Tampere University

HEIDI ANDERSÉN

Determinants of Respiratory Health

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Determinants of Respiratory Health

ACADEMIC DISSERTATION
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Dedication

To my family

ABSTRACT

Respiratory symptoms and diseases are common, and behind them are numerous factors such as environmental exposures, habits, and genetics. Our aim was to analyse the impact of socioeconomic and physical determinants and individual behaviour on respiratory health at the population level by comparing language groups in Western Finland and childhood environments in Western and Southern Finland. With knowledge of the risk factors of respiratory diseases, there is a possibility to prevent the development of respiratory disease.

The study was based on the cross-sectional FinEsS postal survey sent in February 2016 to a random sample of 8,000 persons aged 20 to 69 years in Western and Southern Finland. The response rate was 52.5% in Western Finland and 50.3% in Southern Finland. Analyses comparing language groups included 3,864 subjects from the Western Finland cohort, of which 2,780 (71.9%) were Finnish speaking and 1,084 (28.1%) were Swedish speaking. Analyses comparing childhood environment included 3,767 subjects, of which 2,143 (56.9%) were exposed, and 1,624 (43.1%) were not exposed to childhood farming environment. Southern Finland survey was used to validate childhood environment comparisons and combined data from Western and Southern Finland for prevalence estimates and age-standardised prevalence rates.

Our study showed that Finnish speakers had a higher prevalence of dyspnoea mMRC ≥2 than Swedish speakers, meaning they had to walk slower than other people of their age on the level because of breathlessness. Dyspnoea mMRC ≥2 odds were higher with smoking and obesity, whereas native language or skill level did not increase the odds. Finnish speakers had higher body mass index (BMI); were physically inactive; smoked more often; had more frequent occupational exposure to vapours, gases, dust, or fumes (VGDF); and had lower socioeconomic status based on occupation than Swedish speakers.

Finnish speakers were more likely to be diagnosed with chronic obstructive pulmonary disease (COPD), diabetes, heart failure, reflux disease, chronic kidney disease, and painful conditions than Swedish speakers. Asthma prevalence was 11.5% in both language groups. The prevalence of multimorbidity was higher for Finnish speakers aged from 60 to 69 years than Swedish speakers. In younger age

groups, asthma prevalence was higher for Swedish speakers. Subjects who were smokers, obese, or physically inactive, and those with lower skill levels had higher odds for multimorbidity than others. We proposed a tool for patient education that describes the relationship among smoking, inactivity, and obesity to multimorbidity.

Those with childhood exposure to farming smoked less, exercised more, had lower socioeconomic status based on occupation, and had more occupational exposure to VGDF than those with non-farming childhood. Prevalence of allergic rhinitis was lower among those with childhood exposure to farming environment than those without this exposure. In contrast, prevalence of longstanding nasal congestion was higher in those subjects with farming than non-farming childhood environment. Childhood exposure to farming environment influenced the age at asthma diagnosis. The odds for asthma were lower before and higher after the age of 40 years with childhood exposure to farming environment.

Late-diagnosed asthma is associated with NSAID-exacerbated respiratory disease (N-ERD). Estimated prevalence of N-ERD was 1.4% in Finland. Heredity and cumulative exposure to smoking, passive smoking, or occupational exposure to VGDF were associated with higher odds for N-ERD. Childhood exposure to farming environment increased the age standardised rate of N-ERD by 1.2 times when compared to non-farming childhood environment.

To conclude, our research showed that both belonging to a language group or growing up in a farm was associated with behaviour, socioeconomic status, and environmental factors at a population level, and this affected the respiratory health. Respiratory health inequalities and preventable differences in outcomes do exist in our study populations. These differences might remain undetected when looking at disease prevalence of asthma or multimorbidity alone.

TIIVISTELMÄ

Hengitysteiden oireet ja sairaudet ovat yleisiä kansanterveydellisiä huolenaiheita. Niiden esiintyvyys on alati muuttuva johtuen muutoksista altisteissa, joita kohtaamme elämämme aikana. Tutkimuksen tavoitteena oli selvittää sosioekonomisten ja fyysisten tekijöiden sekä yksilön käytöksen merkitystä hengitysterveyteen väestötasolla vertailemalla kieliryhmiä Pohjanmaalla. Samoin vertaamalla lapsuuden kasvuympäristön merkitystä sekä Pohjanmaalla että pääkaupunkiseudulla.

Tutkimus perustui FinEsS kyselytutkimukseen, joka lähetettiin postitse helmikuussa 2016 satunnaisesti valitulle väestöotokselle (n=16000). Otoksen vastausosuus oli 52,5 % Pohjanmaalla ja 50,3 % pääkaupunkiseudulla. Kieliryhmien välisessä vertailussa Pohjanmaalla oli 2780 (71,9 %) suomenkielistä ja 1084 (28,1 %) ruotsinkielistä. Lapsuuden kasvuympäristön vertailussa oli 3767 aikuista, joista 2143 (56,9 %) oli kasvanut maatilalla ja 1624 (43,1 %) ei ollut altistunut lapsuuden maatilaympäristölle. Pääkaupunkiseudun otosta käytettiin varmistamaan lapsuuden kasvuympäristön yhteys astman sairastumisikään. Yhdistettyä Pohjanmaan ja pääkaupunkiseudun otosta käytettiin esiintyvyyden ja ikävakioidun esiintyvyyden vertailuun.

Tutkimuksessa osoitettiin, että suomenkielisillä oli enemmän hengenahdistusta kuin ruotsinkielisillä, kun hengenahdistuksen määritelmänä oli vastaus ≥2 dyspnea mMRC kyselyyn. Hengenahdistuksen todennäköisyys nousi tupakoinnin ja ylipainon myötä. Sen sijaan kieliryhmä tai ammatin perusteella arvioitu sosioekonominen asema eivät olleet yhteydessä hengenahdistuksen todennäköisyyteen. Suomenkielisillä oli keskimäärin korkeampi BMI, vähemmän fyysistä aktivisuutta, he tupakoivat useammin ja altistuivat useammin työssä pölyille, huuruille ja kaasuille. Lisäksi heidän sosioekonominen asemansa ammatin perusteella oli matalampi kuin ruotsinkielisillä.

Suomenkielisillä oli ruotsinkielisiä suurempi todennäköisyys sairastua keuhkoahtaumatautiin, sydämen vajaatoimintaan, diabetekseen, närästykseen, krooniseen munuaisten vajaantoimintaan ja krooniseen kipuun. Astman esiintyvyys oli 11,5 % molemmissa kieliryhmissä. Monisairastavuutta esiintyi enemmän suomen- kuin ruotsinkielisillä 60-69-vuotiaiden ikäryhmässä. Nuoremmissa ikäryhmissä

astman esiintyvyys ruotsinkielisillä oli suurempi kuin suomenkielisillä. Tupakoitsijoilla, ylipainoisilla, fyysisesti inaktiivisilla, ja matalan sosioekonomisen aseman omaavilla oli suurempi todennäköisyys monisairastavuuteen. Tutkimustulosten pohjalta ehdotimme potilasohjauksen työkalua, joka havainnollistaa tupakoinnin, liikkumattomuuden ja ylipainon välistä yhteyttä monisairastavuuteen.

Tutkimuksemme osoitti myös, että lapsuudessa maatilalla kasvaneet tupakoivat vähemmän, liikkuivat enemmän, heillä oli matalampi sosioekonominen asema ja enemmän työperäisiä altisteita kuin niillä, jotka eivät olleet kasvaneet maatilalla. Allergisen nuhan esiintyvyys oli alhaisempi maatilalla kasvaneilla. Sen sijaan, maatilalla kasvaneilla pitkäaikaisen nenän tukkoisuuden esiintyvyys oli korkeampi verrattuna vastaajiin ilman maatila-altistusta. Lapsuuden altistus maatilaympäristölle oli yhteydessä astman alkamisikään. Astman todennäköisyys oli matalampi ennen ja korkeampi 40 ikävuoden jälkeen maatilalla kasvaneilla.

Myöhemmällä iällä alkava astma liittyi tulehduskipulääkkeiden (NSAID) pahentamaan hengityselinsairauteen, NSAID-exacerbated respiratory disease (N-ERD). N-ERD:n arvioitu esiintyvyys Suomessa oli 1,4 %. Astman ja allergisen nuhan esiintyvyys suvussa sekä kumulatiivinen altistuminen tupakoinnille, passiiviselle tupakoinnille ja työperäisille altisteille lisäsivät N-ERD:n todennäköisyyttä. Maatilalla kasvaminen lisäsi N-ERD:n ikävakioidun esiintyvyyden 1,2-kertaiseksi verrattuna niihin, jotka eivät olleet kasvaneet maatilalla.

Yhteenvetona tutkimus osoitti, että kieliryhmään kuuluminen ja lapsuuden kasvuympäristö olivat yhteydessä käyttäytymiseen, sosioekonomiseen asemaan ja ympäristön altisteisiin väestötasolla. Lisäksi nämä kaikki vaikuttivat hengityselinterveyteen. Tutkimuksessa havaittiin hengityselinterveyteen liittyvää epätasa-arvoa ja ennaltaehkäistävissä olevia eroja sairastavuudessa vertailuryhmien välillä. Nämä erot esimerkiksi astman ja monisairastavuuden kohdalla olisivat voineet jäädä huomaamatta vain sairauksien esiintyvyyttä vertaamalla.

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ABBREVIATIONS

ACO	Asthma-COPD overlap
ACT	Asthma Control Test
AERD	Aspirin-exacerbated respiratory disease
ANOVA	Analysis of variance test
ASQ	Asthma Screening Questionnaire
BMI	Body mass index
BOLD	Burden of Obstructive Lung Disease study
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
COPD	Chronic obstructive pulmonary disease
COPD-DQ	COPD-Diagnostic Questionnaire
CRD	Chronic respiratory disease
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
DALY	Disability-adjusted life years
EAACI	European Academy of Allergy and Clinical Immunology
EDAC	Excessive dynamic airway collapse
EIB	Exercise-induced bronchoconstriction
EILO	Exercise-induced laryngeal obstruction
FEV1	Forced expiratory volume
FinEsS	Finland Estonia Sweden study
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Obstructive Lung Disease
GRRs	Generalized resistance resources
HR	Hazard ratio
HUNT	Trøndelag health study
ICS	Inhaled corticosteroids
ILC2	Innate lymphoid cells group 2
ISCO	International Standard Classification of Occupations
ISEI	International Socio-Economic Index

LABA	Long-acting beta2-agonist
LTRA	Leukotriene receptor antagonist
MET	Metabolic equivalent of task
miRNA	MicroRNA
N-ERD	NSAID-exacerbated respiratory disease
NSAID	Non-steroidal anti-inflammatory drug
OLIN	Obstructive Lung Disease in Northern Sweden
OR	Odds ratio
PAHO	Pan American Health Organization
PM	Particulate matter
PEF	Peak expiratory flow
ROC	Receiver operating characteristic
SABA	Short-acting beta2-agonist
SAAS	Seinäjoki Adult Asthma Study
SCAPIS	Swedish CardiopulmonarybioImage Study
SES	Socioeconomic status
T2	Type 2
Th2	T-helper 2 lymphocytes
TRAP	Traffic-related air pollution
VGDF	Vapours, gases, dust, and fumes
WHO	World Health Organisation
WSAS	West Sweden Asthma Study

ORIGINAL PUBLICATIONS

I Dyspnea has an association with lifestyle: differences between Swedish and Finnish speaking persons in Western Finland. Andersén H, Ilmarinen P, Honkamäki J, Tuomisto LE, Piirilä P, Hisinger-Mölkänen H, Sovijärvi A, Backman H, Lundbäck B, Rönmark E, Lehtimäki L, Kankaanranta H. Eur Clin Respir J. 2020;8(1):1855702. doi: 10.1080/20018525.2020.1855702.

II Multimorbidity in Finnish and Swedish speaking Finns; association with daily habits and socioeconomic status - Nordic EpiLung cross-sectional study. Andersén H, Kankaanranta H, Tuomisto LE, Piirilä P, Sovijärvi A, Langhammer A, Backman H, Lundbäck B, Rönmark E, Lehtimäki L, Ilmarinen P. Prev Med Rep. 2021;22:101338. doi: 10.1016/j.pmedr.2021.101338.

III Influence of Childhood Exposure to a Farming Environment on Age at Asthma Diagnosis in a Population-Based Study. Andersén H, Ilmarinen P, Honkamäki J, Tuomisto LE, Hisinger-Mölkänen H, Backman H, Lundbäck B, Rönmark E, Lehtimäki L, Sovijärvi A, Piirilä P, Kankaanranta H. J Asthma Allergy. 2021;14:1081-1091. doi: 10.2147/JAA.S323504.

IV N-SAID-exacerbated respiratory disease: a population study. Andersén H, Ilmarinen P, Honkamäki J, Tuomisto LE, Hisinger-Mölkänen H, Backman H, Lundbäck B, Rönmark E, Haahtela T, Sovijärvi A, Lehtimäki L, Piirilä P, Kankaanranta H. ERJ Open Res. 2021; 0:00462-2021. doi: 10.1183/23120541.00462-2021.

AUTHOR'S CONTRIBUTION

The author contributed to the planning of the study and data collection and enquired some financial resources needed for the study. The author made the study design for all publications with the assistance of supervisors and other authors. The author analysed the data with the help of supervisors. The author wrote the first draft, was a primary author on all publications and contributed to the final version of the papers. The author submitted the manuscripts to the journals and was corresponding author. The author planned all figures, the custom stick figure art with extended license was purchased from Leremy Gan.

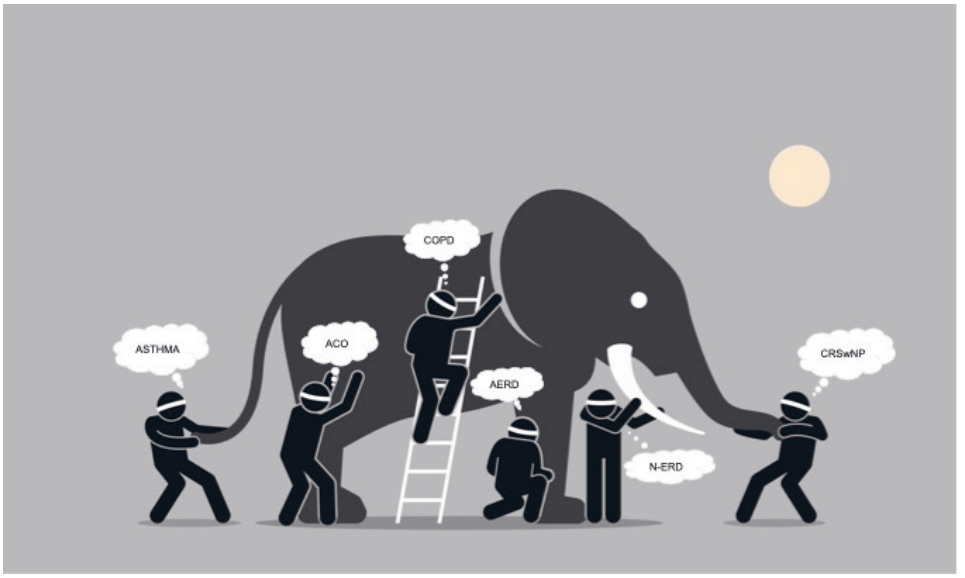
1 INTRODUCTION

Respiratory symptoms such as rhinitis, cough, and dyspnoea are common in the general population, and these symptoms are often associated with respiratory diseases. The risk factors of symptoms vary among populations. Validated questionnaires for symptoms and objective tests to diagnose respiratory diseases have improved the quality of care and have led to better understanding of respiratory diseases. The perception of asthma has changed from a rare disease that affects allergic children to serious global health problem affecting all age groups (GINA, 2021; Scadding, 1959). Asthma and COPD overlap (ACO), comorbidity, and multimorbidity increase with age and should be considered in those aged ≥40 years. One typical asthma phenotype in older adults is aspirin-exacerbated respiratory disease (AERD). This triad includes asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and nonsteroidal anti-inflammatory drug (NSAID)-induced dyspnoea. A new definition of NSAID-exacerbated respiratory disease (N-ERD) was introduced in 2019 (Kowalski et al., 2019a), and it is broader than AERD. These upper and lower respiratory tract diseases and definitions overlap, and some researchers have conceptualised treatable traits for older patients given the significant overlap between diseases using current definitions (Gibson et al., 2010).

Parallels can be drawn between respiratory epidemiology and the tale of the blind men and an elephant, one of the earliest versions of the story is described in Buddha Udana 6.4. In the story, six blind men touch different parts of a new animal, an elephant (Figure 1) and attempt to conceptualise the creature. The moral of the story is that humans tend to claim absolute truth based on their limited experience, although the other perception might be equally valid. Like these blind men, respiratory researchers have different beliefs, opinions, impressions, ideas, and interpretations towards asthma, COPD, or N-ERD. As new knowledge arises, the research community should be willing to change their perception of the concept of chronic respiratory disease.

This thesis aims to bring different views together and weigh the latest definitions and overlaps. The concepts of comorbidity and multimorbidity are in focus. The childhood environment; of non-farming versus farming exposure are of main

environmental interest. Cumulative smoke and occupational exposure are behavioural and environmental factors associated with respiratory diseases and are of study interest. The infographics used throughout the thesis are meant for respiratory researchers and physicians to explain the findings to the public.



Stick figures Leremy Gan

Figure 1. Respiratory epidemiology has parallels to the tale of the six blind men and an elephant. Correct and timely diagnosis is a basis for good treatment outcomes, and consequently, health care is one of the determinants of respiratory health.

2 LITERATURE REVIEW

2.1 Respiratory symptoms

How respiratory symptoms are enquired about in surveys, and which symptoms are considered asthma and COPD related can be dated back to a questionnaire among 192 male and 192 female post office employees in London (Fletcher et al., 1959). The early chronic bronchitis and asthma definitions from the same year described typical symptoms for these diseases, such as cough, breathlessness, and wheezing (CIBA, 1959; Scadding, 1959). It is considered that if a person has more than one respiratory symptom, the odds for respiratory disease increase (GOLD, 2021). Even if respiratory symptoms are included in definitions, the symptoms are not disease-specific (GINA, 2021; GINA & GOLD, 2017; GOLD, 2021). In a recent EpiLung study, the odds for physician-diagnosed asthma were highest for the question on asthma symptoms during the last 12 months; this included intermittent attacks or periodic breathlessness, with or without cough or wheezing/whistling in the chest. However, the odds for COPD were higher with recurrent wheezing, sputum production, chronic productive cough, and dyspnoea (Axelsson et al., 2020). A previous study reported undiagnosed airflow obstruction due to asthma or COPD in 20% randomly selected individuals who reported having respiratory symptoms (Preteroti et al., 2020).

Respiratory symptoms can exist without respiratory disease, but they do increase with disease and are more common among women. In the burden of obstructive disease (BOLD) study, any respiratory symptom such as dyspnoea, cough, productive cough, or wheezing, was reported by 43% subjects with normal lung function, and 91% subjects with very severe COPD (Lamprecht et al., 2013). Among subjects without respiratory disease females reported symptoms almost twofold than males, but there was no sex-based difference in reporting symptoms among subjects with respiratory illness. In the Finland-Estonian-Sweden study (FinEsS), female subjects reported more symptoms from passive smoke exposure than male subjects (Larsson et al., 2003). A possible explanation from neurobiological studies is that women have a higher intrinsic sensitivity to noxious somatic sensations, like dyspnoea (Becklake & Kauffmann, 1999).

Respiratory symptoms are common in the general population. A structural interview from the 1996 FinEsS survey reported that 66%, 65%, and 54% subjects from Finland, Estonia, and Sweden, respectively, had respiratory symptoms, and these symptoms affected daily living and increased health care consumption (Axelsson et al., 2016). Between 2008 and 2016 the prevalence of several respiratory symptoms increased in Sweden with 1-2% (Borna et al., 2019). In contrast to the high prevalence rates in the FinEsS study, the Swedish CardiopulmonarybioImage study (SCAPIS) reported that in an adult population aged 50-64 years, only 13.3% had any respiratory symptom (Torén et al., 2021).

Several factors are associated with respiratory symptoms. Longstanding cough has been associated with presence of chronic rhinitis or oesophageal reflux disease (Koskela et al., 2017). Smoking was a risk factor for respiratory symptoms (Jannus-Pruljan et al., 2004; M. Lindström et al., 2001). Smoke from vehicular traffic at low levels of exposure was related to an increased risk of wheezing among children (Andersson et al., 2011). In a recent review, indoor and outdoor pollutants were associated with respiratory symptoms (Tiotiu et al., 2020). Manual workers belonging to a low socioeconomic group had higher odds ratio (OR) of 1.9 for respiratory symptoms (Pallasaho et al., 2004), and these symptoms were associated with occupational exposure to vapours, gases, dust, and fumes (VGDF) with ORs of 1.2-3.5 depending on the symptom and exposure (Abrahamsen et al., 2017). Occupational exposure to pesticides was associated with respiratory symptoms (Mamane et al., 2015). Exercise is known to transiently narrow the airways, in exercise-induced bronchoconstriction (EIB) in asthma. Either EIB or exercise-induced laryngeal obstruction (EILO) might cause almost half of the exercise-induced symptoms, with an estimated prevalence of 19.2% of EIB and 5.7% of EILO in the adolescent population (Johansson et al., 2015). EILO may be easily misdiagnosed as asthma. To which extent tracheobronchomalacia and excessive dynamic airway collapse (EDAC) imitate asthma and COPD symptoms remains unclear (Murgu & Colt, 2006). Additionally, obesity causes changes to the lung and chest wall mechanics, and these can cause respiratory symptoms such as dyspnoea, wheezing, and airway hyperresponsiveness (Dixon & Peters, 2018). Obesity increases symptom burden and reduces lung function and asthma control in adult patients with asthma (Klepaker et al., 2019). In children, obesity seems to increase respiratory symptoms and asthma risk, but impairs lung function to a lesser extent (Aguirre et al., 2019). Early-onset asthma and wheezing may increase the risk of developing obesity in later childhood (Contreras et al., 2018).

