseline and bronchodilation spirometry, basic lab values, allergy testing when needed, and chest X-ray. Since inhalers are rather expensive and the reimbursement is significant, most patients go through the systematic review needed for 'the official diagnosis'. Asthma is the second most common disease that is given Kela's higher special rate of reimbursement with close to 250 000 recipients in Finland [16]. Both of asthma and COPD diagnostics and treatment is mainly performed in primary healthcare. Only patients suffering from severe COPD (FEV1 < 40% of predicted) will fulfill Kela's reimbursement criteria.

Kela's drug reimbursement registry holds information for all prescription drug purchases done in Finland.

Cause of death registry contains information derived from the death certificates, which includes basic cause of death, imminent cause of death and contributing causes of death. Deaths occurring in Finland and deaths of people with permanent residency in Finland are included.

In FinnGen a total of 13 national health care registries were used: in addition to above mentioned, the registries include Statistics Finland, Finnish Cancer Registry and Mass Screening Registry, Care Register for Health Care, Digital and Population Data Services Agency, Finnish Register of Visual Impairment, Care Register for Social Welfare, Finnish Registry for Kidney Diseases, Finnish National Infectious Diseases Register, Medical Birth Register, Finnish National Vaccination Register and the Register of Congenital Malformations

The data from the registries is conformed and the evolving nomenclature is harmonized to be concordant on the 10th revision of international Classification of Diseases (ICD-10). For medicinal products ATC-codes were used.

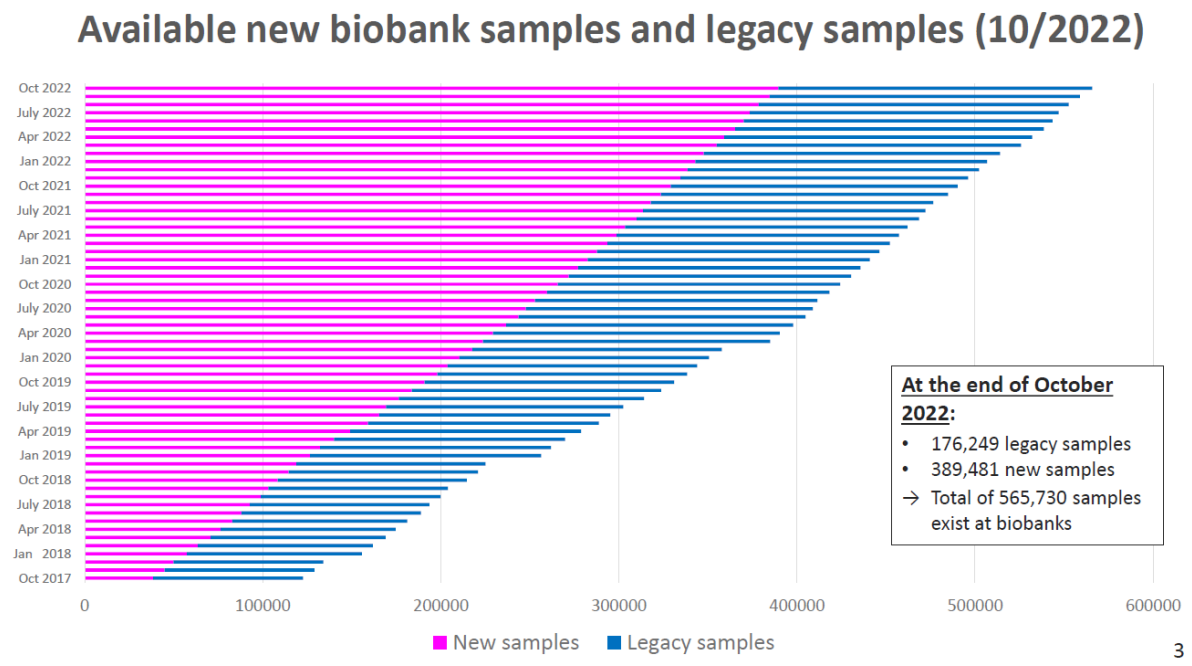

Figure 4. Incremental sample size of FinnGen in the end of October 2022.

Aim of the present study

By using longitudinal health data, our aim is to differentiate asthma, ACO and COPD patients from each other and then further, identify certain clinical subtypes of asthma.

The aims include appraising the usability of longitudinal phenotype-data of multiple registries in defining true asthmatics and identifying different sub-phenotypes as well as improving identification of asthma-COPD-overlap (ACO). To determine differences in drug usage by asthma, COPD and ACO cohorts, and determine comorbidities of pre-determined diseases.

Materials and methods

Source data for study cohort

All the study subjects were identified from the FinnGen cohort (data freeze 10, N=260 231 study subjects) based on diagnostic information in AVOHILMO (primary health care), HILMO (secondary health care), and Cause of Death Registries. Both main and side diagnoses of a visit were included into data extraction. The only exclusion criteria for the initial patient population was the death of the patient before the year 1998.

Drug purchase data for the selected patient populations were taken from Kela's drug purchase registry. Defined daily doses (DDD) were used to estimate dosing in different diseases groups and calculated for each pharmaceutical product according to manufacturer 's instructions.

Target populations were identified using the following diagnostic criteria

CASE COHORTS

Patients with asthma and COPD will be identified, and the population with both diseases, the ACO cohort. Furthermore, five subgroups from the asthma cohort, consisting of allergic asthma, non-allergic asthma, childhood asthma, eosinophilic asthma, and obesity related asthma will be identified.

Asthma cohort: All study subjects who were given ICD10 code J45 and/or J46 (Asthma) with the simultaneous exclusion of COPD (J44).

COPD cohort: All study subjects who were given ICD10 code J44 (COPD) with the simultaneous exclusion of asthma (J45 and J46).

ACO cohort: All study subjects who have been diagnosed both with ICD10 code J45 and/or J46 (Asthma) and J44 (COPD).

CASE COHORTS FOR THE SUBPHENOTYPES OF ASTHMA

According to allergic conditions subgroups 1-3 were excluding each other. In groups 4-7 the patient can belong several gropus

1. **Allergic asthma**

All patients having been diagnosed with allergic asthma (J45.0) and/or any type of asthma (J45 or J46) and one or more of the following allergic conditions at any given time: atopic excema, allergic rhinitis, allergic conjunctivitis, food allergy, hyposensibilitation therapy or pollen allergy (L20.0, L20.8, L20.9, J30.1, J30.2, J30.3, J30.4, H10.1, L23.6, K52.2, Z51.6, J30.19)

2. **Non-allergic asthma**

   All patients having been diagnosed with non-allergic asthma (J45.1) and no mentioning of any atopic conditions which means the exclusion of ICD10 codes J45.0, L20.0, L20.8, L20.9, J30.1, J30.2, J30.3, J30.4, H10.1, L23.6, K52.2, Z51.6, J30.19

3. **Mixed or unknown Asthma**

   Rest of the patients having any type of asthma and did not belong to groups 1-2.

4. **Childhood asthma**

   Any type of asthma diagnosed at age of <16

5. **Eosinophilic asthma**

   Any type of asthma (J45 and J46) and one or more of the following: nasal polyposis (J33), EGPA (M30.1), eosinophilic pneumonia (J82), ASA intolerance (Z88.6), or polypectomy (DHB20, procedure code)

6. **Obesity and sleep apnea related asthma**

   Any type of asthma (J45 and J46) and diagnosed obesity (E66) or sleep apnea (G47.3)

CONTROL COHORT

Control population had not been diagnosed either with asthma or COPD (excluding J44, J45, and J46) during the follow-up. In addition, they did not have any drug purchases for inhaled corticosteroids, long-acting beta-agonists, long-acting muscarine-receptor antagonists, leukotriene receptor antagonists, chromones, biologics or xanthines used in asthma during the follow-up (list of the medicinal products in the Attachment 1).

Comorbidities

1. **Vascular factors / cardiovascular diseases**

   Atherosclerosis: I70 (Including I70.0, I70.1, I70.2, I70.3, I70.4, I70.5, I70.6, I70.8, I70.9)

   Coronary disease: I25.0, I25.1

   Atherosclerosis of cerebrum/cerebral arteries: I67.2

2. **Diabetes mellitus II**

   E11

3. **Depression**

   F32 – F34

4. **Cataract**

   H25, H26.02 premature cataract, H26.3 medication induced cataract

5. **Hypertension**

   I10-I15

The drug groups: ICS, ICS and LABA, LABA, LAMA, LTRA, Chromones, biologics and xanthines were defined in same manner as in a previous FinnGen study and defined daily doses (DDD) of the drug groups were measured with individual dosages per used product (attachment 1) and then divided with the follow-up time of the subject.

Statistical methods

Statistical analysis for comorbidities and drug usage will be done with Fisher exact test and by stratifying by age and gender. Statistical analysis on drug usage will be done with Wilcoxon signed-rank test and presented in box-plots.