Furthermore, respiratory symptoms are associated with increased risk of mortality in adults and in both sexes (Backman et al., 2020). A previous Trøndelag health study (HUNT) reported that lung function was inversely associated with all-cause and cardiovascular mortality. The only respiratory symptom independently associated with all-cause mortality was Modified Medical Research Council Dyspnoea Scale (mMRC) ≥2 (Leivseth et al., 2014) that has been associated with higher mortality in other studies (Backman et al., 2020; Casanova et al., 2015; Whittaker et al., 2021). Moreover, dyspnoea mMRC 2 question, "On a level ground, I walk slower than people of the same age because of breathlessness," is easy to understand. The translations are cross-culturally validated, and within the question, breathlessness is adjusted to age. The mMRC score correlates to airway structure assessed by computed tomography in COPD (Yasui et al., 2019).

Furthermore, the mMRC reflects physical activity and sedentary behaviour better than the COPD Assessment Test (CAT), one of the multiple tools used to assess asthma and COPD patients' respiratory symptoms and health status (Munari et al., 2018). When comparing the association with health care utilization, CAT and mMRC were equal (Cheng et al., 2019). Patients with COPD and ACO reported higher CAT scores than those with asthma (Kurashima et al., 2016). Consequently, CAT scores and severity of airflow obstruction are associated (Ghobadi et al., 2012). CAT has been validated against the Clinical COPD Questionnaire (CCQ) (Tsiligianni et al., 2012) and the Asthma Control Test (ACT) has been compared against the Asthma Control Questionnaire (ACQ). The ACT score relates to lung function and asthma-related quality of life (van Dijk et al., 2020). In conclusion, questionnaires are useful but neither asthma nor COPD are diseases that should be diagnosed based solely on symptoms.

2.2 Chronic respiratory diseases

The WHO uses the umbrella term chronic respiratory disease (CRD), which includes asthma and COPD (Figure 2). Nearly 545 million individuals representing 7.4% of the world's population, currently live with CRD (Soriano et al., 2020). The prevalence increased between 1990 and 2017, but both age-standardized mortality and disability-adjusted life-years declined (Soriano et al., 2020). Asthma accounted for nearly 70% of the total CRD burden and together with COPD contribute to a large proportion of the CRD burden (Xie et al., 2020).

Asthma and COPD likely represent a continuum of different diseases that may share biological mechanisms and present similar clinical features, and these treatable traits require individualised treatment (Agusti et al., 2016). Endotype refers to the molecular and cellular pathways involved in pathogenesis, and phenotype includes the clinical, functional, imaging, and biological features that can be observed (Agusti et al., 2016).

Stick figures Leremy Gan

Figure 2. Not all wheezing is asthma and fits under the umbrella term of chronic respiratory disease (CRD). Asthma is present across all ages, sizes, races, social classes, and both sexes. The risk for COPD is higher with prolonged exposure to smoke and occupational exposures and is seldom diagnosed in patients <35 years of age. Symptoms are common in population, and multiple symptoms increase the odds for CRD. Objective diagnostics are needed for accurate CRD diagnosis.

Some studies have identified treatable traits in CRD, and these traits are divided into pulmonary, extrapulmonary, or lifestyle categories. These traits should be clinically relevant, identifiable, measurable, and treatable (McDonald, Hiles, et al., 2019; McDonald, Osadnik, et al., 2019). The current opinion is to use diagnostic labels and include precise endotype, phenotype, and lifestyle needing action to the label (Chung et al., 2014).

The definitions of asthma and COPD are harmonized, and researchers have collectively decided to follow the latest definitions of the Global Initiative for Asthma (GINA) and Global Initiative for Obstructive Lung Disease (GOLD). Asthma and COPD definitions certainty differ in one aspect. Airflow limitation and symptoms are variable in asthma, but more persistent in COPD. Before these harmonisations there was an active academic debate. In 1961, Orie et al. from the Netherlands, proposed that asthma, chronic bronchitis, and emphysema should be considered a single entity with common genetic origins. This theory subsequently became known as the 'Dutch hypothesis', and the term CRD was introduced to describe this single airway disease (Postma et al., 2015; Sluiter et al., 1991). The Dutch hypothesis was vigorously opposed by researchers in the United Kingdom and the United States. They argued that asthma and chronic bronchitis/emphysema were distinct diseases with different causal mechanisms (Barnes, 2006). Both viewpoints are considered to be partly true, and this argument is discussed with new evidence in the following chapters.

2.3 Asthma

Asthma was redefined in 2021 as *a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.* (GINA, 2021). Asthma affected an estimated 262 million people and caused 461,000 deaths in 2019 (Abbafati et al., 2020). The asthma prevalence estimates are 1-18% of the population worldwide (GINA, 2021) and 11% in Finland (Hisinger-Mölkänen et al., 2019; Honkamäki et al., 2019). The prevalence of asthma in Finland has doubled in the past 20 years. In 1996, the prevalence was 2-8% in the FinEsS study (J. Hedman et al., 1999; Kotaniemi et al., 2002; Pallasaho et al., 2002). The prevalence of physician-diagnosed asthma increase has levelled since 2006 in Helsinki (Hisinger-Mölkänen et al., 2019). However, in Sweden, the growth continued between 2006 and 2016 (Backman et al., 2017). In Sweden, allergic asthma increased from 5.0% to 7.3%, while non-allergic asthma remained stable at 3.4-3.8% during the last 20 years (Backman et al., 2017). Other studies have reported an increase in asthma incidence and a decrease in the age of asthma diagnosis, indicating a change in the asthma phenotype (Radhakrishnan et al., 2014). The prevalence of physician-diagnosed asthma decreased with increasing age in Norrbotten, Västra Götaland, and Helsinki. In contrast, the decrease was followed

by an increase among the eldest age group in Seinäjoki-Vaasa in a 2016 study (Axelsson et al., 2020). In Finland, the prevalence of asthma is high in elderly women, and a most newly diagnosed cases also belong to this population (Kankaanranta et al., 2017).

The incidence of allergic asthma was highest in early childhood (1.8/1000/year) and steadily decreased with advancing age (0.6/1000/year) (Pakkasela et al., 2020). In contrast, the incidence of non-allergic asthma is low (0.7/1000/year) until it peaks in mid-thirties (2.4/1000/year) (Pakkasela et al., 2020). The remission rate of asthma was higher in those diagnosed at a younger age (30.2%) than those diagnosed at an older age (5%) (Honkamäki et al., 2020). In Denmark, asthma incidence and pre-existing symptoms were equally common in younger and older adults. Still, lung function was more reduced at pre-diagnosis and declined more rapidly in older adults (Porsbjerg et al., 2015). Further, bronchodilator response at diagnosis in steroid-naïve asthma patients was constant over an extensive age span (Tommola et al., 2020). To conclude, the proportion of clinical asthma phenotypes differs with the age at asthma diagnosis, and the age at diagnosis relates to prognoses.

2.3.1 Asthma phenotypes

Interaction between environment and genetics produce phenotypes, observable characteristics, or traits. Asthma cluster analyses have changed our understanding of asthma from a homogenous to heterogeneous disease (Wenzel, 2012). Researchers have recognized several overlapping clusters with unsupervised clustering (W. Wu et al., 2014). The Seinäjoki Adult Asthma Study (SAAS) in Western Finland identified five adult asthma clusters, namely (1) predominantly non-rhinitic and nonatopic males with moderate smoking history, (2) older men with heavy smoking history, poor lung function, and persistent obstruction at baseline, who were mostly uncontrolled during follow up, (3) mostly non-smoking symptomatic females with good lung function, (4) obese and symptomatic patients with several comorbidities, and (5) youngest adult-onset group who were mainly atopic with eosinophilic inflammation (Ilmarinen et al., 2017).

Instead of extensive clustering of over 100 variables in 10 categories, some studies have looked at only one behavioural or environmental aspect. Recent publication divided asthma into four phenotypes based on extrapulmonary treatable traits and higher levels of sedentary time, female sex, and anxiety symptoms were associated with increased odds of exacerbation (Freitas et al., 2021). Furthermore, an attempt

to cluster patients based on asthma triggers found different categories, as not all patients react the same way to exposure (Coumou et al., 2019). Asthma symptoms can be triggered by pollution, physical exercise, allergens, moulds, and chemicals. Infections are a common cause of exacerbation of CRDs, which especially increase the hospital burden during flu season. Rhinovirus infection is associated with later atopic asthma and respiratory syncytial virus with later nonatopic asthma with unclear causality (Jartti & Gern, 2017). Behaviour and environment affect asthma phenotype and they have an impact on the immune system and thus asthma endotype.

2.3.2 Asthma endotypes

Patients in one clinical phenotype can have distinct endotypes and these influence the outcomes. Endotypes have a distinct functional or pathological mechanism such as immunity. The immune system has optimized its response to distinct microbes (Figure 3.). The innate and adaptive immune systems converge into type 1 (T1), type 2 (T2), and type 3 (T3) immunity (Annunziato et al., 2015). An allergic response includes an initial complex sensitisation step and T2 polarisation followed by acute antibody recognition (Soh et al., 2019). The generation and maintenance of allergen-specific regulatory T cells (Tregs) and regulatory B cells (Bregs) are essential for the induction of allergen tolerance. (Palomares et al., 2017). These mechanisms fail in allergic asthma. Persistent airway T2 inflammation is a complex construct of innate and adaptive immunity gene expression networks (Peters et al., 2019). T2 immunity plays a crucial role in the pathogenesis of allergic and non-allergic eosinophilic asthma (Coverstone et al., 2020).

T2-high severe asthma can be predicted from raised levels of FeNO, blood, and sputum eosinophil counts (Pavlidis et al., 2019). Interleukin transcripts such as IL-4, IL-5, and IL-13 can be detected in sputum (Rijavec et al., 2021). Immunity is important for treatment choice, and several treatment options are available for T2-asthma. It is reasonable to not increase glucocorticosteroids in patients who do not have apparent T2 inflammation (Sze et al., 2020).

The same clinical asthma phenotype can have T2 or non-T2 inflammation (Han et al., 2021). In severe asthma, sputum-based inflammatory division showed 30% paucigranulocytic, 19% neutrophilic, 33% eosinophilic, and 19% mixed inflammatory profiles (Tanaka et al., 2021). The study used cut-off eosinophils ≥3%, and based on that criteria, half of the patients had T2 immunity. The mixed

inflammatory profile might be due to swift from T2 to T1 immunity associated with autoimmunity or infection.

The perinatal period is critical for the distribution of tissue resident innate lymphoid cells (ILC) within developing organs (Schneider et al., 2019). A phenomenon termed layered ontogeny that seems to play a role in the ILC pool residing in each tissue is the result of waves of development from foetal to adult life and may include different ILC subsets (Meininger et al., 2020). ILC plasticity has been demonstrated in humans (Colonna, 2018). The conversion from ILC2 or ILC3 to ILC1 requires inflammatory cytokines like IL-1b, IL-12, IL-15, and IL-23 and ILC plasticity is likely influenced by infections and autoimmunity (Colonna, 2018). In severe asthma, the sputum microbiome commensal-deficient bacterial profile has been reported to be associated with worse outcomes (Abdel-Aziz et al., 2021).

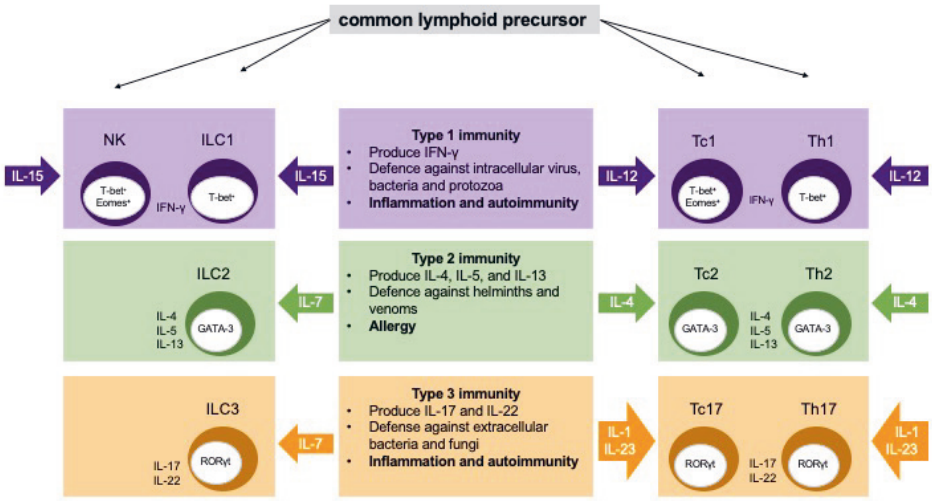


Figure 3. The major types of innate and adaptive cell-mediated immunity. Modified from Annunziato 2015. NK=natural killer cells, ILC=innate lymphoid cells, Tc=CD8+ cytotoxic T cells, Th=CD4+ helper T cells, IL=interleukin, transcription factors used to divide cells: Tbet, Esmet, GATA-3, and RORγt.

Thus far, no easy method is available to measure T1 or T3 immunity in clinical asthma studies; therefore, unspecific terms like non-T2 or T2-low are used instead of specific immunity types. Late-onset asthma is often considered mainly T2-low asthma with activation type 1 or type 3 immunity. Activation of Th1 and Th17 cells leads to neutrophil activation, and both T2 and non-T2 inflammatory pathways lead to airway remodelling (Annunziato et al., 2015). In severe neutrophilic asthma,

neutrophil extracellular traps and inflammasome activation likely play a role, together with Th1, Th17 and several other cytokines including IL-6 and IL-17 (Hudey et al., 2020). In paucigranulocytic asthma, several mechanisms lead to the uncoupling of airway hyperresponsiveness and remodelling (Hudey et al., 2020). Further, obesity-related asthma might more often be non-T2 asthma (Rastogi, 2020). Different asthma phenotypes are shown in relation to age at asthma diagnosis and inflammatory type in Figure 4.

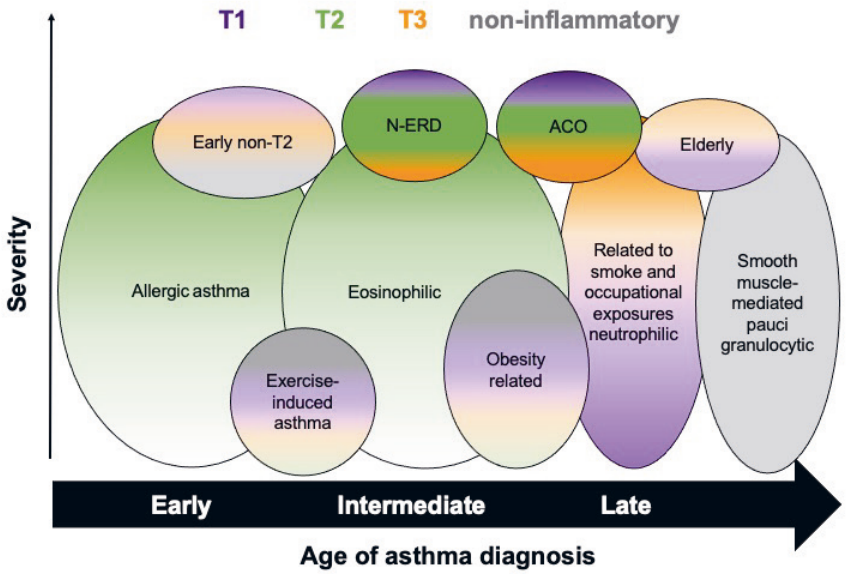


Figure 4. Asthma phenotypes in relation to age of asthma onset and endotype, as suggested by Wenzel 2012 and further modified according to new information by Hudey et al 2020, Rastogi et al 2020, and Honkamäki et al 2020. Phenotypes, endotypes and age at asthma diagnosis are updated from original to current knowledge

2.4 Asthma COPD overlap

ACO shares features with both asthma and COPD (GINA & GOLD, 2017). Because ACO likely includes several different clinical phenotypes and underlying mechanisms, it is not a definition. There is a discordance between patient populations defined by other diagnostic criteria for ACO (Barczyk et al., 2019). In recent meta-analyses, the pooled prevalence of ACO was 2% in the pooled global population (Hosseini et al., 2019). To limit ACO diagnose to those with asthma

diagnosed before age of 40 years and COPD diagnosed after the age of 40 years have been proposed (Sin et al., 2016). ACO might be underdiagnosed if an age limit of 40 years is used for asthma diagnosis (Tommola et al., 2017). ACO was associated with an increased number of hospitalisations, and more extended hospital stays than the asthma and COPD groups (Andersén et al., 2013). The ACO group had more symptoms, worse lung function, and a higher risk for exacerbations and hospitalisations (Menezes et al., 2014). The ACO is associated with low quality of life (Alshabanat et al., 2015; Kauppi et al., 2011).

2.5 COPD

COPD is defined as *a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development. Significant comorbidities may have an impact on morbidity and mortality.* (GOLD, 2021). COPD has a global prevalence of 11.7% (8.4%-15.0%), with an estimated 384 million cases worldwide (Adeloye et al., 2015). COPD is estimated to be the fourth most common cause of death and will likely cause 7.8% of all deaths by 2030 (Mathers & Loncar, 2006). Although the diagnostic criteria and definitions of COPD have changed several times in the past, they have been relatively constant during the last 15 years. COPD consists of chronic bronchitis, emphysema, and chronic obstructive disease. The latter is defined with and post-bronchodilator fixed FEV1/FVC < 0.70 (GOLD, 2021). The FEV1/FVC ratio may overstate illness in elderly patients, but its discriminative accuracy relates to hospitalizations and mortality (Bhatt et al., 2019). In comparison, based on symptoms, higher fixed ratio <0.80 might be justified (Torén et al., 2021). The percentage of predicted FEV1 is used to assess airflow limitation: mild GOLD 1, ≥80%; moderate GOLD 2, 50-79%; severe GOLD 3, 30-49%; and very severe GOLD 4, <30% (GOLD, 2021).

COPD is underreported and underdiagnosed: only half of the patients reported a physician-diagnosis consistent with COPD (Lindberg et al., 2006) and even greater underdiagnosis has been reported (Lindberg et al., 2005). The prevalence of GOLD-COPD was as follows: mild, 8.2%; moderate, 5.3%; severe, 0.7%; and very severe, 0.1%; all subjects with severe COPD were symptomatic (Lindberg et al., 2006). The prevalence of physician-diagnosed chronic bronchitis was markedly higher at 11% in Tallinn than 3-4% in Finnish and Swedish centres in the FinEsS 1996

questionnaire (J. Hedman et al., 1999; Kotaniemi et al., 2002; Pallasaho et al., 2002). In the 2006 FinEsS cohort, the COPD prevalence and symptoms remained at the same level in Helsinki (Kainu et al., 2016). The latest FinEsS survey 2016 reported a lower prevalence of 2-3% in four centres in Sweden and Finland (Axelsson et al., 2016). In the FinEsS 1995 Estonian survey, the non-Estonian minority smoked more and often had more symptoms and were diagnosed with chronic bronchitis than Estonian majority. The asthma prevalence of 2% was identical in both ethnic groups (Jannus-Pruljan et al., 2004).

COPD is a multifaceted entity, where classic phenotypes of emphysema such as "pink puffer" and chronic bronchitis such as "blue bloater" have changed to more treatment-driven groups (Dornhorst, 1955; Miravitlles et al., 2013). The COPD exacerbator phenotype refers to patients with two or more exacerbations annually (Hurst et al., 2010). Airflow limitation, low body mass index (BMI), age, and clinical manifestations such as dyspnoea, exacerbations, and hospitalisations together with comorbidity were associated with mortality (Burgel et al., 2017). Since 2011 GOLD has determined four clinical severity groups of COPD. These groups consider airflow limitation, symptoms, and exacerbation rate. A cut-off point for severe symptoms can be either mMRC ≥2 or CAT ≥10, and a limit for moderate to severe exacerbations can be either two exacerbations per year or one leading to hospital admission.

COPD is associated with T1 and T3 immunity, neutrophil inflammation, activation of the inflammasome, and activation of Th1 and Th17 cells. T2 immunity with eosinophilic inflammation is present in symptomatic and severe cases with rapid lung function decline with observed autoimmunity and chronic inflammation. Corticosteroids are effective in those with evidence of eosinophilic inflammation, whereas the response to anti-interleukin-5 biologicals is limited (Ponce-Gallegos et al., 2017; Weaver et al., 2013).