Ethics

FinnGen study is performed under the Finnish Biobank Act [17]. The act determines in detail the participants' rights and the duties of the biobanks both in regard to the samples and health data used. All the participants have either given their written consent or in the case of old legacy cohorts, the transfer of the cohorts into biobanks has been done according to the demands of the legislation (using opt out principle). The new biobank

concept allows for samples from biobanks to be used for a variety of purposes ranging from medical research and health promotion to product development.

The ethics committee of Helsinki University Hospital and all the Scientific Advisory Boards of the participating biobanks have approved the scientific study approach.

The new biobank concept allows for samples from biobanks to be used for a variety of purposes ranging from medical research and health promotion to product development. The Finnish Medicines Agency FIMEA oversee the biobanks.

It is a global endeavor with hundreds of employees. Collaboration with Finnish health registries, THL, hospitals and hospital districts, biobanks and international pharmaceutical companies is essential in reaching the goals.

Results

The study included three main cohorts, asthma-cohort (N=49 406), COPD-cohort (N=12 935), and ACO-cohort (N=9 263) who had both the diseases (Table 1). As expected, asthma group was the largest and youngest with female dominance of 67,6%.

Six asthma sub-cohorts, allergic asthma, non-allergic asthma, mixed or unknown asthma, eosinophilic asthma, childhood asthma, and obesity or sleep apnea related asthma. The three forementioned cohorts enclose all the asthma patients (N=58669) which includes pure asthmatics and ACO-patients.

Table 1. Comparison of the study cohorts.

	Asthma N= 49406	COPD N=12935	ACO N= 9263	Controls N=188627	P value *
Proportion of females	33410 (67,6%)	2817 (21,8%)	3699 (40,0%)	109064 (57.8%)	
Age at onset					
<20 yr	6259 (12,7%)	7 (0,1%)	75 (0,8%)		
20-60yrs	27298 (55,3%)	2418 (18,7%)	3539 (38,2%)		
>60 yrs	15849 (32,1%)	10494(81,1%)	5649 (61,0%)		
Co-morbidities					
Cardiovascular diseases	6315 (12,8%)	6591 (51,0%)	3837 (41,4%)	23953 (12,7%)	0.62 <0.001 <0.001
Hypertension	16791 (34,0%)	6617 (51,2%)	5185 (55,2%)	51714 (27,4%)	<0.001 <0.001 <0.001
Depression	8623 (17,5%)	1588 (12,3%)	1715 (18,5%)	21149 (11,2%)	<0.001 <0.001 <0.001
Diabetes type 2	9345 (18,9%)	3836 (29,7%)	3150 (34,0%)	30320 (16,1%)	<0.001 <0.001 <0.001
Cataract	8467 (17,1%)	4502 (34,8%)	3334 (36,0%)	27414 (14,5%)	<0.001 <0.001 <0.001

*P-values for asthma-cohort compared with COPD-cohort, Asthma-cohort compared with ACO-cohort, and COPD-cohort compared with ACO-cohort.

Table 2. Drug usage of asthma, COPD and ACO-cohorts

Use of respiratory medicines	Asthma N= 49406	COPD N=12935	ACO N= 9263	P-value *
ICS				
N of users	43461 (88,0%)	4647 (35,9 %)	7495 (80,9 %)	<0.001 0.13
DDD median, SD	74.2, 402.3	35.5, 372.5	79.2, 364.4	<0.001
LABA				
N of users	9023 (18,3 %)	2135 (16,5 %)	2832 (30,6 %)	<0.001 <0.001
DDD median, SD	19.9, 201.6	43.4, 259.3	42.5, 278.0	<0.001
LAMA				
N of users	5966 (12,1 %)	6305 (48,7 %)	5812 (62,7 %)	<0.001 <0.001
DDD median, SD	23.8, 177.1	111.2, 395.9	111.11, 423.3	0.68
ICS&LABA combination				
N of users	30722 (62,2 %)	5502 (42,5 %)	7694 (83,1 %)	<0.001 <0.001
DDD median, SD	121.2, 468.3	96.5, 337.7	208, 374.4	<0.001
LTRA				
N of users	20056 (40,6 %)	639 (4,9 %)	3196 (34,5 %)	<0.001 <0.001
DDD median, SD	30.4, 261.5	12.9, 197.1	52.6, 206.5	<0.001
Biologics				
N of users	101 (0,2 %)	7 (0,1 %)	10 (0,1 %)	0.54 0.68
DDD median, SD	19.8, 43.2	33.1, 19.8	24.9, 2	0.61
Chromones				
N of users	5278 (10,7 %)	290 (2,2 %)	549 (5,9 %)	0.12 <0.001
DDD median, SD	5.8, 89.6	6.5, 68.6	4.4, 44.4	<0.001
Xanthines				
N of users	3918 (7,9 %)	1979 (15,3 %)	2155 (23,3 %)	<0.001 <0.001
DDD median, SD	7.75 392.7	69.4, 435.8	40.4, 450.2	<0.001

*P-values for asthma-cohort compared with COPD-cohort, Asthma-cohort compared with ACO-cohort, and COPD-cohort compared with ACO-cohort.

ACO-cohort has the highest percentage of users in ICS and LABA combination group, LABA and LAMA groups and Xanthines.

When comparing allergic asthma to non-allergic asthma, no significant results were found between the usage of biologics or chromones. Comparing the drug usage of allergic asthma to non-allergic asthma, the drug usage was higher in non-allergic asthma in every examined group where significant results were found. The ICS usage and LABA and ICS combination usage was higher in non-allergic subcohort (mean 177 DDD vs 218 DDD and 315 DDD vs 214 DDD) P <0,001.

Table 3. Distribution of asthma subpehotypes in the Finngen cohort

Asthma Subphenotypes	N of the patients N= 58 669
Allergic asthma	24 683 (42,1 %)
Non-allergic asthma	11 586 (19,7%)
Mixed or unknown asthma	22 400 (38,2%)
Eosinophilic asthma	1 006 (1,7%)
Obesity and sleep apnea related asthma	15 143 (25,8%)
Childhood asthma	5 028 (8,6%)

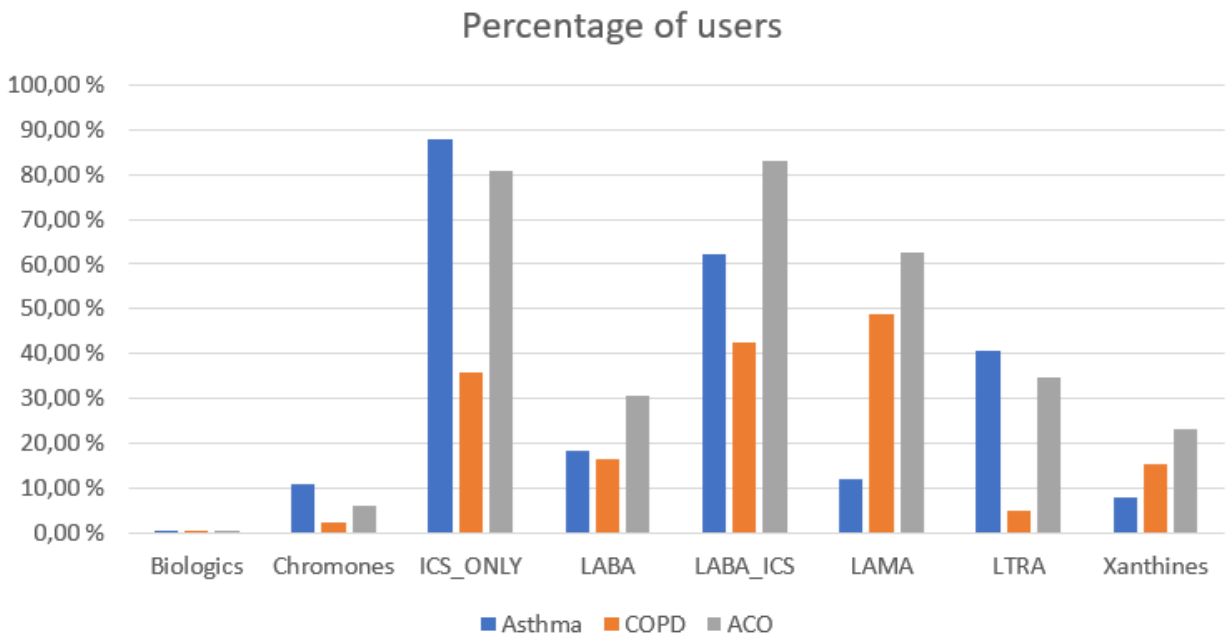

Figure 5.
Proportion of patients who have purchased pharmaceutical products during the follow-up period.

ICS= inhaled corticosteroids, LABA= long-acting beta2-agonists, LAMA= long-actig muscarine antagonists, LTRA= leukotriene receptor antagonists

ICS and combination terapy ICS/LABA was used most frequently by asthma and ACO-patients. (Table x and Figure y). The usage of biologics is minimal, 0,19% in asthma group and 0,05% in COPD group. Nobody in ACO group used biologic drugs.