2.6 Allergic rhinitis and chronic rhinosinusitis

In urban Helsinki, the prevalence of allergic sensitisation was 46.9% when measured with at least one positive skin prick test (SPT). The prevalence was 56.8% in the age group of 26-39 years, and 35.6% in the age group of 50-60 years (Pallasaho et al., 2006). The sensitisation rate in Finnish young adults was higher than in children in Northern Sweden. Moreover, the Northern Sweden prevalence of any positive SPT

increased from 21% in 1996 to 30% in 2006 in children aged 7-8 years (Rönmark et al., 2009).

Sensitisation to multiple allergens has been reported to double the risk of allergic rhinitis, conjunctivitis, wheeze, and asthma in Finland (Pallasaho et al., 2006). The FinEsS study reported a prevalence of 41.6% of physician-diagnosed allergic rhinitis and 4.4% of nasal polyposis in 1996 in Southern Finland (J. Hedman et al., 1999). Nasal blockage, rhinitis, and symptoms of chronic rhinosinusitis were associated with multi-symptom asthma (Lötvall et al., 2010). In comparison, non-infectious rhinitis was associated with early-onset COPD but not with late-onset COPD (Bergqvist et al., 2020). Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterised by tissue eosinophilia and high local IgE levels; hence, lower airway comorbidities such as asthma share similar pathophysiology (Laidlaw et al., 2021). Patients with CRSwNP show a type 2 immune signature and often have severe and recurrent disease (Laidlaw et al., 2021).

2.7 AERD and N-ERD

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may exacerbate respiratory symptoms in sensitive individuals. Samter and Beers described a triad of aspirin-induced dyspnoea, asthma, and rhinosinusitis with nasal polyps in 1968 and later a term called aspirin-exacerbated respiratory disease (AERD) was used (Samter & Beers, 1968). Recently, a new definition of NSAID-exacerbated respiratory disease (N-ERD) was introduced by The European Academy of Allergy and Clinical Immunology (EAACI) (Kowalski et al., 2019a). According to the definition, *"N-ERD is a chronic eosinophilic inflammatory disorder of the respiratory tract occurring in patients with asthma and/or rhinosinusitis with nasal polyps (CRSwNP), whose symptoms are exacerbated by NSAIDs, including aspirin"* (Kowalski et al., 2019a). The definitions of AERD and N-ERD are not interchangeable, although the disease mechanism is the same. N-ERD includes a subgroup of patients with rhinosinusitis whose symptoms are exacerbated by NSAIDs. This subgroup is not included in AERD.

The NSAID-induced dyspnoea prevalence is reportedly 1.9% in a European multicentre study, 1.2 % in Finland, and 1.3% in Sweden (Eriksson et al., 2015; J. Hedman et al., 1999; Makowska et al., 2016). In another multicentre study, the prevalence was reported to be the lowest in the city of Skopje (0.9%) and highest in the city of Katowice (4.9%), suggesting an environmental role in pathogenesis (Makowska et al., 2016). Hypersensitive individuals present with upper and/or lower

airway symptoms, usually within 30-180 min after ingestion of aspirin or other NSAIDs (Eastman et al., 2017; Kowalski et al., 2019b). The reaction in N-ERD is most often due to the drug's pharmacological effect, i.e., inhibition of the cyclooxygenase (COX)-1 enzyme (Wöhrl, 2018). However, NSAIDs reactions can seldom be true immunologically mediated allergies against a single NSAID (Doña et al., 2018; Kowalski et al., 2019b; Wöhrl, 2018).

Most of the epidemiological data come from AERD studies. The pathological mechanism involves chronic immune dysregulation, T2 immunity with eosinophils, mast cells, ILC2 infiltration, and genetic variation in arachidonic acid metabolism (Dahlin & Weiss, 2016; Eastman et al., 2017; Kowalski et al., 2019b). AERD risk factors were family history of AERD, occupational exposure to VGDF, and smoke exposure (Bavbek et al., 2012; Chang et al., 2012; Eriksson et al., 2015). NSAID hypersensitivity may occur before the onset of apparent respiratory disease (Kowalski et al., 2019b) and upper airway symptoms might precede asthma by 1-5 years in N-ERD (Stevenson & Szczeklik, 2006). Upper airway disease in N-ERD is usually CRSwNP (Fokkens et al., 2020a). The onset of symptoms is in the third to fourth decade of life in subjects with AERD (Szczeklik et al., 2000).

2.8 Comorbidity and multimorbidity

The following example tries to clarify the terms and their pitfalls for the reader. *An over 40 years old smoker exposed to occupational exposures in their factory work has CRSwNP, NSAID-hypersensitivity, asthma, and COPD. The overlaps could be called ACO and N-ERD in this case. Comorbidities for asthma are CRSwNP, NSAID-hypersensitivity, and COPD.* The patient has multimorbidity because of morbidity count ≥2. Or should the upper and lower respiratory tract diseases be grouped as manifestations of the same united airway disease and counted as one?

Newly diagnosed CRD is associated with many comorbidities, asthma to a lesser extent than COPD due to younger age distribution. For example, relative risk of cardiovascular comorbidities was 1.9 times in COPD and 1.4 times in asthma when compared to patients without CRD (Soriano et al., 2005). These conditions may; influence CRD control, its phenotype, and response to treatment; and be more prevalent in CRD patients but without evident influence on this disease (Boulet & Boulay, 2011). Diseases aggregate modules with meaningful syndromic associations; and an influential group of highly related comorbidities (Divo et al., 2015).

Comorbidities are more frequent in severe asthma than in mild-to-moderate disease (Rogliani et al., 2020). Questionnaires can be used to detect comorbidities in severe asthma (Radhakrishna et al., 2017). Severe asthma and asthma with comorbidities are different, although respiratory symptoms may be caused by comorbidities which are associated with asthma (Brussino et al., 2018). The effects of obesity are inconsistent in literature, but obesity likely affects respiratory symptoms and possibly asthma pathogenesis (Contreras et al., 2018; Holguin et al., 2011; Klepaker et al., 2019; Rastogi, 2020). Moreover, treatment of asymptomatic gastroesophageal reflux does not improve asthma control (Boulet & Boulay, 2011; Kauppi et al., 2015). Patients with asthma are more likely to develop osteoporosis than the general population due to oral and inhaled corticosteroids with hazard ratio (HR) of 1.12 (Chalitsios et al., 2021). It has been suggested that asthma and anxiety disorders might be associated (Katon et al., 2004). For example, asthma patients with allergies seem to have more anxiety and depression than asthma patients without allergies (Blöndal et al., 2021).

Comorbidity prevalence does not always correlate with severity of CRD (Singhvi & Bon, 2021). Low-grade systemic inflammation is mostly comparable among comorbidity clusters (Vanfleteren et al., 2013). Systemic inflammation may initiate or worsen comorbid diseases such as ischaemic heart disease, heart failure, osteoporosis, normocytic anaemia, lung cancer, depression, and diabetes (Barnes & Celli, 2009). Prevalence of depression and anxiety in COPD are generally reported to be higher than in other advanced chronic diseases (Maurer et al., 2008). Elevated Charlson Comorbidity index (CCI) of 3-4 increased odd ratios (OR 1.24) of 30-day readmission, mortality, and delivery of fewer treatments known to be beneficial among patients with COPD exacerbation (Spece et al., 2018). The CCI is the most extensively studied co-morbidity index for predicting mortality and is useful in clinical studies (de Groot et al., 2003).

Multimorbidity means co-occurrence of more than two health conditions in an individual, and most studies use disease counts (Nguyen et al., 2019). Multimorbidity is associated with a negative circle to functional impairment, limitations in mobility, cognition, and strength (Singer et al., 2019). In addition, multimorbidity is related to frailty in older adults (Vetrano et al., 2019). Multimorbidity is especially relevant for respiratory physicians. A longitudinal study found that among patients with a single disease, those with asthma (HR 1.33) or COPD (HR 2.32), had the highest risk of developing multimorbidity during the 10-year follow up (Mounce et al., 2018). Multimorbidity in asthma patients is associated with polypharmacy, allergy, and metabolic syndrome, and these were related to poor asthma prognosis (Chanoine et

al., 2018). Most, 81.9% of newly diagnosed COPD patients had co-existing diseases at the time of diagnosis (Ajmera et al., 2015). Polypharmacy i.e., taking ≥3 medications, is associated with adverse events like falls in COPD patients (Hanlon et al., 2018). COPD, type-2 diabetes, and atherosclerosis share the same risk factors, and neutrophil inflammation might be a common therapeutical and preventive target (Hughes et al., 2020).

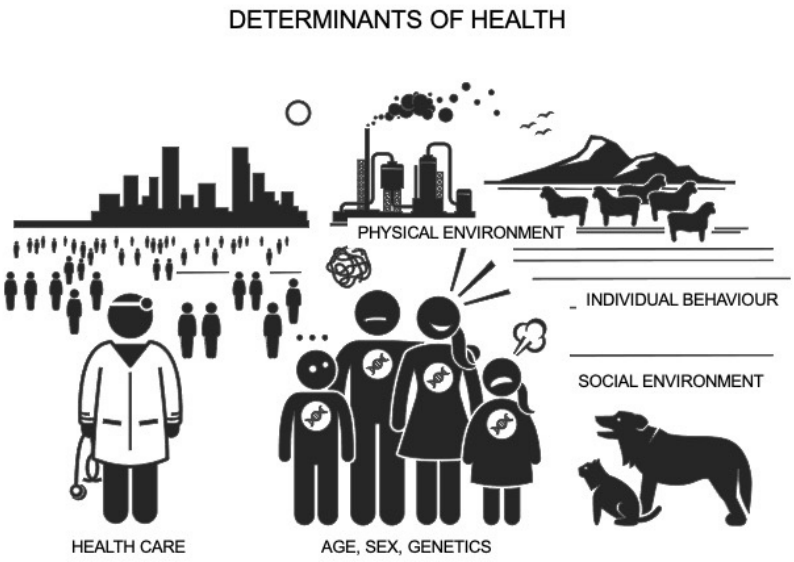
A healthy lifestyle in relation to BMI, smoking status, alcohol intake, physical activity, and Mediterranean diet is inversely associated with multimorbidity of cancer and cardiovascular disease (HR 0.75) (Freisling et al., 2020). Low socioeconomic status, older age, and female sex are associated with multimorbidity (Marengoni et al., 2011; Sakib et al., 2019). The risk of multimorbidity at a younger age was higher in more deprived areas (Barnett et al., 2012). Health inequalities for complex multimorbidity and limitations were more significant (Singer et al., 2019).

Multimorbidity is an emerging health priority. Multimorbidity increases health care utilisation (Cassell et al., 2018) and affects the overall quality of life (Fortin et al., 2004). A multidisciplinary approach to treat patients, not just the condition, is recommended with a focus on identifying individuals' preferences and goals (Forman et al., 2018). The treatment should be tailored within the context of an individual's health risks, conditions, and objectives (Tinetti et al., 2012). For a successful treatment plan, individuals' determinants of health should be considered before shared decision-making and before treatment alternatives are discussed.

2.9 Determinants of respiratory health

The constitution statement of WHO defines health in the following way '*Health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity*' (WHO, 1948). The statement conceptualises health as much as a social construct as a biological characteristic that is the product of a complex interaction of factors at both the individual and population levels. '*Every human being without distinction of race, religion, political belief, economic or social condition should enjoy the highest attainable standard of health'* (WHO, 1948).

During a pandemic, it is easy to understand that health is a global priority. Health is influenced by interconnecting factors, which may generally be organized into categories known as determinants of health: health care, social environment, physical environment, individual behaviour, and genetics (Figure 5). The social determinants of health encompass socioeconomic conditions that influence the health of people and communities (WHO, 2008). The virtual world has changed our lives and might change traditional social determinants of health (Rice & Sara, 2019).

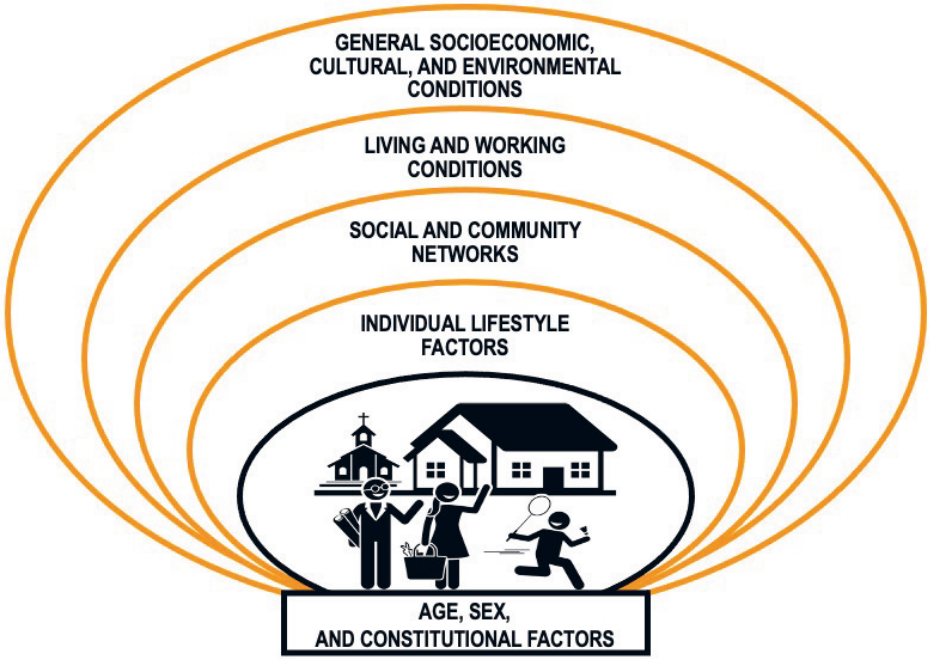


Stick figures Leremy Gan

Figure 5. Determinants of health are socioeconomic and physical environment, individual behaviour, genetics, and health care

2.9.1 Social determinants of health

There are several social determinants of health models. Three main accepted theories are shortly presented from the European, Global, and American aspects. The first, the Dahlgren and Whitehead European model describes the social determinants of health (Figure 6). The model has been used in several studies during the last 30 years. The model includes elements of the social, economic, and physical environments that interact with individual biological factors and behaviours and shape health status (Whitehead & Dahlgren, 1991).



Stick figures Leremy Gan

Figure 6. The Dahlgren and Whitehead model of the social determinants of health. Modified from Dahlgren G and Whitehead M (1991)

Dahlgren and Whitehead's model describes the relationship between the individual, environment, and disease (Dahlgren & Whitehead, 1991). Individuals are at the centre with their constitutional factors such as age, sex, and genes. Factors that influence health surround the individual and are referred collectively as the social determinants of health. In the model, these factors are structured into four layers. The first layer is an individual's lifestyle, and personal behaviour can promote or

damage health. The next layer is social and community networks that affect and support our behaviour. The mutual network can either provide support or have a negative effect. The third layer includes structural factors: housing, working conditions, access to services, and provision of essential facilities. The fourth layer captures the broader political, cultural, and environmental conditions in which all these other factors occur. (Dahlgren & Whitehead, 2006)

The second model was built in response to the increasing concern on disparities in health status by WHO (WHO, 2008). The Commission's final report, 'Closing the gap in a generation', included a conceptual framework through which to understand the social determinants of health (Figure 7). This interactive model with constant feedback illustrates how the socio-economic and political context has a role in determining the position of an individual in society. The model divides social determinants into two categories structural and intermediary determinants. Bridging them are concepts of social cohesion and social capital as a cross-cutting determinant. The structural factors affect health and well-being by affecting intermediate factors and the likelihood of exposure to health-compromising environments. (WHO, 2008)

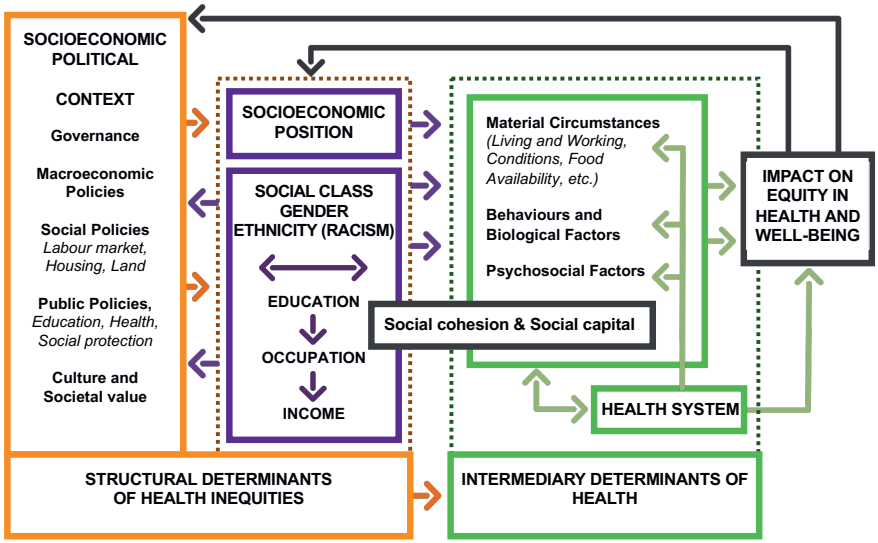


Figure 7. Global Commission on social determinants of health model, modified from WHO (2008)

The WHO Regional Office for the Americas created a commission to address the need to reduce inequalities in health in the Americas in 2016. The Pan American Health Organization (PAHO) proposed a conceptual framework on social

determinants of health (Figure 8). The model extended the global framework beyond it in meaningful ways (PAHO, 2018). The model recognizes a dignified life and health equality as a desired outcome. In the model, there is a greater emphasis on structural racism, environment, and climate change. There is a focus on human rights and inequities according to sex, ethnicity, migration, sexual orientation, life stage, and disability. Further, the model illustrates how the socioeconomic, political, and cultural contexts shape health and illness. These drivers include governance, policy, and dominant cultural and societal norms and values. Everyday circumstances in which people live represent the Conditions of Daily Life. The quality of these conditions affects people's material circumstances, psychosocial control, and social connection and can be protective or damaging to health. A comprehensive strategy to health inequities includes taking actions that address the social structures and processes. that systematically distribute the determinants of health unequally in society. (PAHO, 2018)

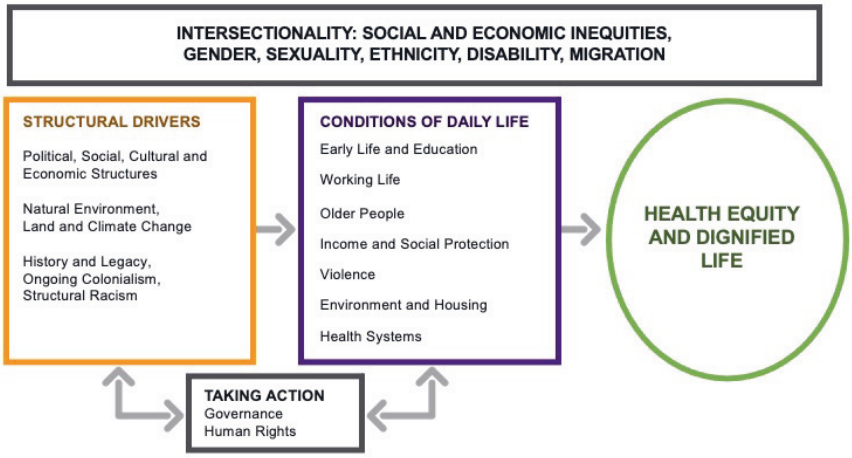


Figure 8. Health Equity and Dignified Lives model, modified from PAHO (2018)

These three concept framework models are complementary to each other. Socioeconomic main drivers of health are often not in focus. Research suggests that 15% of the population health is determined by biology and genetics, 10% by physical environments, 25% by the actions of the health care system, with 50% being defined by socioeconomic environment (Canadian Medical Association, 2013). Socioeconomic conditions have a direct impact on health (Figure 9). The effect is

30-50% on the populations' health and the estimate of impact has changed during last 20 years (Donkin et al., 2018).

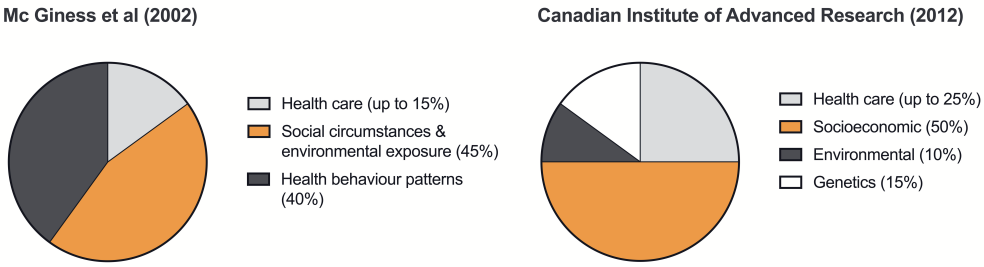


Figure 9. Estimates of the impact of the main drivers of health status modified from Donkin et al. (2017)

2.9.2 Health care

Notably, many of the determinants of health lie outside of the control of the health care system (Whitehead & Dahlgren, 1991). Less than 25% of health benefits are contributed by health care (Figure 9) (Donkin et al., 2018). The health care access is better in urban areas than rural areas (Douthit et al., 2015). In rural areas in the USA, racial and ethnic residential segregation is also greater than in urban areas (Caldwell et al., 2017). Rural residents are reported to have a higher age-adjusted prevalence of COPD, hospitalizations, and deaths caused by COPD than residents living in urban areas (Croft et al., 2018). Those transitioning from paediatrics to adult care are recognised to have worse health care access than adults (Chua et al., 2013). In Finland, waiting times particularly for the elderly for appointments with general practioners tends to be prolonged (Tolvanen et al., 2018).