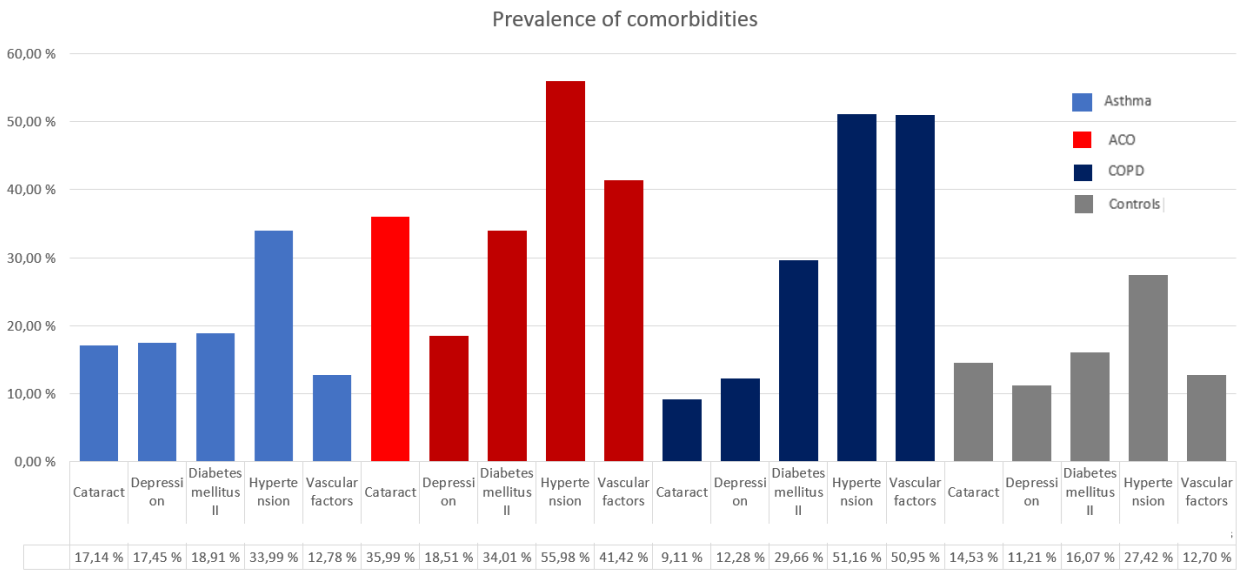

Figure 6. Proportion of patients in main cohorts having cataract, depression, DM2, hypertension and CVD (vascular factors)

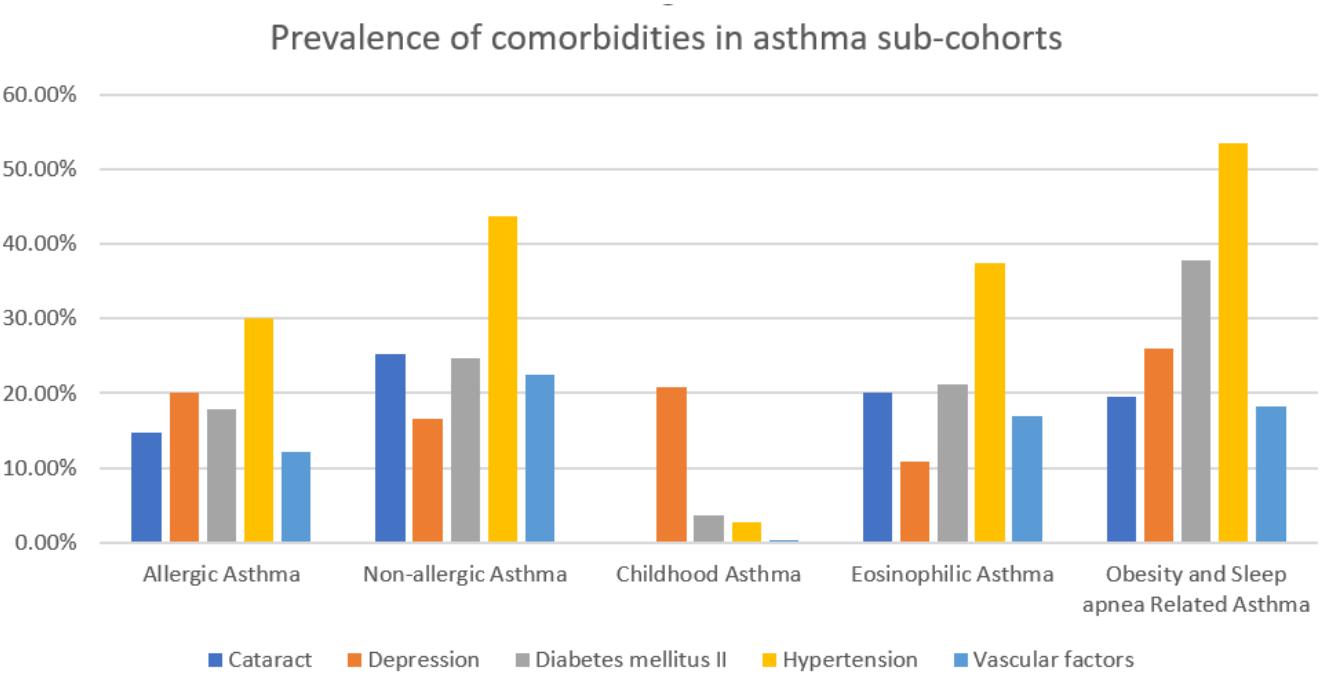

Figure 7. Proportion of patients in the five subcohorts having cataract, depression, DM2, hypertension and CVD (vascular factors)

All main cohorts had more frequently co-morbidities than the control group (Figure 6 and table 1). In the ACO-cohort co-morbidities were more frequent than in any other group except CVD in COPD. Control population is the healthiest in all categories considering the comorbidities. The highest comorbidity is found on ACO cohort with 56,0% prevalence in hypertension.

The risk for vascular factors was found to be significantly increased in the COPD-cohort (OR: 7,1, p<0.001) and ACO-cohort (OR 4,9, p<0.001)

In obesity and sleep apnea related asthma, the risk for all five of the studies comorbidity groups were increased, with particularly high risk for DM2 (OR: 3,2) and hypertension (OR: 3,0).

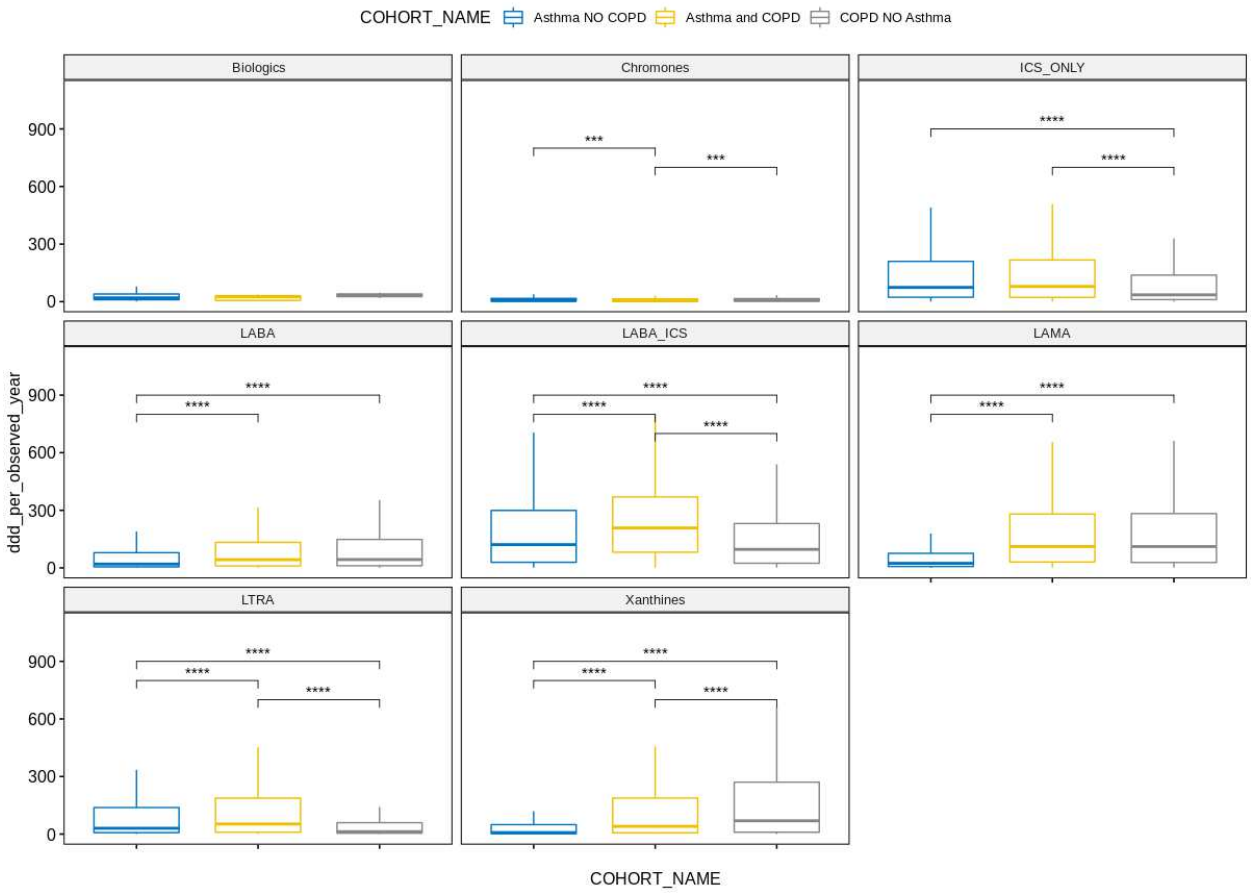

Figure 8. Comparisons of drug usage (DDDs per year) between asthma, COPD and ACO groups.