Globally, in low-income countries only 50% individuals with asthma had access to bronchodilators and short-acting beta2-agonist (SABA), and less than one in five had access to inhaled corticosteroids (ICS) (WHO, 2020b). The Finnish reimbursement system covers the whole population. However, the European Commission considered Finland's reimbursement model to violate the directive on patient's rights (Heinonen et al., 2019). The Finnish reimbursement system requires high co-payments from patients and does not account for either social status or income, which can create barriers for patients in accessing medicines (WHO, 2018). The system also impacts diagnostic criteria for CRDs and shifts the diagnostics from COPD to asthma owing to reimbursement benefit with asthma diagnosis. COPD medicines are reimbursed when FEV1 is < 40% or <50% and the patient has

received treatment of severe exacerbations needing hospitalisation or several treatments with corticosteroids or antibiotics. To conclude, CRD reimbursement has built-in structural barriers in Finland leading to inequality that require action.

2.9.3 Social and economic environment

Socioeconomic status (SES) is a measure of persons resources based on occupation, education, and income. SES can change over time, and it is needed to understand inequality in or between societies, races, or sexes. SES is an important outcome, risk factor, or adjusting factor in studies. SES can be measured with several composite measures or univariate measures of income, wealth, or educational attainment. In Finland, one has studied 9 years for primary education, 12 years for secondary education, and >12 years for tertiary and university-level education. It is possible that those with higher educational levels have a better health literacy and can manage self-care.

SES has various aspects in relation to CRD. Individuals with low educational levels have a higher risk of developing asthma (OR 2.1) and respiratory symptoms (OR 1.4-2.5) (Eagan et al., 2004). Exposure to multiple adverse childhood events increased the risk of asthma in adulthood, and the association was mediated by severe life events such as severe financial difficulties, smoking, allergic rhinitis, low education level, and obesity (Lietzén et al., 2021). In Sweden, manual workers had an increased risk for asthmatic wheeze and manual workers in service had an increased risk for current asthma, especially allergic asthma; whereas, primary school education was associated with nonallergic asthma (Schyllert et al., 2020). A lower educational level was a risk factor for uncontrolled adult-diagnosed asthma in Nordic countries (Ilmarinen et al., 2021). Lower educational level is associated with non-allergic asthma and chronic bronchitis (Ellison-Loschmann et al., 2007). Higher education levels were associated with co-existing asthma, higher lung function, and lower mortality in a COPD cohort (Lutter et al., 2020).

Lower education, lower household income, and lower composite SES index (OR 1.23) were associated with COPD among low- and middle-income countries (Grigsby et al., 2016). Similar phenomena exist in high-income countries. Low SES, assessed based on the length of school education, is associated with COPD exacerbations and a higher risk of all-cause mortality in Denmark (Lange et al., 2014). In California, both lower education and lower income were independently related to a greater risk of acute COPD exacerbation (Eisner et al., 2011). Hospital readmission

risk was associated with low socioeconomic status and residential instability in patients hospitalised for COPD (Gershon et al., 2019). In the COPDGene study, the low-income group had faster smoking-related disease progression and forced expiratory volume in 1 s (FEV1) decline in a <5-year follow-up (Lowe et al., 2018).

The relationship between health and SES is moderated by social expenditure (Álvarez-Gálvez & Jaime-Castillo, 2018). SES affects housing, working conditions, access to clean air, healthy diet, exercise facilities, and health care. Of the rural population with COPD, 12.6% were uninsured compared to 10.4% in urban areas, and rural residents were more likely to have not seen a doctor owing to the costs (Gaffney et al., 2020). Rural residents were poorer, had less education, worse health, and more disability than urban residents. In adult asthma and COPD study, racial, ethnic, and socioeconomic disparities or health care affordability did not improve during the study period between 1997 and 2018 (Gaffney et al., 2021).

2.9.4 Physical environment

Environmental exposures influence the phenotype of allergic diseases, such as atopic eczema, food allergy, asthma, and allergic rhinitis (Burbank et al., 2017). Global trends of increasing urbanisation and rapid population growth contribute to changes in lifestyle and environmental exposures affect atopic allergic mechanisms (Murrison et al., 2019). The environmental exposures early in life contribute to the development of allergic disease and asthma in later life. The influence on allergic mechanisms likely differs based on host genetics, host immunologic milieu, timing, and other factors (Murrison et al., 2019).

Environmental microbial exposures have been studied in farming milieu. In children exposed to farming, high microbial diversity in the environment has been associated with lower allergy and asthma risk (Birzele et al., 2017; Douwes et al., 2007; von Ehrenstein et al., 2000). A decrease in environmental symbiosis with parasites, bacteria, and microbiome diversity influences immunoregulation and increases allergy and asthma prevalence (Lambrecht & Hammad, 2017). Exposure to diverse microbes was inversely related to the risk of asthma in the age group 6-13 years (Ege et al., 2011).

Dog and cat allergen exposure reduces the risk of developing allergic disease (Fall et al., 2015; Gergen et al., 2018). Early-life dog or cat ownership reduced sensitisation to ≥1 aeroallergen and decreased asthma risk in children at age 6 years (Fall et al., 2015). Polysensitisation to ≥3 allergen molecules from cats or dogs was a predictor

allergy symptoms by cat or dog (Asarnoj et al., 2016). Furthermore, dog allergen among dog-sensitive and cat allergen among cat-sensitive individuals increased asthma attack prevalence (Gergen et al., 2018). To conclude, early constant exposure builds tolerance. Those with cat and dog sensitisation have a risk for allergic and asthma symptoms when exposed to the allergen.

In a Swedish birth cohort, no association was observed between mould or dampness indicators and IgE sensitisation. Mould or dampness indicator exposure during infancy increased risk of allergic asthma and allergic rhinitis, and nonallergic asthma and non-allergic rhinitis (OR 1.29-1.80), up to 16 years of age, but not after (Thacher et al., 2017). A meta-analysis estimated a 36-48% increase of asthma symptom exacerbation with exposure to *Cladosporium, Alternaria, Aspergillus*, and *Penicillium* species (Sharpe et al., 2015).

Living within 50–200 m of major roadways is associated with increased risk of eczema, allergic rhinitis, atopy, and asthma (Bowatte et al., 2017). Increased risk of asthma development is associated with black carbon, nitrogen dioxide, and particulate matter (OR 1.03-1.08) (Khreis et al., 2017). Diesel exhaust augmented allergen effects in lower airways of atopic individuals (Carlsten et al., 2016). Owing to urbanisation and more time spent indoors, exposure to polluted air has increased (Chatkin et al., 2021).

Workplace exposures and smoking have a strong cumulative association with an increased risk of COPD (Blanc et al., 2009). Occupational exposure to VGDF are associated with COPD (OR 2.7), airflow limitation (OR 1.8), and emphysema (OR 1.8) (Torén et al., 2017). In addition, occupational exposure to VGDF increased the risk of asthma (OR 1.4) and concomitant asthma and rhinitis (OR 1.6) (Schyllert et al., 2016). Pre- or postnatal maternal smoking increased the risk of incident wheezing (OR 1.70) and incident asthma (OR 1.85) in children ≤2 years (Burke et al., 2012). In the U.S. Black Women's Health Study, former active smoking (HR 1.37), current active smoking (HR 1.43), and passive smoking (HR 1.21) increased the risk for incident asthma compared with the never exposed group (Coogan et al., 2015). The worldwide burden of disease from second-hand smoke affects more women and children (Öberg et al., 2011).

2.9.5 Genetics

Alfa-1-antitrypsin deficiency is a common autosomal recessive disorder in adults leading to emphysema, bronchiectasis, and liver disease and should be screened at

least in young patients with emphysema due to high prevalence of deficiency alleles of 20-30/1000 in Finland (Häggblom et al., 2015; Miravitlles et al., 2017). Most diseases like asthma and COPD develop in interaction with individual habits, environment, and genes. Implicated genes in asthma suggest a role for communication of epithelial damage to the adaptive immune system and activation of T-cell regulation, inflammation and airway remodelling (Moffatt et al., 2010; Olafsdottir et al., 2020). Several genome wide association studies have found partly shared and partly distinct genetic risk factors for childhood-onset and adult-onset asthma (Ferreira et al., 2019; Pividori et al., 2019). Several regulatory genes have been identified in asthma, and some of these are shared, some typical for children and some associated with mild disease (Do et al., 2021). The ACO is associated with novel genetic variants (Hardin et al., 2014). Moreover, there is a significant gene expression overlap between asthma and COPD (Christenson et al., 2015). The UK Biobank study identified genetic link between obesity and asthma subtype with onset after 16 years and the shared immune- and cell differentiation related pathways (Zhu et al., 2020). In addition, the UK Biobank study reported shared genetics between asthma and anxiety, major depressive disorder, and attention deficient hyperactivity disorder (Zhu et al., 2019).

Epigenetic changes are changes that occur to the genetic blueprint of life by the environment and they can be inherited (Egger et al., 2004). Epigenetic changes such as DNA methylation, histone modification, and noncoding RNA action influence gene activity without changing the DNA sequence. The epigenetic imprint during the perinatal period is important to the early origins of chronic obstructive disease (Duijts et al., 2014). Methylation data exist on numerous loci involved in response to maternal smoking in pregnancy with persistence into later childhood (Joubert et al., 2016). Exposure to traffic-related air pollution induces changes in epigenetics and has been implicated in asthma development, persistence, and exacerbation (Egger et al., 2004). Air pollution causes epigenetic changes in asthma (Ji et al., 2016; Ntontsi et al., 2021). Smoking can accelerate the epigenetic age of human respiratory organs but can be reversed by smoking cessation (X. Wu et al., 2019). The upregulation or downregulation of methylation in different genes is associated with COPD development (Duijts et al., 2014; Machin et al., 2017). Dysregulation of microRNAs (miRNA), a class of non-coding RNAs alters susceptibility to COPD by regulating cellular response to DNA damage (Zhang et al., 2020). The impairment of epigenetic mechanisms promotes the alteration of gene expression underlying several aging-related diseases such as COPD (Pagiatakis et al., 2021).

2.9.6 Individual behaviour

Hand washing and use of masks, and physical distancing have been the focus of the COVID-19 pandemic. Other areas of discussion have been how the physical isolation changes our cultures, alters our habits, and how individual behaviour has a butterfly effect on masses. Traditionally, smoking, diet, physical activity, alcohol use, and loneliness are the big five behavioural drivers. High BMI, alcohol intake, and smoking were estimated to affect social and socioeconomic outcomes adversely, and in turn, loneliness was associated with smoking, high BMI, and last, maybe without causality asthma was related to decreased household income, lower education, and loneliness (Harrison et al., 2020).

Fifty years' observation on cause specific mortality among British male doctors revealed that prolonged cigarette smoking from early life tripled age-specific mortality rates, and cessation at age 60 or 30 years gained, respectively, 3 or 10 years of life expectancy (Doll et al., 2004). The mortality risk of smoking is dose-dependent (Doll et al., 1994). Furthermore, e-cigarettes were an independent risk factor for respiratory disease in addition to cigarette smoking. The most common pattern, dual use, is riskier than using either product alone (Bhatta & Glantz, 2020). Electronic cigarette use is most common among younger male smokers, and dual users had the highest prevalence of respiratory symptoms (L. Hedman et al., 2018).

Smoking and ambient particulate matters are the risk factors for COPD, followed by household air pollution, occupational particulates, ozone, and second-hand smoke (Soriano et al., 2017). Smoking and occupational substances that can cause an individual to develop asthma upon exposure, explain 16.5% of asthma disability-adjusted life years DALYs (Soriano et al., 2017). Recent quitting of smoking seems to be associated with increased risk of both atopic and non-atopic asthma (Lajunen et al., 2021). In female patients, regular smoking was associated with atopic asthma and in male patients former smoking was associated with non-atopic asthma (Lajunen et al., 2021). Smoking seems to have a dose-dependent relationship to frequent hospitalisations and number of co-morbidities in adult-onset asthma (Tommola et al., 2019).

Asthma likely has a U-shaped relation to alcohol. Never drinkers and heavy daily drinkers have a higher prevalence of asthma than moderate drinkers (Lieberoth et al., 2012). These observational relations may not be causal (Skaaby et al., 2019). Alcoholic drinks can trigger asthma symptoms in sulphite and salicylate sensitive patients (Vally et al., 2000). Furthermore, the rare alcohol-induced asthma was reported among Japanese patients caused by acetaldehyde dehydrogenase 2 genotype

variant resulting in increased blood acetaldehyde concentration (Matsuse et al., 2001; Shimoda et al., 2017). Alcohol use is not a causal risk factor for COPD independent of tobacco use, but heavy alcohol consumption is prevalent among COPD patients (Greene et al., 2008).

Dietary patterns such as following a Western diet, which includes high intake of refined grains, processed and red meats, and desserts, have pro-inflammatory effects. By contrast, the Mediterranean diet, which is defined by high intake of fruits and vegetables, has anti-inflammatory properties (Guilleminault et al., 2017). High adherence to the Mediterranean diet and fresh fruit intake reduced the risk of uncontrolled asthma (Barros et al., 2008). Nutrient intake and dietary patterns have also been associated with lung function measures and the development and progression of COPD (Hanson et al., 2014).

Baseline obesity was associated with asthma risk in a twin study in Finland (Huovinen et al., 2003). Early-onset asthma may contribute to an increased risk of developing obesity in later childhood (Contreras et al., 2018). In-adult-onset asthma, patients obese at diagnosis mostly remained obese and had more exacerbations and respiratory-related hospital admissions in the 12-year follow-up (Ilmarinen et al., 2021). For obese adults with asthma, a caloric restriction seems to be the best dietary intervention (Forte et al., 2018). Weight reduction in obese patients with asthma improves symptoms and lung function (Stenius-Aarniala et al., 2000). In contrast, obesity has a protective effect against mortality in severe COPD (Hanson et al., 2014). In other words, being underweight increases the risk for infection, frailty, and death among those with poor lung function. In a randomised controlled trial, the combination of exercise and a healthy diet improved asthma control in non-obese patients (Toennesen et al., 2018).

Physical activity and exercise are different entities. Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure (WHO, 2020a). The evidence reaffirms that all adults should undertake regular physical activity and should aim to achieve at least 150 min of moderate-intensity, or 75 min of vigorous-intensity aerobic physical activity per week, or some equivalent combination of the two (WHO, 2020a). Low physical activity, defined as less than 240 min daily, is independently associated with faster decline in lung function among adult patients with asthma (Loponen et al., 2018). Exercises include planned aerobic physical activity that uses the body's long muscles, balance training, and bone-strengthening activities. Physical inactivity is defined as an insufficient physical activity level to meet present physical activity recommendations, not doing at least 150 min of moderate-intensity, or 75 min of vigorous-intensity physical activity per

week, or any equivalent combination of the two (Bull et al., 2020). Sedentary behaviour is any waking behaviour characterised by an energy expenditure of 1.5 metabolic equivalent of tasks (MET) or lower while sitting, reclining, or lying (Bull et al., 2020). Sedentary jobs are more common for those with office work or those that commute with car. Watching television at home is an example of sedentary behaviour. For health both occupational and leisure sedentary behaviour counts.

2.10 Health inequities

The health equity normative concept is based on social justice, fairness, and human rights. It is defined as *"The absence of unfair and avoidable or remediable differences in health among population groups defined socially, economically, demographically or geographically"* (WHO, 2008). Equality exists when all individuals are given equal treatment regardless of need or outcome, whereas equity focuses on more equal results with custom tools. The term disparity is used within the equity concept to address the avoidable differences among social groups to achieve more equal outcomes. Health equity is measured through health inequalities that are observable differences between subgroups within a population. Justice is achieved when structural limitations in the system are fixed. The social determinants of health set the conditions for individuals and populations and if not distributed fairly they can lead to health inequities. The health inequities have social and economic costs such as sick-leave and productivity loss owing to illness. Social stratification is a result of the unequal distribution of power, money, and resources. (Marmot et al., 2012)

The conditions in which people live are key determinants of health equity (Marmot et al., 2012). The effect from structural drivers to respiratory health might be positive or negative and detecting and erasing the structural barrier justice in health within a population is possible (Figure 10). Loss of culture or unhealthy culture can lead to a vicious circle of an unhealthy diet, sedentary lifestyle, smoking, alcohol, and drug use. Culture changes individual behaviour and influences disease prevalence in the population.

Social inequities in health are invisible in everyday life, where diseases are often perceived as affecting family and friends quite randomly, and the lack of measurement is a barrier for recognizing the problem (Dahlgren & Whitehead, 2006). The exposure to preventable health hazards that arises from social determinants contributes to socioeconomic inequities in health between and within countries. There are marked differences in obesity and education level relationship

among European countries (WHO, 2013). These differences may lead to a situation where lower socioeconomic groups are better off in equal countries than in more unequal countries. The difference is in social gradient in health, where health outcomes progressively improve with increasing social positions (Kelly, 2010). To reduce the steepness of the social gradient we need equity measures that are proportionate to the level of disadvantage.

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Figure 10. The measurable difference between groups is health inequality

The social divide leads to a health divide, and populations might be blinded to the problems within the most vulnerable groups without objective measures (Aldridge et al., 2018). Homeless people, individuals with substance use disorders, sex workers, and imprisoned individuals experience extreme health inequities in morbidity and mortality across a wide range of health conditions (Aldridge et al., 2018). The relative effect of exclusion is greater in female than male individuals (Aldridge et al., 2018). More resources are needed for a vulnerable population, while less resources are needed for those with existing healthy lifestyles. With these balancing acts, it is possible to decrease the health divide in a population.

Several respiratory health programs have increased and measured respiratory health in Finland. The latest of these is the Finnish allergy programme, which emphasized prevention, and the theme was "endorsing nature close" based on a biodiversity hypothesis to increase tolerance in a population. The programme enforced between 2008 and 2018, educated health care networks and residents (Haahtela et al., 2021). During that time, several improvements were observed: 1) hospitalisations of asthma reduced by 50%, 2) food allergy diets in day care and schools decreased by half, 3) occupational allergies were reduced by 45%, and 4)

direct and indirect costs of allergic diseases and asthma were 30% less in 2018 than in 2007 (Haahtela et al., 2021). All observed improvements might not be associated with the Finnish allergy program. The hospital structures changed from inpatient to outpatient care and likely reduced hospital stay more than the allergy program. Furthermore, some respiratory medicine prices have become more affordable because of generic drugs.

2.10.1 Disparities between the Finnish-speaking and Swedish-speaking Finns

Language is a social and cultural construct. Finnish and Swedish-speaking Finns share the same welfare system and environment. Further, they belong to a same Western Finnish subgroup (Kerminen et al., 2017). The population offers a unique partly fixed model to study the interconnection between socioeconomic and behavioural factors that might lead to a positive or vicious health circle. Consequently, the study of health behaviour between Finnish and Swedish-speaking Finns has generated research interest.

Social capital is valuable as a connecting network, a resource that can lead to healthy development. This network's connectedness and solidarity can lead to social cohesion and reduces inequality and socioeconomic disparities. These terms were included in the WHO 2008 model as a bridging component and explained health inequality between language groups. Social participation, voluntary work, and friendship are related to good self-rated health among Swedish-speaking Finns and increase social capital (Hyyppä & Mäki, 2001; Reini & Nyqvist, 2017).

Swedish-speaking Finns have higher social capita and generalised resistance resources (GRRs) than Finnish-speaking Finns (Volanen et al., 2006). GRRs relate to how individuals and the community rely on each other during challenging times such as divorce. High GRRs, better psychosocial living conditions in childhood, and working conditions in adulthood among Swedish speakers facilitate advanced individual's sense of coherence (SOC) (Volanen et al., 2006). SOC is an individual's capacity to manage stress, find solutions, resolve tension, and sustain healthy habits. SOC is related to mental health and health in general (B. Lindström & Eriksson, 2006). Volanen et al. speculate that by increasing GRRs, the SOC gap between the Finnish and Swedish speakers could diminish and result in health equity. The model above, Antonovsky's model, has been used to explain health behaviour in the area (Volanen et al., 2006).

The main health resources and strategies were related to social activities and personality traits among Swedish-speaking Finns (Kulla et al., 2006). Young Swedish-speaking Finns are confident in online contact and face-to-face communication in English and develop trilingual identity (Vincze & Joyce, 2018). These language skills might be helpful in health literacy. High educational level correlates to children being affiliated to the Swedish-speaking community in mixed couples (Obućina & Saarela, 2020). Family migration among Swedish-speaking Finns is gender equal and has a family equation and return migration has been greater among those with higher educational levels (J. Saarela & Finnäs, 2013).

The language groups differ in social capital and cohesion, and it has an impact on individual habits. According to previous reports, Swedish speakers have a healthier diet and more moderate alcohol consumption than Finnish speakers. The recent Finnish Health in Teens study showed a healthier eating pattern for Swedish speakers than Finnish speakers (de Oliveira Figueiredo et al., 2019). The drinking pattern is also more harmful, including more frequent drunkenness and hangovers for Finnish-speaking Finns than Swedish-speaking Finns (Paljärvi et al., 2014).

Swedish-speaking schoolchildren are healthier than Finnish-speaking schoolchildren in terms of objective measures of health (J. M. Saarela & Finnäs, 2004). Swedish-speaking Finns have a longer active life than Finnish-speaking Finns as a result of higher social cohesion and social capital (Hyyppä & Mäki, 2001). The mortality difference between language groups is highest in deaths related to alcohol, suicide, and other external causes. The difference is steepest in the age group of 30-49 years in both women and men (Sipilä & Martikainen, 2009). The mortality disadvantage of the Finnish-speaking Finns is associated to non-favourable geographic location and socioeconomic position, and a 20% excess mortality of the Finnish-speaking majority persists after adjusting for structural differences, mainly for cardiovascular and non-natural causes of death (Koskinen & Martelin, 2003).

Migration, that has been more common for Finnish speakers than Swedish speakers, is associated with mortality (Martikainen et al., 2008). The family origin correlates to mortality, and the relative death risk compared to Finnish speakers born in western Finland was 1.13 for Finnish speakers born in eastern Finland and only 0.60 for Swedish speakers (J. Saarela & Finnäs, 2011). To our knowledge, before this study, there were no data on respiratory physical activity, obesity, respiratory symptoms, and diseases or multimorbidity between these two language groups in Western Finland.

3 AIMS

The present study aimed to evaluate determinants of respiratory health related to asthma, N-ERD, COPD, and multimorbidity. These determinants included social environment, physical environment, and individual behaviour.

The detailed aims were:

To assess how individual behaviour and language groups are associated with respiratory symptoms in Finnish- and Swedish-speaking Finns in Western Finland. (I)

To evaluate link between observed behavioural differences and prevalence of chronic diseases and multimorbidity in language groups in Western Finland and propose a tool describing the relationship between multimorbidity and smoking, inactivity, and obesity. (II)

To study the association between childhood exposure to farming environment and the age at asthma diagnosis. (III)

To estimate the prevalence of N-ERD and AERD in Finland and analyse the features of individuals identified by N-ERD definition and the factors associated with N-ERD. (IV)

4 MATERIAL AND METHODS

4.1 FinEsS study design

The Obstructive Lung Diseases in Northern Sweden (OLIN) studies were initiated during 1985-1996 as postal surveys followed by structural interviews and lung function tests. In 1996, the FinEsS survey was conducted with a similar clinical cohort. The FinEsS studies included to 2016 survey a new centre of Western Finland that included Seinäjoki and Vaasa Hospital districts. The epidemiology of asthma and chronic COPD in adults has been studied both cross-sectionally and longitudinally in these studies.

The data used in publications I-IV are obtained from the FinEsS cross-sectional population-based survey. The postal questionnaire was sent to random samples of population aged 20-69 years in Western and Southern Finland. The same questionnaire was used in both centres. The surveys were sent in February 2016, and two reminders were sent to those that did not respond. The response rate was 52.5% in Western Finland and 50.3% in Southern Finland. We had planned to carry out a telephonic analysis of non-responders, but the ethics committee did not allow us to contact the non-responders. We excluded those with missing data on smoking from our analysis (Figure 11).

The FinEsS questionnaire was developed from the OLIN questionnaire and contains features from the ATS and Tucson questionnaires (Juniper et al., 1999; Lebowitz & Burrows, 1976; Lundback et al., 1991). The part of the questionnaire has been validated in a Swedish clinical cohort previously (Lundbäck et al., 1993). A bilingual translator produced an independent translation of the questionnaire from Swedish to Finnish. The translator was aware of the study's objective and had expertise in the study topic. An expert translator blinded to the study's objectives estimated the quality and limitations of the final translation for this thesis. The translation and cross-cultural adaptation were performed according to existing guidelines (Guillemin et al., 1993).

We conducted the analysis related to dyspnoea, multimorbidity, and childhood exposure to a farming environment (I-III) with data on Finnish and Swedish speakers in Western Finland; the population size was 3,864 after languages other

than Finnish or Swedish were excluded (n=103). This was done to have a partly fixed model to study the determinants of respiratory health. These partly fixed determinants were genetics, education, health care, geographical area, physical environment, and probably childhood environment owing to the low migration rate in the area (Martikainen et al., 2008). Finnish- and Swedish-speaking Finns are part of the same Western subgroup of Finns, while the population in Southern Finland is more heterogeneous and part of another Western Finnish subgroup (Kerminen et al., 2017). We proposed a hypothesis that the social environment such as belonging to a language group or being exposed to a farming environment since childhood modified the habits adopted by children (I-III). Childhood exposure to farming environment and its association to age at asthma diagnosis was first analysed in the Western Finland cohort and then validated in the Southern Finland cohort that is more urban (III). We used data from both cohorts and all language groups (n=7,930) in the N-ERD analyses owing to low prevalence of N-ERD (IV).

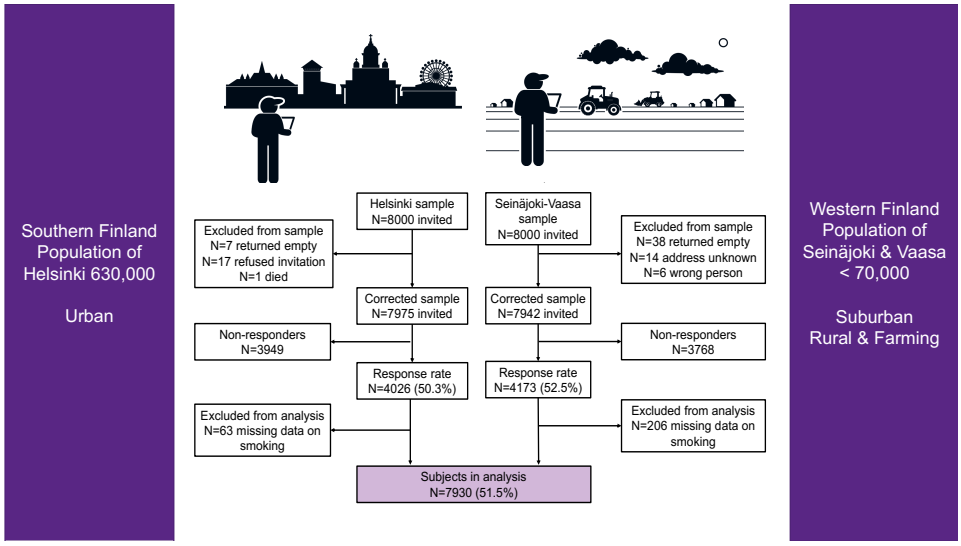

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Figure 11. Cross-sectional FinEsS 2016 survey in Western and Southern Finland

4.2 Definitions

The following definitions based on previous FinEsS and OLIN publications were used. The definitions of AERD and N-ERD were adapted from recent guidelines (Kowalski et al., 2019a). Physical inactivity was adapted from WHO recommendations and recent publication (Loponen et al., 2018; WHO, 2020a). We created a variable of cumulative smoke, second-hand smoke, and occupational exposure to VGDF for this thesis by grouping the correlated variables to detect a nonlinear dose-relationship.

AERD: was defined as an affinitive answer to NSAID-induced dyspnoea, asthma, and rhinitis

Age at asthma diagnosis: What age were you when a doctor diagnosed you as having asthma?

Body Mass Index (BMI): was based on self-reported height and weight and was categorised as follows: under and healthy weight <25 kg/m2, overweight 25.0–29.9 kg/m2, obesity grade I 30.0–34.9 kg/m2, and obesity grade II ≥35.0 kg/m2.

Childhood farming environment: Did you live on a farm during your first 5 years?

Childhood rural environment: Did you live in a rural area during your first 5 years?

Childhood urban environment: Neither farming nor rural childhood environment.

Constant nasal blockage: Have you had longstanding nasal congestion? The question was used as a proxy for **CRSwNP**.

Cumulative smoke and occupational exposure: were assessed using a scale of 0-3 exposures of smoking (current or ex-smoking), second-hand smoke (at home or work), and occupational exposure to VGDF.

Dyspnoea mMRC score ≥2: Do you have to walk slower than other people of your age on the level because of breathlessness?

Exercise on your free time: How often do you exercise at least 30 min so that you are at least slightly short of breath and get sweaty? Choose one from the following alternatives: daily, 4-6 times a week, 2-3 times a week, once a week, 2-3 times a month, more seldom, I cannot exercise due to injury or illness.

Family history of allergic rhinitis: Do you have a family history of allergic rhinitis?

Family history of asthma: Do you have a family history of asthma?

Longstanding cough: Have you had longstanding cough during the last 12 months?

N-ERD: was defined as an affinitive answer to NSAID-induced dyspnoea and asthma or rhinitis.

NSAID-induced dyspnoea: Have you ever experienced difficulties breathing within 3 hours of taking a pain killer?

Occupational exposure to VGDF: Are you now, or have you been heavily exposed to gases, dust, or fumes at work?

Physically active: How many hours in a day do you spend moving/being/physically active at your free time or at work? Participants were considered physically active if they were physically active for at least 3 h (≥180 min) per day.

Physician-diagnosed allergic rhinitis: Has a doctor diagnosed you as having allergic rhinitis caused by pollen (e.g., birch, grass, mugwort)? or Has a doctor diagnosed you as having allergic rhinitis caused by animal exposure, e.g., cat or dog?

Physician-diagnosed asthma: Has a doctor diagnosed you as having asthma?

Physician-diagnosed COPD: Has a doctor diagnosed you as having chronic bronchitis, COPD, or emphysema?

Rhinitis: was defined as a positive response to one of the following questions: Have you been diagnosed by a doctor as having allergic rhinitis caused by pollen (e.g., from birch, grass, mugwort)? Have you been diagnosed by a doctor as having other allergic rhinitis (e.g., caused by cat or dog, but not caused by pollen)?; Do you have now, or have you had previously, allergic rhinitis (e.g., hay fever)?; Have you had longstanding nasal congestion?; and Have you had longstanding rhinitis?

Severe allergic reaction: Have you had severe generalised allergic reactions (anaphylaxis) any time in the last 12 months?

Sputum production: Do you have productive cough, or do you have phlegm that is difficult to bring up?

Smoking status: was divided into current smokers, ex-smokers (stopped smoking ≥12 months before), and never-smokers (neither a current smoker nor an ex-smoker).

Second-hand smoke exposure at home: Have you been heavily exposed to tobacco smoke at home?

Second-hand smoke exposure at work: Have you been heavily exposed to tobacco smoke at work?

Sedentary behaviour: How much time do you spend daily sitting in front of a TV, a computer, a tablet, a game console etc.? 1 h, 2 h, 3 h, 4 h, >5 h

Tightness in the chest: Have you awakened with a feeling of tightness in your chest at any time in the last 12 months?

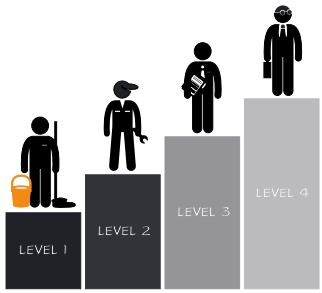
Wheeze: Have you had wheezing or whistling in your chest at any time in the last 12 months?

4.2.1 Age at asthma diagnosis

Most studies use terms of early-onset or late-onset asthma even though age at asthma diagnosis might differ from onset. The cut-off age for late-diagnosed asthma varies from 12 years (Holguin et al., 2011), 18 years (Azim et al., 2020), 40 years, to 65 years (Baptist et al., 2013; Brusselle et al., 2017; Chaudhuri et al., 2016). Most studies have used a cut-off point of 12 years, and in these studies, female subjects had higher odds for asthma diagnosis after 12 years than male subjects (Tan et al., 2015). After approximately 40 years of age, most of the new cases of asthma are non-allergic (Pakkasela et al., 2020). Based on sex and allergic differences, ages 12 and 40 years were used to delineate the three age-at-diagnosis groups. There is no consensus on how asthma should be categorised to age at onset groups. Therefore, these cut-off points and terms are still debateable. We categorised asthma into early- (0-11 years), intermediate- (12-39 years), and late-diagnosed (40-69 years) (Honkamäki et al., 2019).

4.2.2 Socioeconomic status based on occupation

We used International Standard Classification of Occupations (ISCO-08) skill level to estimate socioeconomic status. The main occupation was asked in the survey. We classified occupations according to ISCO-08 and categorised to ISCO-08 skill level (ILO, 2012). ISCO skill level is a composite variable on both occupation and education needed for the occupation. The first digit of ISCO-08 tells the major occupational group (Figure 12). Managers, professionals, technicians, and associate professionals form skill levels 3-4, occupations with a high level of education. Most occupational groups are in medium level 2, like clerical support workers, services and sales workers, craft and related trades workers, and plant and machine operators and assemblers. Elementary occupations form level 1 with a low level of education. ISCO-08 skill level 1 is the primary level of education, and level 4 is higher education. Skill levels 1 and 2 form low SES and skill levels 3 and 4 high SES. Compared to the International Socio-Economic Index (ISEI), ISCO skill level yielded qualitatively the same results in social inequalities (von Gablenz & Holube, 2017).



ISCO-08 skill level	ISCO-08 class	ISCO-08 major occupation group
3-4	1	Managers
3-4	2	Professionals
3-4	3	Technicians and Associate Professionals
2	4	Clerical Support Workers
2	5	Services and Sales Workers
2	6	Skilled agricultural, forestry and fishery workers
2	7	Craft and Related Trades Workers
2	8	Plant and Machine Operators and Assemblers
1	9	Elementary Occupations
Armed forces	0	Armed Forces Occupations

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Figure 12. The ISCO-08 skill level and major occupation groups

4.2.3 Multimorbidity

Questions related to chronic diseases and multimorbidity were new for the FinEsS 2016 questionnaire and were planned for this and other studies utilising the data. The assessment of multimorbidity was based on self-reported diseases or medical conditions and defined as the disease count ≥2 in any individual responder. The rationale for diseases included was based on four independent factors. A previous multimorbidity publication was used as a guide (Barnett et al., 2012). The second guide was the most common comorbidities found in the SAAS-cohort in the same area (Ilmarinen et al., 2016). The third basis was the knowledge in the literature on comorbidities in adult asthma (Kankaanranta et al., 2016) The last factor was the limited space in the questionnaire. Because of limitations, only non-contagious diseases important for public health were included.

The 15 chronic diseases included in estimating multimorbidity were self-reported. They were asked the following question: Has a doctor diagnosed you with any one of the following diseases? To enumerate: 1) asthma, 2) COPD, 3) hypertension, 4) coronary heart disease, 5) atrial fibrillation or another cardiac arrhythmia, 6) heart failure, 7) stroke or transient ischemic attack, 8) diabetes, 9) depression, 10) panic attack or anxiety, 11) treated dyspepsia/reflux disease, 12) chronic kidney failure, 13) sleep apnoea, 14) osteoporosis, and 15) painful condition requiring daily analgesic medication?

4.3 Ethical permission

The Ethics Committee of the Department of Medicine of Helsinki University Central Hospital approved this study (approval number 200/13/03/00/15). The study was conducted in accordance with the tenents of the Declaration of Helsinki. General Data Protection Regulation (EU) 2016/679 was followed.

4.4 Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics software version 26 (IBM Corporation, Armonk, NY, USA). P <0.05 was considered to indicate statistical significance. The normality of data distribution was evaluated visually and with the Kolmogorov-Smirnov's test. We used the Student's t-test for comparison of two groups and one-way analysis of variance (ANOVA) for three or more groups with normally distributed continuous data. Pearson's chi-square test was used to compare categorical variables with z-test multiple categories. Mann-Whitney U test between two groups or Kruskal-Wallis test between three or more groups were used for group comparisons on continuous data with skewed distribution. Tukey's test was used for post-hoc analyses.

Multivariable logistic regression analyses were performed to analyse associations with odds ratios (OR) and 95% confidence intervals (CI) between independent and dependent variables. We build the models so that the independent variables in the models were not strongly correlated (I-IV). Furthermore, diseases were grouped to ensure clinically relevant disease groups (II). A compound variable of cumulative smoke, second-hand smoke, and occupational exposure to VGDF was used to detect the dose-dependent relationship (IV). Cox time to event analysis with hazard ratios (HR) was used to analyse the association between age at asthma diagnosis and childhood exposure to farming environment.

We used the total population of Western and Southern Finland as a standard population for age standardisation outcome rates, and these indigenous standards were used to evaluate inequalities within Finland (Robson et al., 2007). These rates estimate the relative risk between the standard population and the population under study. The age-standardised disease ratio was counted as actual prevalence of disease divided by expected diseases with indirect standardisation. Rates were calculated as the sum of outcome per 1000 people in 10-year interval age groups.

5 RESULTS

5.1 Description of the study population in Western Finland

Our main analyses included 3,864 subjects from the Seinäjoki-Vaasa cohort, of which 2,780 (71.9%) were Finnish-speaking and 1,084 (28.1%) were Swedish-speaking. In Western Finland, the participation rate for Finnish speakers was 51.4% (2,932 out of 5,704) and for Swedish speakers was 60.0% (1,132 out of 1,886). The median age of responders was 54 years for Finnish speakers and 50 years for Swedish speakers (P<0.001) and a slight dominance of women over men was observed in both groups. The characteristics of language groups are presented in Table 1. (I)

Based on the self-reported height and weight, Finnish speakers showed significantly higher mean and median BMI and prevalence of obesity (BMI≥30 kg/m^2) than Swedish speakers. The mean BMI was 27.1 kg/m^2 for Finnish speakers, and 26.0 kg/m^2 for Swedish speakers, (P<0.001). Prevalence of obesity was 23.0% vs 15.9% for Finnish speakers and Swedish speakers, respectively (P<0.001). As a confounding factor, obesity increased with age; 15.0%, 22.7%, and 23.6% were obese in age groups 20-39, 40-59, and 60-69 years, (P<0.001) respectively. (I-II)

Another significant aspect was physical activity and exercise. Physical activity and mean time spent moving daily was 3 h (SD: 3.2) for Finnish speakers and 4 h (SD: 3.4) for Swedish speakers (P<0.001). With a cut-off point of 3 h, 50.7% of Finnish speakers and 67.6% of Swedish speakers were physically active (P<0.001). However, the trend in exercise seemed the opposite. The prevalence of physical activity based on exercise more than twice a week was 75.7% vs 71.8% for Finnish and Swedish speakers, respectively (P=0.133). Physical activity and exercise patterns did not fully correlate in language groups, and they are different entities (Loponen et al., 2018). Therefore, in further analysis, prevalence of combined physical activity < 3 hours daily and exercise less than 2-3 times a week was 11.3% in Western Finland, 12.3% in males, 10.4% in females (P=0.155), 12.1% in Finnish speakers and 9.3% in Swedish speakers (P<0.001) (unpublished result). The prevalence of inactivity did not increase with age: 11.6%, 12.4%, and 9.9% were inactive in the age groups of 20-39, 40-59, and 60-69 years, respectively (P=0.168) (unpublished results). (I-II)

Table 1. Characteristics of the populations grouped based on language in Western Finland (n=3864)

	Finnish speakers n=2,780	Swedish speakers n=1,084	P-value
Female sex	1468 (52.8%)	549 (50.6%)	0.227
Mean age (years) Median age (years)	51 (14.3) 54 (40-63)	49 (15.1) 50 (36-63)	<0.001
Mean BMI (kg/m2) Median BMI (kg/m2)	27.1 (5.0) 26.3 (23.7-29.7)	26.0 (4.5) 25.4 (22.9-28.2)	<0.001
Allergic (allergic rhinitis)	492 (17.7%)	200 (18.5%)	0.584
Exercise at least 2-3 times per week	2030 (73.7%)	763 (71.2%)	0.133
Physically active at least 3 h/day	1307 (50.7%)	676 (67.6%)	<0.001
Sedentary behaviour less than 1 h/day	330 (12.1%)	173 (16.3%)	0.001
Current smokers	653 (23.5%)	175 (16.1%)	<0.001
If current smoker, heavy smoker (daily ≥15 cigarettes)	217 (34.3%)	41 (24.3%)	0.016
Ex-smokers	792 (28.5%)	278 (25.6%)	0.078
Never smokers	1384 (49.8%)	636 (58.7%)	<0.001
Second-hand smoke at home	285 (10.6%)	102 (9.6%)	0.389
Second-hand smoke at work	294 (10.8%	97 (9.2%)	0.144
Occupational exposure to VGDF	1105 (40.8%)	290 (27.8%)	<0.001
Childhood environment Urban Rural Farming	 795 (29.8%) 699 (26.2%) 1171 (44.0%)	 260 (24.1%) 384 (35.7%) 434 (40.2%)	<0.001
ISCO-08 skill level 1 (lowest) 2 3 4 (highest)	 124 (5.3%) 1415 (60.1%) 491 (20.9%) 323 (13.7%)	 34 (3.8%) 511 (57.0%) 189 (21.1%) 162 (18.1%)	0.007
Socioeconomic status Academic and higher civil servants Middle-level civil servants Non-manual assistant employees Manual workers in industry Manual workers in service Self-employed other than academics Student Housewife/male equivalent	 322 (12.7%) 491 (19.3%) 108 (4.2%) 479 (18.8%) 706 (27.8%) 325 (12.8%) 96 (3.8%) 15 (0.6%)	 163 (16.6%) 186 (18.9%) 36 (3.7%) 166 (16.9%) 263 (26.7%) 111 (11.3%) 53 (5.4%) 4 (0.4%)	0.022
Employed Unemployed Pension Disability pension	1666 (60.6%) 155 (5.6%) 639 (23.3%) 105 (3.8%)	704 (66.0%) 23 (2.2%) 245 (23.0%) 18 (1.7%)	<0.001

Data are shown as n (%) or mean (SD) or median (25^{th} and 75^{th} percentiles)

The language groups showed differences in cumulative smoke and occupational exposure. For example, current smoking was more common among Finnish speakers than Swedish speakers, respectively (23.5% vs 16.1%; P<0.001), and Finnish speakers were more often heavy smokers (Table 1). A minor trend of more exposure for Finnish than Swedish speakers was seen among second-hand smoke exposure at home and work. Further, the prevalence of occupational exposure to VGDF was higher for Finnish than Swedish speakers (40.8% vs. 27.8%; P<0.001) (Table1). (I) Last, childhood environment exposed Finnish speakers for more pollution than Swedish speakers. Swedish speakers had a more frequent rural childhood environment than Finnish speakers, whereas Finnish speakers had more frequent exposure to urban or farming environment in childhood (Table 1). (III) To conclude, Finnish- and Swedish-speaking Finns in Western Finland had marked behavioural and environmental differences.