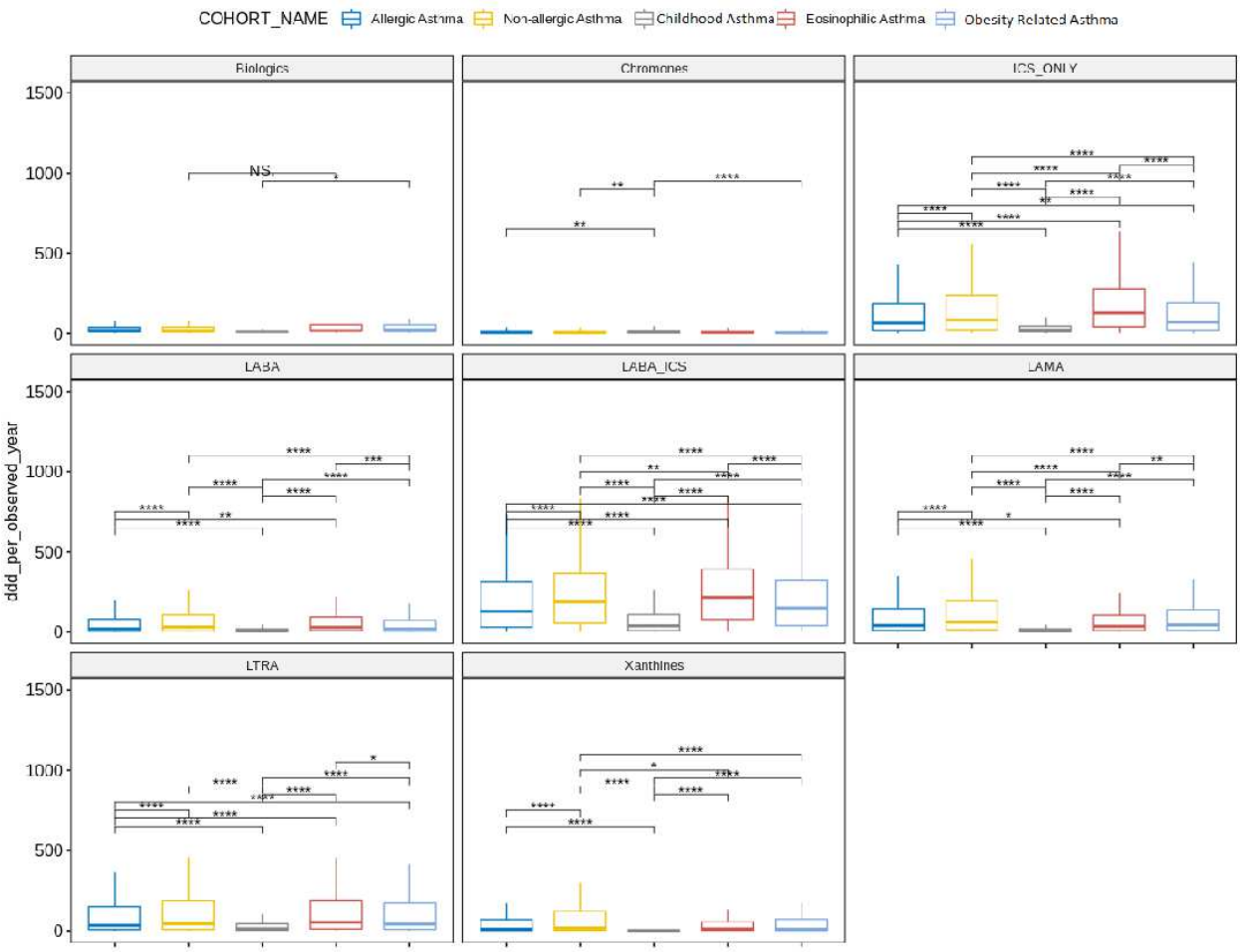

Figure 9. Significant differences were found in majority of drug groups between most sub-cohorts.