In addition, socioeconomic difference was observed between language groups (Table 1). Finnish speakers had lower SES score based on ISCO-08 skill level than Swedish speakers (P=0.007). (I-II) SES was also significantly different between language groups with occupation classification used in previous OLIN and FinEsS studies (Pallasaho et al., 2004). Furthermore, employment status was significantly different between language groups, and unemployment rates and disability pension rates were higher among Finnish than Swedish speakers (Table 1, unpublished data).

Childhood environment can be another independent social divider to spoken language. Swedish- and Finning-speaking Finns had differences in childhood environment. What stands out in this is that the differences between social dividers did not fully correlate with previously discussed factors (Tables 1 and 2). Comparison between those with non-farming and farming environment showed differences. For example, those with childhood exposure to farming environment were older, had lower socioeconomic status, exercised more, and smoked less but had more occupational exposure to VGDF than those without childhood exposure to farming environment (Table 2). There was no difference in COPD or asthma prevalence; however, those with childhood exposure to farming environment had less allergies than those without exposure (Table 2). (III)

Table 2. Demographics of the 3,767 participants in Western Finland with known childhood environment

	Childhood non-farming environment n=2,143 (56.9%)	Childhood farming environment n=1,624 (43.1%)	P-value
Female sex	1161 (54.2%)	805 (49.6%)	0.005
Mean age (SD) Median age	46 (14.7) 48 (34-60)	55 (12.9) 59 (48-65)	<0.001
Mean BMI (SD) Median BMI	26.5 (4.9) 25.8 (23.1-28.9)	27.1 (4.7) 26.3 (23.7-29.7)	<0.001
Family history of allergy	742 (34.6%)	431 (26.5%)	<0.001
Family history of asthma	550 (25.7%)	421 (25.9%)	0.857
Current farmers	25 (1.4%)	179 (12.6%)	<0.001
Skill level ≤2*	1033 (58.1%)	1003 (71.1%)	<0.001
Physical activity more than 3 h/day	1036 (51.6%)	914 (61.1%)	<0.001
Physical exercise more than 2–3 times a week	1525 (71.7%)	1208 (75.0%)	0.023
Occupational exposure to VGDF	670 (31.8%)	697 (44.3%)	<0.001
Smoking status Never smokers Ex-smokers Current smokers	 1073 (50.1%) 580 (27.1%) 490 (22.9%)	 911 (56.1%) 449 (27.6%) 264 (16.3%)	<0.001
Physician diagnosed asthma Age group 20–39 years 40–59 years 60–69 years	250 (11.7%) 109 (14.2%) 82 (9.8%) 59 (10.9%)	184 (11.3%) 35 (14.1%) 58 (9.7%) 91 (11.7%)	0.749
Current asthma medication	250 (11.7%)	194 (11.9%)	0.792
Allergic rhinitis Age group 20–39 years 40–59 years 60–69 years	442 (20.6%) 209 (27.1%) 170 (20.4%) 63 (11.7%)	240 (14.8%) 58 (23.4%) 102 (17.1%) 80 (10.3%)	<0.001
Physician diagnosed COPD Age group 20–39 years 40–59 years 60–69 years	48 (2.2%) 3 (0.4%) 17 (2.0%) 28 (5.2%)	46 (2.8%) 1 (0.4%) 14 (2.3%) 31 (4.0%)	0.248

Data are shown as n (%) or mean (SD) or median (25th and 75th percentiles). Those with missing information on childhood exposure to farming environment were excluded (n=97).

*Skill level ≤2 indicates low socioeconomic status.

Last, the populations in Western and Southern Finland had differences in their age at asthma diagnosis and childhood environment. The age at asthma diagnosis was known for 426 (95.9%) out of 444 participants with physician-diagnosed asthma in Western Finland. Of the responders with physician-diagnosed asthma, 114 (26.8%) had early-, 173 (40.6%) had intermediate-, and 139 (32.6%) had late-diagnosed asthma. Whereas in the Southern Finland cohort 434 subjects had physician-diagnosed asthma, and the age at diagnosis was known for 415 (95.6%) responders. Of those, 131 (31.6%) had early-, 184 (44.3%) had intermediate-, and 100 (24.1%) had late-diagnosed asthma. (III) Combined data from Western Finland and Southern Finland were used for N-ERD prevalence estimate. (IV)

5.2 Respiratory symptoms

Above described differences in individual behaviour and environmental exposure in Finnish- and Swedish-speaking Finns inspired us to analyse more closely six current respiratory symptoms: dyspnoea mMRC score ≥2, tightness in the chest, wheeze, longstanding cough, sputum production, and constant nasal blockage. Prevalence of three respiratory symptoms was significantly different between language groups: 1) Dyspnoea mMRC ≥2 (11.1% vs 6.5%, P<0.001); 2) tightness in the chest (16.5% vs 11.6% P<0.001); and 3) constant nasal blockage (24.0% vs 16.5%, P<0.001) were more common in the Finnish-speaking than among the Swedish-speaking Finns, respectively. (I)

Dyspnoea mMRC ≥2 correlates to mortality (Backman et al., 2020; Leivseth et al., 2014) and therefore the odds for this symptom were counted separately with multivariate binary logistic regression. In these analyses, odds for Dyspnoea mMRC ≥2 was higher with COPD, asthma, older age, female sex, smoking, occupational exposure to VGDF, overweight, and obesity; whereas, native language, skill level, and time spent moving or sitting did not increase the odds in adjusted analyses (Table 3). Belonging to a language population per se was not a risk factor for dyspnoea, even though the prevalence difference between language groups was statistically significant. (I)

Table 3. Factors associated with dyspnoea assessed by binary logistic regression analyses

	Dyspnoea mMRC ≥2 (n=380)			
	Crude		*Adjusted	
	OR	95% CI	OR	95 % CI
Age groups (20-39 years ref.)				
40-59 years	1.68	1.22-2.30	1.39	0.91-2.14
60-69 years	2.49	1.82-3.39	2.20	1.44-3.37
Female sex	1.59	1.28-1.97	2.38	1.71-3.30
Finnish-speaking	1.78	1.37-2.33	1.29	0.89-1.88
Smoking status (never smoker ref.)				
Ex-smoker	1.62	1.27-2.08	1.07	0.75-1.51
Current smoker	1.85	1.42-2.42	1.59	1.08-2.35
Occupational exposure to vapours, gases, dust or fumes	1.74	1.40-2.17	1.47	1.07-2.02
BMI (<25 ref.)				
Overweight (25-29.9)	1.68	1.24-2.27	1.57	1.06-2.33
Obesity grade I (30-34.99)	4.42	3.21-6.07	3.51	2.30-5.37
Obesity grade II (35-)	10.37	7.20-14.93	9.74	6.01-15.81
Time spent moving (continuous)	0.96	0.92-0.99	0.96	0.91-1.01
Time spent sitting (continuous)	1.05	0.97-1.14	1.04	0.92-1.17
ISCO-08 skill level (4-highest ref.)				
1 (lowest)	2.32	1.25-4.30	1.21	0.56-2.58
2	2.15	1.43-3.26	1.41	0.86-2.31
3	1.41	0.87-2.27	1.040	0.59-1.82
Physician-diagnosis of asthma	5.25	4.12-6.68	4.78	3.41-6.71
Physician-diagnosis of COPD	17.17	11.79-25.00	10.94	5.91-20.26

*The model was adjusted for all covariates shown in the table. Study population Western Finland (n=3,864).

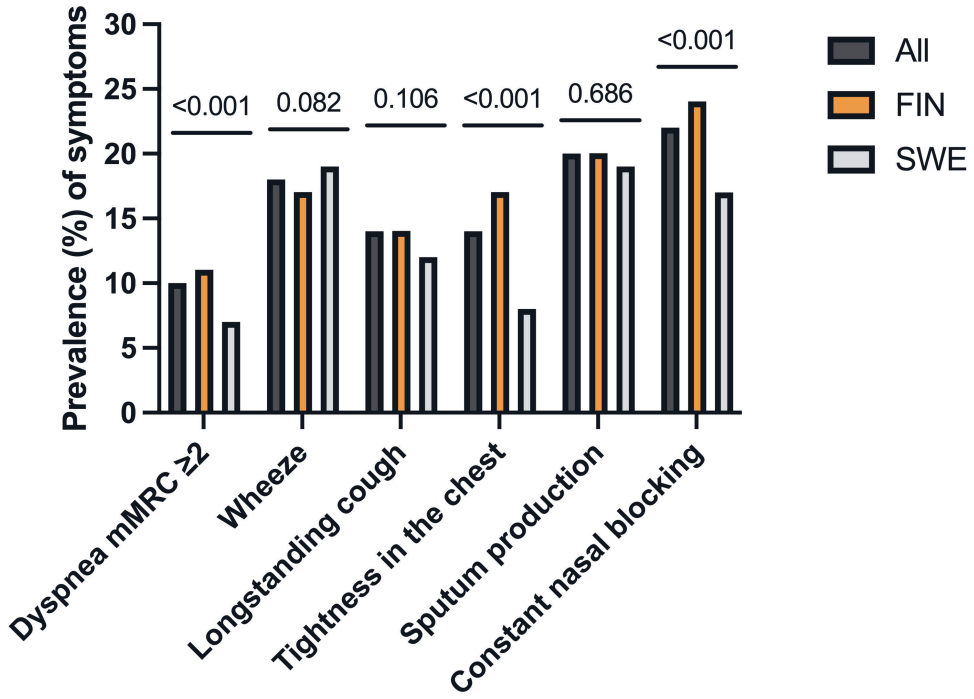


Figure 13. Prevalence of six respiratory symptoms in Western Finland, among Finnish and Swedish speakers (n=3864). The overall P-value is shown among groups

5.3 Respiratory diseases

An important part of the questionnaire was the self-reported diagnosis. The prevalence of physician-diagnosed asthma was 11.5% in Western Finland, 10.3% for males, and 12.5% for females (P=0.032) and 11.5% for Finnish and Swedish speakers (P=0.961). The prevalence of physician diagnosed COPD was 2.5% overall (2.9% for males vs. 2.1% for females P=0.116). Interestingly, COPD prevalence was higher for Finnish speakers than Swedish speakers (3.0% vs 1.3% P=0.002). (II) COPD was more common in the low SES group than in high SES group. By contrast, allergic rhinitis and asthma had less clear social gradient patterns (Figure 14, unpublished data).

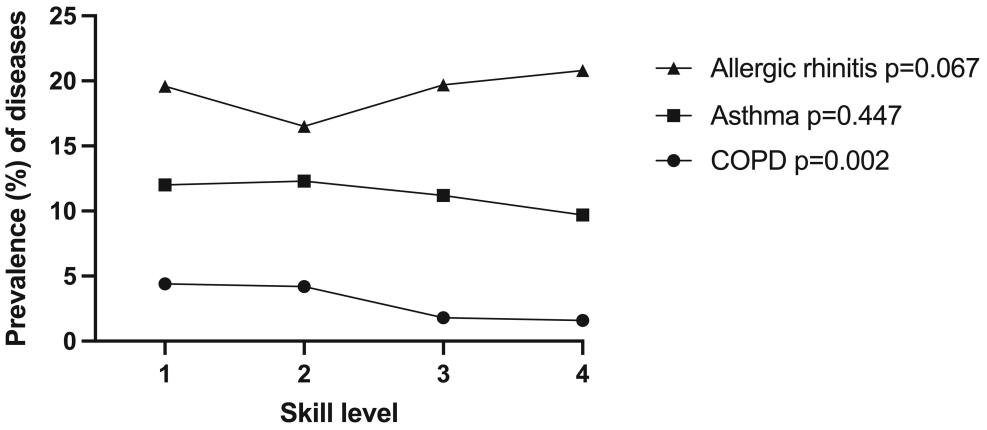


Figure 14. Prevalence of allergic rhinitis, asthma, and COPD in different skill levels in Western Finland, only COPD had social gradient with higher prevalence in low skill levels (Pearson Chi-Square, overall p-value)

On the question to factors linked to asthma, odds were higher with physician diagnosed allergic rhinitis, family history of asthma, smoking and occupational exposure, and obesity (Table 3). In an unpublished analysis, cumulative smoke and occupational exposure had a dose-response relationship to asthma in adjusted analyses for age, sex, and BMI. The odds ratio was with one exposure OR 1.26: 0.97-1.64, two exposures OR 1.92: 1.43-2.56 and three exposures OR 2.21: 1.48-3.30. Skill level was not associated with asthma in adjusted analyses for age, sex, and BMI (data not shown). (III)

There was a difference in age at asthma diagnosis between Western and Southern Finland. For example, asthma was diagnosed more often after 40 years in Western Finland (32.6%) than in Southern Finland (24.1%). The prevalence of late-diagnosed asthma was 3.8% in Western Finland and 2.5% in Southern Finland (P=0.001). Further, childhood exposure to farming environment was more common in Western Finland (42.4%) than in Southern Finland (11.5%) among those with physician-diagnosed asthma with a known age at diagnosis. The above observations have led to a hypothesis of dual effect of farming environment on age at asthma diagnosis. Therefore, we planned further analyses. (III)

Table 4. Factors associated with self-reported physician-diagnosed asthma assessed by binary logistic regression analysis

	Physician-diagnosed asthma (n=444)			
	Crude		*Adjusted	
	OR	CI 95%	OR	95% CI
Age	0.99	0.99-1.00	1.00	0.99-1.01
Female sex	1.24	1.02-1.52	1.21	0.95-1.54
Physician-diagnosed allergic rhinitis	6.80	5.51-8.40	6.64	5.23-8.44
Childhood exposure to farming environment	0.97	0.79-1.19	1.10	0.87-1.40
Family history of asthma	2.91	2.37-3.56	2.38	1.88-3.02
Family history of allergy	2.08	1.70-2.54	0.90	0.70-1.16
Smoking status, never smoker (ref.)				
Ex.smoker	1.43	1.14-1.73	1.54	1.19-1.99
Current smoker	1.12	0.86-1.46	1.21	0.89-1.64
Occupational exposure to VGDF	1.41	1.15-1.73	1.32	1.04-1.67
BMI <25 kg/m2 (ref.)				
BMI 25-29.99 kg/m2	0.90	0.71-1.13	0.87	0.67-1.14
BMI ≥30 kg/m2	1.37	1.06-1.77	1.38	1.03-1.84

*The model was adjusted for all covariates shown in the table. Study population Western Finland (n=3,864).

The prevalence of asthma was the same for those with non-farming and farming childhood environment (Table 2). We did not observe increased odds for asthma with childhood exposure to farming environment in adjusted regression analysis (Table 3). However, the mean age at diagnosis was lower for non-farming than farming environment (Figure 15A). In Cox time to event analyses, 50% had their asthma diagnosis by the age of 20 years for those with non-farming childhood environment whereas the median was 37 years for those exposed to a farming environment in their childhood (Figure 15B). (III)

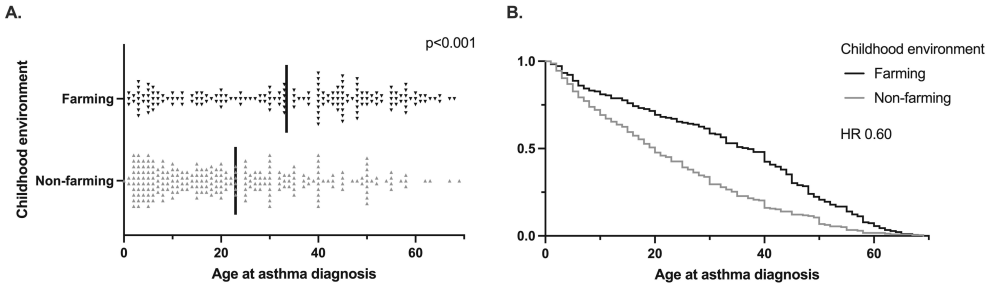


Figure 15. A. Mean age at asthma diagnosis with farming and non-farming childhood environment, B. Cox time to event analyses to age at asthma diagnosis with farming and non-farming environment

Based on the above results, we performed further analysis with multivariable binary logistic regression analysis for different groups according to age at asthma diagnosis. In these analyses, the odds for early-diagnosed and intermediate-diagnosed asthma were lower and odds for late-diagnosed asthma were higher with childhood exposure to farming environment (Figure 16A). Most reliable adjusted analysis for age, sex, allergic rhinitis, family history of asthma, family history of allergy, smoking status, occupational exposure to VGDF and BMI results are shown in Figure 16B, the population for early-diagnosed asthma included age 20-69 years, intermediate-diagnosed asthma ≥40 years, late-diagnosed asthma ≥60 years. Childhood exposure to farming environment had higher odds to late-diagnosed asthma in sensitivity analyses excluding COPD and current farming (Figure 16D). The result was validated in a Southern Finland, Helsinki cohort (Figure 16C). (III)

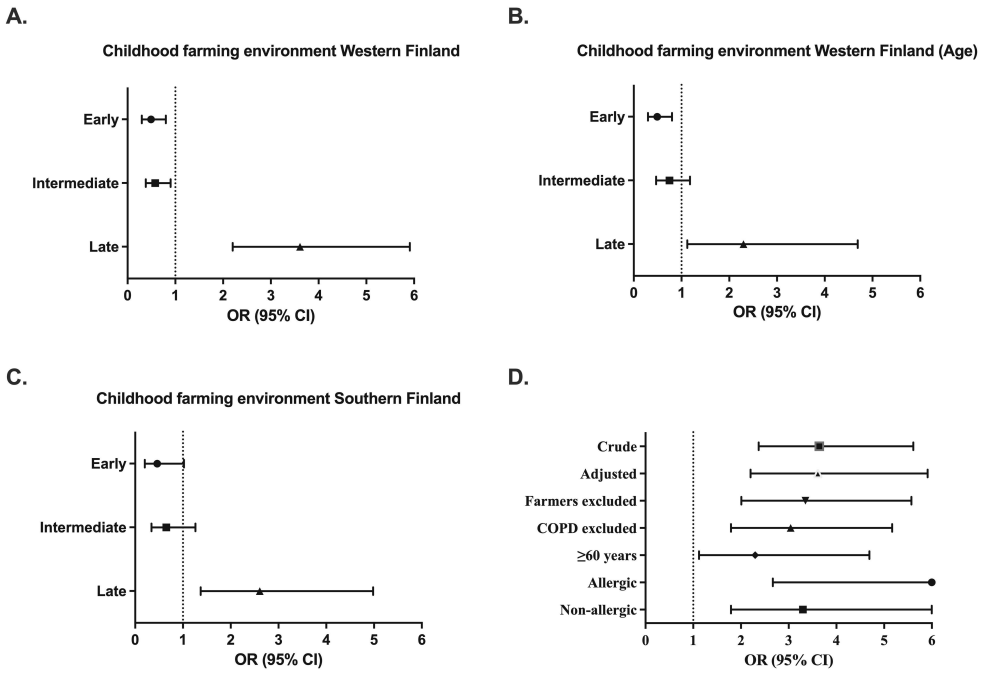
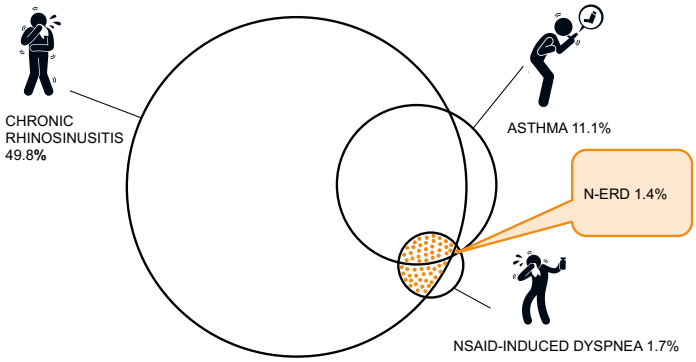


Figure 16. Association of age at asthma diagnosis with childhood farming environment in adjusted logistic regressions in Western Finland (A), adjusted additionally for age (population early 20-69 years, intermediate ≥40 years, late ≥60 years) in Western Finland (B), and validated with adjusted analyses in the Southern Finland population (C). Analyses 16A and 16C were adjusted for sex, allergic rhinitis, family history of asthma, family history of allergy, smoking status, occupational exposure to VGDF and BMI, 16B was additionally adjusted for age. Sensitivity analyses in Western Finland (D), crude analyses, adjusted analyses, adjusted analyses excluding current farmers, adjusted analyses excluding COPD, age adjusted analyses for those ≥60 years, analyses for allergic and non-allergic persons.

5.4 N-ERD

There was no difference between Finnish and Swedish speakers with respect to the prevalence of wheeze (17.0% vs 19.4%, P=0.082); longstanding cough (14.2% vs 12.2%, P=0.106); or sputum production (19.9% vs 19.3%, P=0.686) (Figure 13). The idea for this section came from the following observation that there was a significant difference in constant nasal blockage between language groups in Western Finland. The prevalence of constant nasal blockage was 24.0% in Finnish speakers versus 16.5% in Swedish speakers (P<0.001) (I, Figure 13). Constant nasal blockage is a typical but non-specific symptom of CRSwNP associated with N-ERD (Fokkens et al., 2020b). We had a hypothesis that difference between language groups might indicate possible behavioural or environmental causes for N-ERD.



Stick figures Leremy Gan

Figure 17. Prevalence of rhinitis, asthma, and NSAID-induced dyspnoea in Finland (n=7,930)

Analyses were conducted with combined data from Western and Southern Finland because N-ERD is an uncommon disease. The N-ERD has been defined as an overlap of NSAID-induced dyspnoea and asthma or chronic rhinosinusitis; whereas AERD as a triad of all three abovementioned diseases (Kowalski et al., 2019a). Chronic rhinosinusitis with or without nasal polyposis is the typical upper airway disease in AERD or N-ERD (Kowalski et al., 2019a). Rhinitis was asked with four different questions and included allergic rhinitis. NSAID-induced dyspnoea included all reporting respiratory symptoms after ingestion of pain killers, and asthma

included those reporting physician-diagnosed asthma. With the overlap of these three conditions, the prevalence of N-ERD and AERD were estimated. In these analyses, population-based prevalence of NSAID-induced dyspnoea was 1.7%, N-ERD was 1.4%, and AERD was 0.7% (Figure 17). (IV)

Further analysis of associations between N-ERD and behavioural and environmental factors were done with multivariable binary logistic regression models that included those factors that were significant in crude models. Smoking, second-hand smoking and occupational exposure were reclassified as one variable to get a stronger model and dose-relationship. Table 5 displays the results of these analyses. The odds for N-ERD were higher with older age, family history of asthma or allergic rhinitis, cumulative smoke, and occupational exposure (Table 5). Childhood farming environment had higher odds only in the unadjusted analyses. A dose-response relationship was observed with cumulative smoke and occupational exposure. (IV)

Table 5. Factors associated with N-ERD determined by multivariable binary logistic regression

	Crude		Adjusted*	
	OR	95% CI	OR	95% CI
Age 20-39 years (ref.)				
Age 40-59 years	2.15	1.25-3.68	2.11	1.19-3.76
Age 60-69 years	2.90	1.68-4.99	3.08	1.68-5.64
Female sex	1.57	1.06-2.33	1.46	0.94-2.28
Family history of asthma	2.98	2.04-4.34	2.34	1.53-3.57
Family history of allergic rhinitis	2.46	1.68-3.59	2.47	1.60-3.83
Cumulative smoke and occupational exposure (ref no exposure)**				
1 exposure	1.63	0.97-2.75	1.49	0.86-2.59
2 exposures	2.65	1.53-4.57	2.41	1.34-4.34
3 exposures	3.83	1.98-7.39	3.68	1.82-7.46
BMI <25 kg/m^2 (ref.)				
BMI 25-29.99 kg/m^2	1.27	0.82-1.98	1.02	0.64-1.64
BMI ≥30 kg/m^2	1.72	1.05-2.81	1.14	0.67-1.95
Childhood exposure to farming environment	1.75	1.18-2.57	1.38	0.90-2.12

Reference category = without N-ERD, n=7,930, *Adjusted to all variables in the model, **Cumulative smoke and occupational exposure was classified from 0-3 exposures calculating smoking (current or ex-smoking), second-hand smoke (smoke exposure at home or at work), and occupational exposure to VGDF.

5.5 Multimorbidity

After analysing respiratory diseases, we focused our attention on language groups and chronic diseases and morbidity. As shown in Table 5, it is apparent that Finnish speakers were significantly more often diagnosed with COPD, heart failure, diabetes, dyspepsia/reflux disease, chronic kidney failure, and painful conditions than Swedish speakers (Table 6). However, in some diseases such as asthma and hypertension there was no significant difference between language groups. (II)

Table 6. Prevalence of chronic diseases in Western Finland (n=3,864)

	Finnish speakers	Swedish speakers	P-value
Asthma	319 (11.5%)	125 (11.5%)	0.955
COPD	83 (3.0%)	14 (1.3%)	0.002
Hypertension	634 (22.8%)	253 (23.3%)	0.733
Coronary heart disease	84 (3.0%)	29 (2.7%)	0.597
Atrial fibrillation	215 (7.7%)	70 (6.5%)	0.193
Heart failure	47 (1.7%)	5 (0.5%)	0.002
Stroke and transient ischemic attack	61 (2.2%)	29 (2.7%)	0.406
Diabetes	224 (8.1%)	55 (5.1%)	0.001
Depression	278 (10%)	101 (9.3%)	0.548
Panic attack or anxiety	160 (5.8%)	69 (6.4%)	0.495
Treated dyspepsia	201 (7.2%)	53 (4.9%)	0.008
Chronic kidney failure	25 (0.9%)	2 (0.2%)	0.016
Sleep apnoea	139 (5.0%)	50 (4.6%)	0.678
Osteoporosis	75 (2.7%)	24 (2.2 %)	0.429
Painful conditions	272 (9.8%)	55 (5.1%)	<0.001

Data are shown as n (%)

We carried out sensitivity analyses because of complex comorbidity patterns between these diseases. The prevalence of multimorbidity was 26.0% in Finnish speakers and 22.3% in Swedish speakers, P=0.016. We used age groups for comparison between language groups. In the age group 60-69 years, Finnish speakers were more often multimorbid (41% vs. 32%, P=0.018) than Swedish speakers. There was no significant difference in multimorbidity between Finnish and Swedish speakers in the age groups of 20-39 years (9% vs. 12%, P=0.202) or 40-59 years (23% vs. 20%,

P=0.427). (II) The association between lifestyle factors and multimorbidity was evaluated with a logistic regression model shown in Table 7. The odds for multimorbidity were higher with older age, smoking, inactivity, overweight, and obesity in adjusted models. However, lower skill level and language groups had higher odds only in unadjusted models. (II)

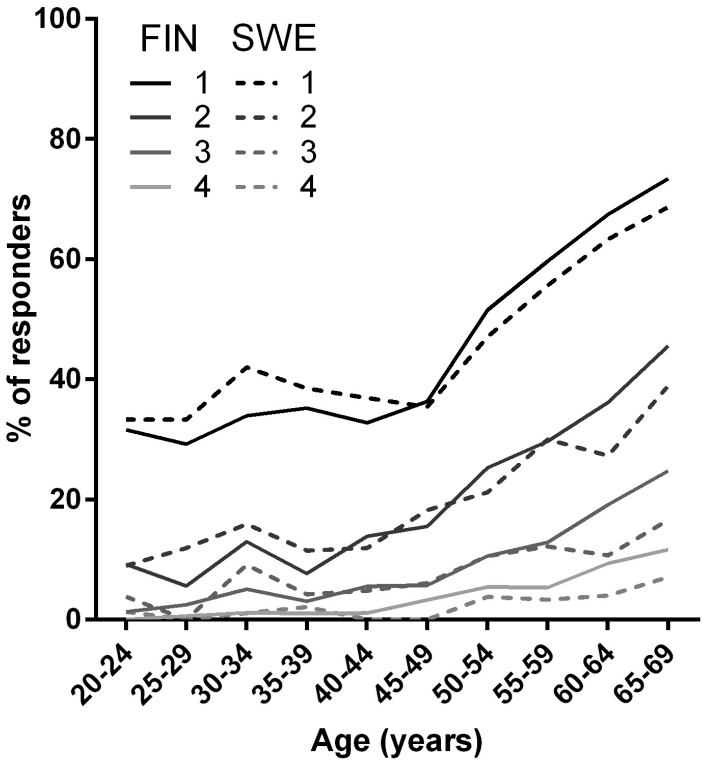


Figure 18. The number of diseases increased with age in both language groups. Multimorbidity was more common in older age groups among Finnish speakers than Swedish speakers

Table 7. Factors associated with multimorbidity (morbidity count ≥2) in univariate and multivariate logistic regression analyses with prevalence

	Disease count <2 n (%)	Multimorbidity n (%)	Crude OR (95% CI)	*Adjusted OR (95% CI)
Age groups (20-39 years ref.)	929 (90.0%)	103 (10.0%)	1	1
40-59 years	1132 (78.0%)	320 (22.0%)	2.55 (2.01-3.24)	2.35 (1.74-3.16)
60-69 years	837 (60.7%)	543 (39.3%)	5.85 (4.65-7.37)	5.91 (4.40-7.93)
Male sex (ref.)	1390 (75.3%)	457 (24.7%)	1	1
Female sex	1508 (74.8%)	509 (25.2%)	1.03 (0.89-1.19)	1.32 (1.09-1.60)
Finnish speaking (ref.)	2056 (74.0%)	724 (26.0%)	1	1
Swedish speaking	842 (77.7%)	242 (22.3%)	0.82 (0.69-0.96)	1.13 (0.92-1.40)
Never smoker (ref.)	1628 (80.5%)	395 (19.5%)	1	1
Current smoker	563 (72.6%)	212 (27.4%)	1.55 (1.28-1.88)	1.85 (1.43-2.38)
Ex-smoker	707 (66.3%)	359 (33.7%)	2.09 (1.77-2.48)	1.82 (1.47-2.25)
BMI (<25 kg/m^2 ref.)	1281 (85.1%)	225 (14.9%)	1	1
Overweight (25-29.9 kg/m^2)	1110 (74.9%)	371 (25.1%)	1.90 (1.58-2.29)	1.53 (1.23-1.91)
Obesity grade I (30-34.99 kg/m^2)	353 (61.6%)	220 (38.4%)	3.55 (2.85-4.42)	2.73 (2.09-3.56)
Obesity grade II (≥35 kg/m^2)	98 (44.1%)	124 (55.9%)	7.20 (5.33-9.73)	5.62 (3.88-8.15)
Physically active ≥3h/day (ref.)	1532 (77.3%)	449 (22.7%)	1	1
Physically active < 3 h/day	1190 (74.7%)	402 (25.3%)	1.15 (0.99-1.35)	1.23 (1.01-1.49)
Skill level 4 (ref.)	391 (80.6%)	94 (19.4%)	1	1
Skill level 3	548 (80.6%)	132 (19.4%)	0.94 (0.75-1.36)	0.98 (0.71-1.36)
Skill level 2	1395 (72.4%)	531 (27.6%)	1.59 (1.24-2.04)	1.24 (0.93-1.65)
Skill level 1	108 (68.4%)	50 (31.6%)	1.94 (1.29-2.90)	1.58 (1.00-2.51)

*Adjusted for all variables in the table

As stated above, the odds for multimorbidity were higher with current and ex-smoking, physical inactivity, and obesity. Therefore, prevalence of multimorbidity in relation to smoking status, physical activity, and BMI was calculated and charted as shown below. The prevalence of multimorbidity in different behavioural patterns can be seen from the chart. For example, the prevalence of multimorbidity was 12.2% in the non-smoking, physically active, and healthy weight group; whereas, it was 57.4% in the smoking, grade II obese, and physically inactive group (Figure 18). This chart is proposed to be used as a risk evaluating and motivational tool. (II)

	BMI <25	BMI 25-29.9	BMI 30-34.9	BMI ≥35
Never smoker physically active	12.2	18.0	30.0	43.2
Never smoker physically inactive	11.1	20.3	33.1	56.5
Current or ex-smoker physically active	17.8	28.0	34.1	55.0
Current or ex-smoker physically inactive	19.5	30.2	53.6	57.4

Variables: multimorbidity=morbidity count ≥2, physically active=duration of daily physical activity ≥3 h, physically inactive=duration of daily physical activity <3 h, current smokers=active smokers or stopped less than 12 months before, ex-smokers=stopped smoking more than 12 months before, never smokers=neither a current smoker nor an ex-smoker, BMI groups: under and normal weight <25 kg/m2, overweight 25.0–29.9 kg/m2, obesity grade I 30.0–34.9 kg/m2 and obesity grade II ≥35.0 kg/m2

Figure 19. The prevalence of multimorbidity increases with obesity, physical inactivity, and smoking. The prevalence is in percentage, data Western Finland (n=3,525)

5.6 Observed morbidity in Western Finland

The final part of the results compares morbidity between populations. These prevalence results were published in individual papers (I-IV) and age standardised rates for N-ERD in combined population in paper IV. The combined population aged 20-69 years from Finnish cohorts was used as a standard population and observed prevalence and age standardised rates were compared to those in Western Finland. Comparison is provided to 1) Western Finland cohort, 2) Finnish speakers in Western Finland, 3) Swedish Speakers in Western Finland, 4) Farming childhood environment in Western Finland, and 5) non-farming childhood environment in Western Finland.

Age standardised rates estimated the relative risk between the standard population and the population under study. They were counted as actual prevalence of disease divided by expected diseases with indirect age standardization using both cohorts as a standard population. Interestingly, as shown in Table 7 below, asthma prevalence and age-standardised rates were similar between language and childhood environment groups. The allergic rhinitis rate was same for language groups, but it was, lower (0.9) for farming and higher (1.3) for non-farming childhood environment. Swedish speakers had a lower COPD rate (0.5) than Finnish speakers (1.1). Furthermore, those with childhood exposure to farming environment had lower rate (0.9) than those without (1.0). Finnish speakers had higher N-ERD rate (1.3) than Swedish speakers (0.4). Last, those with childhood exposure to farming environment had higher rate (1.2) of N-ERD than the total population. In summary, these results suggest that there is a clear association between respiratory morbidity and social and physical environment.

Table 8. Disease prevalence and age-standardised rate

	Finland	Western Finland	Finnish speakers	Swedish speakers	Farming childhood environment	Non-farming childhood environment
Asthma						
prevalence	11.1%	11.2%	11.5%	11.5%	11.3%	11.7%
age-standardized rate	1.0	1.0	1.1	1.1	1.1	1.0
Allergic rhinitis						
prevalence	22.5%	17.8%	17.7%	18.5%	14.8%	20.6%
age-standardized rate	1.0	1.0	1.0	1.0	0.9	1.3
COPD						
prevalence	2.2%	2.5%	3.0%	1.3%	2.8%	2.2%
age-standardized rate	1.0	0.9	1.1	0.5	0.9	1.0
N-ERD						
prevalence	1.4%	1.6%	2.1%	0.6%	1.9%	1.5%
age-standardized rate	1.0	1.1	1.3	0.4	1.2	1.0
Multimorbidity						
prevalence	22.4%	25.0%	26.0%	22.3%	29.0%	21.6%
age-standardized rate	1.0	1.0	1.0	1.0	1.0	1.0

Data are %/age-standardized rate

6 DISCUSSION

6.1 Methodology

The study was based on a cross-sectional FinEsS survey 2016 in Seinäjoki Vaasa region. The sample was selected randomly from a population aged 20-69 years in the area. A random population sample avoids selection bias compared to health service-attendance studies, even though those with the disease, female subjects, and older subjects are more eager to respond than others. As a limitation, the responder rate was 52.5%, lower than we hoped for, and which may cause a lack of representativeness and selection bias. The response rate in those aged ≥40 years and ≥60 years was 61.7%, and 73.8%, respectively. Non-responders were more often male and <40 years old. Nonresponse did not affect respiratory symptom and asthma prevalence estimates in Sweden, where the non-responder pattern was similar (Räisänen et al., 2020). Furthermore, the results have less bias for older participants, and we can generalise these results. Swedish speakers had a higher response rate than Finnish speakers (60.0% vs. 51.4%). The results might underestimate health inequality among language groups for the reason that participation has been reported to be associated with survival, higher socioeconomic status and less symptoms and diseases (Langhammer et al., 2012). The main results in the present study were gained from the age group of 60-69 years that had a response rate of 73.8%, therefore, we consider our results to be reliable. In questionnaire studies, the response rates have been declining recently. However, we do not consider our rate to be low as several studies performed approximately at the same time reported even lower response rates. For example, respiratory cough questionnaire studies performed in Finland had a response rate of 26.4% (Lätti et al., 2018), and the multi-national survey in asthma had a response rate of 15.0% (Price et al., 2014).

The FinEsS 2016 questionnaire was used both in Western and Southern Finland. The FinEsS questionnaire is based on the OLIN questionnaire. The questionnaire layout and wording may influence prevalence and risk estimates; however, identical questions yield similar prevalence estimates (Ekerljung et al., 2013). Therefore, only limited alterations have been made to the questionnaire between years. Cooperation

with core questions in Nordic countries offers a reliable way to compare morbidity and symptom burden. Some of the questions, like mMRC 2, are used very widely. Other questions are of more local and Nordic interest. The OLIN questionnaire has been validated with structural interviews and spirometry and methacholine tests (Lundbäck et al., 1993). In addition, the quality of translations is essential for the comparison of different language groups.

We excluded those with other languages than Finnish and Swedish to get a partly fixed model regarding genetics, physical environment, and health care (I-III). The population in the area comprise the same Finnish Western genetic subgroup (Kerminen et al., 2017). Therefore, the differences in age at asthma diagnosis might be explained by different environments and epigenetic changes. However, further genetic studies are needed to exclude enrichment of risk genes in language groups. Migration rate in the Seinäjoki and Vaasa suburban or rural area is low and is usually within the area (Martikainen et al., 2008; J. Saarela & Finnäs, 2013). However, there might have been selective migration from farms, such as those with asthma moved away from farms after completing their education to different occupation. In addition, the Finnish asthma program has worked with accessibility to physicians and spirometry and the area is well covered with medical services, and each GP office has spirometers available. The study area is also served with two central hospitals having separate respiratory medicine units for adults with asthma and paediatric departments for children with asthma. The authors believe that there is no major difference in asthma diagnostics between rural and suburban areas based on clinical experience and due to Finnish asthma program reports from the area (Tuomisto et al., 2004). However, we acknowledge that there might have been more differences after the wars in health care access between rural and suburban Western Finland that might have delayed asthma diagnosis for some older individuals. This did not affect results, as childhood exposure to farming environment increased odds for late-diagnosed asthma after the age of 40 years and 60 years.

The participants shared a physical environment, Western Finland, during 2016. However, the environment and nutrition during childhood differed when comparing the cohorts youngest and oldest age groups. All individuals were born after the wars. Finland was a poor country in 1946 when the oldest participants were born. In comparison, the standard of living was ranked among the top 20 in the world in 1996 when the youngest subjects of the study cohort were born. The tuberculosis incidence has gone down during this period, and it might be a confounding factor to immunity and lung function. There has been a significant change in the physical and social childhood environment during this period. Because of urbanisation, many

subjects aged 60-70 years grew up on a farm but had different occupations later on life. The family-owned farms used to be small. Childhood exposure to farming often continued throughout childhood and occasionally even in adulthood. Usually, one of the children in the family continued with the farm duties, and the other siblings chose different occupations. The praxis to help with farm work after moving out still exists. Currently, in the Seinäjoki-Vaasa area, the main agricultural fields are dairy farms and swine meat production. Selective migration from a farm is known to exist for those with asthma (Timm et al., 2019).

We used language groups to model how the social environment can affect our behaviour and cause morbidity. The other model we used was the childhood farming environment as an example of the physical environment. There is an interplay between social environment and physical environment that has a compound effect. For example, those with farming backgrounds often had lower educational levels and were more exposed to occupational exposure to VGDF. However, the cumulative exposure was similar between non-farming and farming childhood as those with farming backgrounds smoked less.

Cross-sectional studies are excellent for prevalence estimates. The definition of N-ERD is broader than that of AERD. The former includes those with two diseases and the latter those with a triad of diseases. In our population, the prevalence of AERD was half that of N-ERD. The result is logical and an example of how the prevalence estimates can change with changes in diagnostic framework. The analyses have limitations owing to the retrospective design and self-reported diagnosis. Several measures of multimorbidity exist. Simple counts estimate prevalence as well as more complex methods that have a benefit of disease severity (Huntley et al., 2012). The disease count ≥2 is a simple and widely accepted concept to define multimorbidity that has been used in several studies (Nguyen et al., 2019). As a limitation, this simple concept does not consider disease severity, or the variety of diseases included. Two conditions can co-occur by chance selection bias or causal associations. For example, the risk that a Finnish speaker has asthma and depression by chance is 1.2% (0.115*0.10=0.0115) in the current study. Age-standardised ratios provided as a guide for the magnitude of the effect when comparing populations or groups as their demographics do differ. We used combined results from both cohorts as a standard population and compared age standardised prevalence in each subpopulation to the standard population.