Significant differences were found in most groups. Long acting beta2-agonists were the most used drug group in the comparison. As daily defined doses, ACO-cohort had the highest mean consumption of LABA and ICS drugs with a mean of 292 DDD compared with COPD cohort and asthma cohort (179 and 248 DDD) P-value 5.8e-163 and 6.0e-202.

Significant differences were not found between the usage of biologics. Significant differences between the three groups were mostly found between the drug usage of asthma-cohort, which found twelve (12) instances of significant differences between ACO-cohort and COPD-cohort, compared with eleven with both the ACO-cohort and COPD-cohort.

The usage of ICS was highest in asthma-cohort with a mean usage of 194 DDD (+4,20% more compared with ACO-cohort and +31,91% more compared with COPD-cohort) and the highest prevalence of users of 88%.

The usage of the combination medication ICS and LABA on the other hand was highest in the ACO-cohort with a mean usage of 291,66 DDD (+17,41% more compared with asthma-cohort and +62,94% more compared with COPD-cohort)

Discussion

The present study showed significant differences between the three main groups in age and sex distribution, various therapeutic drug usages and comorbidities. Asthma-cohort was female represented, where in COPD and ACO-cohorts were male dominant. The age of disease onset was later in COPD-cohort and with a greater proportion of elderly population, than asthma-cohort.

The considerable follow-up time of the study gives us a unique opportunity to follow a patient and better understand the development of the disease over years. The patients included in the study that make up roughly 500 000 samples are not randomly selected, as the biobank consents are mainly gathered during patients' hospital appointments. The patient cohort represents a non-randomized Finnish population.

This study used multiple health registries and comprehensive longitudinal data to define endpoints for obstructive lung diseases and it is useful for future genetic studies.

Based on registry data on diagnostics and drug usage division of obstructive airway diseases (asthma, COPD and ACO cohorts were shown to be reliable. Age and gender distributions support the hypothesis, ACO cohort having smoking related co-morbidities. Control population was defined to be without inhalable corticosteroids, Population that had prescription drug purchases for asthma or COPD without the diagnoses, were ruled out from the study, and this might suggest that we are missing true asthma, COPD or ACO cases. We have shown that using drug purchase data we can have a pure control group, when excluding study subjects with repetitive drug usage.

Clinical subtypes of asthma might also differ in molecular etiology of the disease. However, in clinical practice the refined diagnostics are often forgotten since the treatment remains the same. In Finland adult asthma and COPD diagnostics and treatment is mainly performed in primary health care and only the patients who need

special diagnostic examinations or who have therapeutical challenges are referred to specialist care. This would lead to a more selected population, which would have more comorbidities and a heavier medication.

Using data on other, especially airway allergies we might find differentiate allergic asthma from non-allergic asthma in a more reliable way. Our analyses showed higher drug usage within non-allergic asthma. Mixed or unknown asthma will be interesting to analyse in future studies. Based on our approach there is approximate 35-40% asthmatics in mixed or unknown asthma.

Eosinophilic asthma is associated with high eosinophil count and IgE-level in blood. The analyses will benefit from the laboratory values, that will be included in the definitions in the future. In the present study, we do not have laboratory values available, and the group of eosinophilic asthma is most likely greatly underestimated.

Childhood asthma: Studies suggest that there are several phenotypes of asthma where the disease starts at later adult age [18]. These phenotypes usually are more severe and usually do not remit. Recent epidemiological studies have proposed that adult-onset disease, in fact, is very common. One previous study evaluated the genetics of adult-onset asthma and did not find marked differences, but it may be criticized on the definition of adult-onset disease. The age for childhood asthma was chosen to be <16 years for this study.

Obesity is a known risk factor for asthma. However, obesity diagnosis is rarely given if the patient is not morbidly obese. Sleep apnea is often associate with increased BMI, and metabolic and vascular diseases. This is concordant with our results, which found increased risk for DM2 and hypertension and vascular factors.

Interestingly, depression was most common in ACO-cohort (18,5%) followed with asthma cohort (17,5%) and lowest in COPD-cohort with 12,3%. The prevalence of depression in Health 2011 study in Finland was 7,4% [19]. Differences could in part be explained with the age difference between the groups and the difference in follow-up time. In COPD-cohort there were 81% over the age of 60 years, compared with 32% in asthma-cohort. ACO-cohort was set in the middle ground, with 61% being over 60 years. For comparing the comorbidities age and gender stratified results are needed.

Still there remains aspects to be explored, such as mixed or unknown asthma. Future studies will have the benefit of this groundwork.

In conclusion our study showed that in Finland using longitudinal health registries we can identify different obstructive airways entities, sort out certain asthma subpopulations, and find obstruction free control populations for genetic studies.

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