Recall bias is possible with age at asthma diagnosis. However, self-reported asthma onset has been considered accurate (Torén et al., 2006). In 2014, 4.6% of the Finnish population had asthma reimbursement, according to the Social Insurance

Institution of Finland (Kauppi et al., 2015), much lower than the reported prevalence in the study. Criteria for asthma medication reimbursement strictly follow international guideline (Chung et al., 2014). According to these criteria, variable airflow limitation is objectively shown in spirometry, peak expiratory flow (PEF), or bronchial responsiveness to histamine or methacholine is moderately or severely increased. The risk of error with PEF-based asthma diagnosis exists, although PEF lability correlates with asthma (Enright et al., 2001). However, these objective tests are not specific to asthma (Tashkin et al., 2008). In Finland, some COPD patients might be diagnosed having asthma due to reimbursement benefits. In Finland, new asthma diagnosis and prevalence seem to concentrate on women in elderly populations (Kankaanranta et al., 2017). The problem of structural misdiagnosis seems to be minor, because women in elderly populations have typically smoked less.

The possibility of bias is smaller with habits as self-reported and measured estimates correlate and these habits persist without intervention to a high degree (Aarts et al., 1997; Loponen et al., 2018). The study analysed associated factors to respiratory symptoms, asthma, age at diagnosis groups, N-ERD, and multimorbidity. Many confounding factors play a role in these associations, and because of the study design, we are unable to confirm causality, although the dose-relationship with exposures and existing literature strongly supports causality with smoke exposure and respiratory disease (Coogan et al., 2015; Hisinger-Mölkänen et al., 2018; Larsson et al., 2003; M. Lindström et al., 2001; Tommola et al., 2019). We choose to use the term determinants and did not talk about risk factors often used in spoken language. Odds ratios were used to measure the size of the effect in original papers. Compared to relative risks, odds ratios overstate the effect size. However, when the prevalence is low, <15%, they are close (VanderWeele, 2020). Hazard ratios represent instantaneous risk over the study period, whereas odds ratios and relative risks ratios are cumulative over the entire study period. A cross-sectional study design limits our ability to draw causality conclusions even if we have a retrospective design with asthma diagnosis.

6.2 Social and physical environment links to individual behaviour

The social environment impacts health significantly based on previous estimations (Donkin et al., 2018), and our results were in agreement with previous estimations.

A group consists of different people making individual choices. These individuals share values, influences, and habits and therefore the choices of a group are quite uniform. Outliers do exist in all groups, and it is not beneficial to stereotype. However, we identified groups that might need more support for health equity in a population.

In this study, we used an assumption that language is a divider of social environment, and with this assumption, a difference was seen in BMI, smoking, and physical inactivity. Diet was not considered a part of the study but based on previous reports we can assume that the eating pattern was unhealthier for Finnish speakers than Swedish speakers (de Oliveira Figueiredo et al., 2019). Obesity might be partly explained with physical inactivity. However, the sex difference was contrary to a previous report in which the global age-standardised prevalence of physical inactivity was 27.5% in 2016, with a prevalence difference between men and women (23.4% vs 31.7%, respectively) (Guthold et al., 2018). (I-II)

Childhood environment influences skill level, occupational exposure, physical activity, and smoking. Those who grew up on a farm were less likely to be smokers, and that might balance the health effects of more occupational exposure linked to lower skill levels. For example, the age-standardised COPD rate was not increased for those with childhood exposure to farming environments. A low skill level does not cause COPD, but one was more likely to have an occupation with exposure to VGDF and be a smoker. Low SES is associated with obesity, smoking, and occupational exposure to VGDF (Eisner et al., 2011; Harrison et al., 2020; Pallasaho et al., 2004). In our study, COPD prevalence was higher with low SES, reported previously in low- and middle-income countries (Grigsby et al., 2016).

In our population, a social gradient was not seen in asthma. However, a lower SES has been linked to increased asthma risk (Eagan et al., 2004). In Sweden, low SES was associated with non-allergic asthma (Schyllert et al., 2020). Swedish speakers had higher SES, less farming exposure, and less cumulative smoke exposure, and they had lower rates of N-ERD and COPD. Environment affected the odds to have N-ERD and we observed differences in prevalence in language groups and childhood exposure groups.

6.3 Childhood exposure to farming environment and asthma

Despite our study limitations, childhood exposure to farming environment was associated with lower odds to early diagnosis and higher odds to later diagnosis of

asthma. We hypothesise that in addition to microbial biodiversity, the childhood farming environment expose to early harmful irritants that predispose to the development of T2-low late-onset asthma. (III)

The childhood farming environment association to lower risk of allergy and allergic asthma development is well documented in several prospective studies in children and young adults (Wells et al., 2014; Wlasiuk & Vercelli, 2012). The protective effect against early-diagnosed asthma in our study was similar to that reported in studies from alpine areas and suburban Europe (Alfvén et al., 2006; Illi et al., 2012). The childhood exposure to farming environment is related to higher expression levels of innate immunity genes (Ege et al., 2007). A better-balanced innate immunity is associated with low allergy prevalence (Ruokolainen et al., 2020). Long-term early-life exposure to stables and farm milk was associated with the highest protective effect against asthma development in children (Riedler et al., 2001). Further, farm-like indoor microbiota in nonfarm homes protected children from asthma development (Kirjavainen et al., 2019). One proposed explanation for the increase of allergic asthma prevalence in children and young adults has been urbanisation and biodiversity loss (von Hertzen & Haahtela, 2006).

Moreover, not all childhood exposure to farming is protective. Exposure to dairy feeding operations in childhood increases the asthma risk (Omland et al., 2011). Children exposed to swine animal feeding operations had increased asthma risk (Omland et al., 2011; Pavilonis et al., 2013). Childhood exposure to either pollution from traffic or dust and pesticides at the farm might influence asthma risk later in life (Chatkin et al., 2021; Mamane et al., 2015; Tiotiu et al., 2020).

The development of nonatopic asthma among current farmers in Norway had a significant dose-response association with amount of exposure to VGDF (Eduard et al., 2004). In contrast, livestock reduced asthma risk among atopic farmers (Eduard et al., 2004). Current farmers more often had neutrophilic airway inflammation as a part of their chronic respiratory disease (Douwes et al., 2002) and this neutrophilic inflammation may indicate either asthma or COPD (Kaur & Chupp, 2019). Occupational agricultural exposures were associated with the development of COPD remodelling (Eduard et al., 2009). We excluded current farmers and COPD in our sensitivity analyses. The results remained consistent, and the association was seen in both allergic and non-allergic participants.

To conclude previous evidence, the protective effect on allergic asthma is associated with microbiota and exposures to VGDF are associated with increased asthma risk. Further epigenetic studies are needed to identify the factors responsible for these observed differences. For example, the reasons might be different

childhood environments, immunity, cumulative smoke exposure, habits, and epigenetic differences because of selective migration.

6.4 N-ERD and cumulative exposures

N-ERD prevalence was higher among Finnish speakers than Swedish speakers in Western Finland, and higher for those with childhood exposure to farming environment than those without. N-ERD is a relatively uncommon disease and therefore we used combined Western and Southern data for prevalence and morbidity estimates. N-ERD was not based on self-reported diagnosis, rather it was based on the overlap of three diseases. To include mild and undiagnosed asthma rhinitis was defined with several questions including allergic rhinitis. Those diagnosed with this method were symptomatic, although those with asthma and AERD were even more symptomatic. The prevalence of self-reported severe allergic reactions was higher in N-ERD than asthma without N-ERD. N-ERD was associated with heredity of asthma or allergic rhinitis. NERD was associated with smoking, second-hand smoking and occupational exposure to VGDF with a dose-response relationship indicating causal association. Childhood exposure to a farming environment was associated with N-ERD only in the unadjusted analysis.

6.5 Lifestyle and multimorbidity

The multimorbidity rate was not increased in Western Finland compared to Finnish cohorts in general. Further, farming, and non-farming childhood environment or language groups did not affect the age-standardised multimorbidity rate. However, in the age group 60-69 years, Finnish speakers were more multimorbid than Swedish speakers. In multimorbidity, diseases may co-occur in patterns: 1) cardiovascular disease, asthma, and COPD; 2) diabetes, obesity, and hypertension; and 3) arthritis and depression patterns were identified across several countries in a previous study (Garin et al., 2014). A very similar clustering of diseases was seen in Western Finland. The multimorbidity definition and patterns do not consider disease severity or inter-relationships. If risk factors are associated, clusters of diseases are more likely to occur. We performed sensitivity analysis by grouping diseases together. (II)

Several diseases have intricate causality patterns. Furthermore, these complex patterns have many associated and non-associated factors such as age, sex, genetics,

environment, disease inter-relationships, socioeconomics, and lifestyle. Most diseases share common risk factors, or the same risk factor can affect conditions differently. One explanation might be that there are several causal models. These causality models are not mutually exclusive, and the cause should be interpreted with caution from cross-sectional studies.

As an example, the Interheart study showed a prime example of complexity (Yusuf et al., 2004). The study investigated risk factors for myocardial infarction and population attributable risks (PAR). PAR for myocardial infarction was 36% for smoking, 20% for abdominal obesity, 12% for physical inactivity, 14% for lack of daily fruits and vegetable consumption, 7% for regular alcohol intake, 18% for hypertension, and 10% for diabetes. The PAR for four lifestyle factors namely smoking, physical inactivity, lack of daily fruits and vegetables, and alcohol intake was almost 70%. To conclude, lifestyle-associated factors are significant causal and risk-modifying factors. Physical activity, smoking and BMI were related to multimorbidity. One out of ten who were never smokers, had normal weight and were physically active were multimorbid, whereas one out of two among obese physically inactive smokers were multimorbid (Figure 20). Healthy smoker bias was observed in our study. Unfortunately, many stop smoking first after being diagnosed with a chronic disease. (II)

Stick figures Leremy Gan

Figure 20. Prevalence of multimorbidity relates to smoking, physical inactivity, and BMI. In Western Finland one out of ten non-smoking, physically active and normal weight individuals were multimorbid whereas one out of two smoking, physically inactive and obese individuals were multimorbid

6.6 Observed inequalities

The differences between language groups were seen with several factors discussed above. These factors include BMI, smoking, physical activity, and exercise. These

behaviours have a compound effect, and they increase the odds to have symptoms, diseases such as COPD and diabetes, and multimorbidity. The language group or SES did not increase the odds for multimorbidity per se and the asthma prevalence was the same in both language groups. However, employment status was significantly different between language groups, and unemployment rates and disability pension rates were higher for Finnish than Swedish speakers in agreement with a previous report (Hyyppä & Mäki, 2001). In addition, childhood environment was associated with habits, occupation, and occupational exposure to VGDF.

We recognised three points needing further community-based research and action: 1) cumulative exposure to smoking and occupational exposure among those with low SES, 2) physical activity among those with higher social status, and 3) habits of younger males with lower response rate. To reduce the observed health inequalities, we need to educate the population and increase trust to health care. Physicians have gained knowledge that trust is essential for a successful patient-doctor relationship. The interventions with patient education on health literacy with informed decision-making have showed low benefit (Kew et al., 2017).

In shared decision-making, the patient's values and preferences are known in advance and the diagnosis is objective. Further, both participants have the same individual information. Discussion on the treatment and behavioural actions ideally include the number needed to treat or harm with each intervention. This health numeracy is needed for both patients and physicians to understand what effort gains most benefit. During times of misinformation, we encounter new roadblocks. Time and trust are required for those with firm beliefs outside commonly accepted ones based on misinformation. The benefit of reserving more time and continuity for the patient is seen in severe asthma clinics that have been successful in their effort. Patient-centeredness discussed above is a good starting point together with cultural competence, including language skills. In Finland, there has been little or no research effort to accommodate bias, stereotyping, or discrimination in health care. Evidence from the United States shows that discrimination and racism in health care is an unrecognised problem (Caldwell et al., 2017; Eisner et al., 2011).

The rapidly urbanising world is facing severe biodiversity loss with global warming and pollution that might influence the prevalence of respiratory disease and its phenotypes in the future. Thus, epidemiological research will continue to be crucial. Biodiverse natural environments are dependent on planetary health, which should also be a priority among health care professionals (Haahtela, 2019). Restoring biodiversity has a societal impact, for example on city planning, food and energy production, and nature conservation (Haahtela, 2019; Hanski et al., 2012). This has

been considered in the Finnish Allergy Program that had a message for individuals for health and well-being (Haahtela et al., 2021). The complexity of health issues relating to climate change highlights the need to collaborate across sectors (Dahlgren & Whitehead, 2006). Quite clearly, we need new strategies to improve the environment, social network, and behaviour to improve the lives of many. This strategy planning is challenging as the same environment might protect and harm, as seen in our examples on childhood environment and language groups.

6.7 How should we diagnose and treat chronic respiratory diseases?

The unique complexity of CRD needs to be targeted with structural strategy that includes self-monitoring. Artificial intelligence can likely help with our objectivity and thus reduce stereotype bias with diagnosis. Labels and specific definitions are helpful in epidemics research, and even unspecific labels tend to increase the quality of care. However, these labels do not consider susceptibility states or pre-clinical disease manifestations and cannot be used to understand disease-related causal molecular pathways (Collins & Varmus, 2015). For example, the age at asthma diagnosis is associated with different characteristics and varying prognoses needing different diagnostic and treatment plans. These characteristics discussed above are summarised in Table 8.

Table 9. Characteristics of early- (0-11 years), intermediate- (12-39 years), and late-diagnosed asthma (40-69 years)

Age at asthma diagnosis		
Early	Intermediate	Late
Male sex	Female sex	Female sex
Allergic	Allergic	Non-allergic
Childhood non-farming environment	Childhood non-farming environment	Childhood farming environment
T2	T2 or non-allergic T2-high	Non-allergic T2-high or non-T2
High remission rate	Medium remission rate	Low remission rate

Instead of unspecific asthma or COPD labels, we might have precise future strategies that include respiratory determinants and treatable traits. These models are possible in high-income countries but not in low-income countries. Severe asthma clinics already use systematic assessment (von Bülow et al., 2017; Wardlaw et al., 2021). For

example, these models could consider: 1) genetic profile, 2) immunity, 3) inflammation, 4) colonisation or sputum microbiome, 5) lung function, 6) imaging, 7) endoscopy, 8) exercise capacity, 9) exacerbation rate, 10) symptom profile, 11) lifestyle, 12) environment, and 13) socioeconomic situation.

7 SUMMARY AND CONCLUSIONS

In summary:

I Prevalence of dyspnoea mMRC ≥2 was higher among Finnish speakers than Swedish speakers. In multivariable logistic regressions, odds for dyspnoea mMRC ≥2 was higher with smoking and obesity, whereas native language or skill level did not increase the odds. Finnish speakers had lower skill level than Swedish speakers in Western Finland. Furthermore, Finnish speakers smoked more and were less physically active and more obese than Swedish speakers. The difference between language groups in prevalence of dyspnoea seemed to be explained by differences in lifestyle.

II COPD, diabetes, and multimorbidity prevalence was higher for Finnish speakers than Swedish speakers. The odds for multimorbidity were higher with obesity, physical inactivity, and smoking. Again, the difference between language groups was explained by differences in lifestyle and habits. We proposed a tool that describes the relationship between smoking, inactivity, and obesity relationship to morbidity and multimorbidity.

III Childhood exposure to farming environment influenced the age at asthma diagnosis. Odds for asthma were lower before and higher after the age of 40 years with childhood exposure to farming environment. Those with childhood exposure to farming smoked less, exercised more, had lower skill level and had more occupational exposure to VGDF than those without childhood exposure to farming. We generated a hypothesis that exposure to farming microbiome protects from early onset allergic asthma whereas cumulative exposure to air pollutants causes asthma at later age.

IV Prevalence of N-ERD was 1.4% and prevalence of AERD was 0.7% in Finland. N-ERD was more symptomatic than asthma without N-ERD and was associated with morbidity. Factors associated with N-ERD were older age, family

history of asthma or allergic rhinitis, cumulative exposure to smoking, secondhand smoking and occupational exposure to VGDF. N-ERD is often associated with adult-onset non-allergic asthma. Interestingly therefore, late-diagnosed asthma and N-ERD shared associating factors such as cumulative exposure to smoking, secondhand smoking and occupational exposures.

Respiratory health inequalities were observed in relation to exposure to smoking, secondhand smoking, and occupational exposure to VGDF. Therefore, future community-based participatory research projects to reduce these exposures are important together with physical activity interventions. It is essential to increase communication, health literacy, and trust to improve health care. These educational projects should be in concordance with current values and the needs of the respective population. Last, equity is simple to measure but difficult to achieve. The intervention effort should increase health in whole population and not by reducing health benefits of subpopulations. To overcome inequalities, we need sustainable strategies to improve health outcomes and achieve optimal health care.

REFERENCES

Aarts, H., Paulussen, T., & Schaalma, H. (1997). Physical exercise habit: On the conceptualization and formation of habitual health behaviours. *Health Education Research*, *12*(3). https://doi.org/10.1093/her/12.3.363

Abbafati, C., Abbas, K. M., Abbasi-Kangevari, M., Abd-Allah, F., Abdelalim, A., Abdollahi, M., Abdollahpour, I., Abegaz, K. H., Abolhassani, H., Aboyans, V., Abreu, L. G., Abrigo, M. R. M., Abualhasan, A., Abu-Raddad, L. J., Abushouk, A. I., Adabi, M., Adekanmbi, V., Adeoye, A. M., Adetokunboh, O. O., … Murray, C. J. L. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, *396*(10258). https://doi.org/10.1016/S0140-6736(20)30925-9

Abdel-Aziz, M. I., Brinkman, P., Vijverberg, S. J. H., Neerincx, A. H., Riley, J. H., Bates, S., Hashimoto, S., Kermani, N. Z., Chung, K. F., Djukanovic, R., Dahlén, S. E., Adcock, I. M., Howarth, P. H., Sterk, P. J., Kraneveld, A. D., & Maitland-van der Zee, A. H. (2021). Sputum microbiome profiles identify severe asthma phenotypes of relative stability at 12 to 18 months. *Journal of Allergy and Clinical Immunology*, *147*(1). https://doi.org/10.1016/j.jaci.2020.04.018

Abrahamsen, R., Fell, A. K. M., Svendsen, M. v., Andersson, E., Torén, K., Henneberger, P. K., & Kongerud, J. (2017). Association of respiratory symptoms and asthma with occupational exposures: Findings from a population-based cross-sectional survey in Telemark, Norway. *BMJ Open*, *7*(3). https://doi.org/10.1136/bmjopen-2016-014018

Adeloye, D., Chua, S., Lee, C., Basquill, C., Papana, A., Theodoratou, E., Nair, H., Gasevic, D., Sridhar, D., Campbell, H., Chan, K. Y., Sheikh, A., & Rudan, I. (2015). Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. *Journal of Global Health*, *5*(2). https://doi.org/10.7189/jogh.05.020415

Aguirre, B., Linares-Segovia, B., Bermúdez-Perez, R. S., Monroy-Torres, R., & Jiménez-Garza, O. (2019). LUNG FUNCTION, ALLERGIC DISEASES, AND RESPIRATORY SYMPTOMS IN CHILDREN WITH AND WITHOUT OBESITY. *Chest*, *155*(6). https://doi.org/10.1016/j.chest.2019.04.070

Agusti, A., Bel, E., Thomas, M., Vogelmeier, C., Brusselle, G., Holgate, S., Humbert, M., Jones, P., Gibson, P. G., Vestbo, J., Beasley, R., & Pavord, I. D. (2016). Treatable traits: Toward precision medicine of chronic airway diseases. In *European Respiratory Journal* (Vol. 47, Issue 2). https://doi.org/10.1183/13993003.01359-2015

Ajmera, M., Sambamoorthi, U., Metzger, A., Dwibedi, N., Rust, G., & Tworek, C. (2015). Multimorbidity and COPD medication receipt among medicaid

beneficiaries with newly diagnosed COPD. *Respiratory Care*, *60*(11). https://doi.org/10.4187/respcare.03788

Aldridge, R. W., Story, A., Hwang, S. W., Nordentoft, M., Luchenski, S. A., Hartwell, G., Tweed, E. J., Lewer, D., Vittal Katikireddi, S., & Hayward, A. C. (2018). Morbidity and mortality in homeless individuals, prisoners, sex workers, and individuals with substance use disorders in high-income countries: a systematic review and meta-analysis. *The Lancet*, *391*(10117). https://doi.org/10.1016/S0140-6736(17)31869-X

Alfvén, T., Braun-Fahrländer, C., Brunekreef, B., von Mutius, E., Riedler, J., Scheynius, A., van Hage, M., Wickman, M., Benz, M. R., Budde, J., Michels, K. B., Schram, D., Üblagger, E., Waser, M., & Pershagen, G. (2006). Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle - The PARSIFAL study. *Allergy: European Journal of Allergy and Clinical Immunology*, *61*(4). https://doi.org/10.1111/j.1398-9995.2005.00939.x

Alshabanat, A., Zafari, Z., Albanyan, O., Dairi, M., & FitzGerald, J. M. (2015). Asthma and COPD overlap syndrome (ACOS): A systematic review and meta analysis. *PLoS ONE*, *10*(9). https://doi.org/10.1371/journal.pone.0136065

Álvarez-Gálvez, J., & Jaime-Castillo, A. M. (2018). The impact of social expenditure on health inequalities in Europe. *Social Science and Medicine*, *200*. https://doi.org/10.1016/j.socscimed.2018.01.006

Andersén, H., Lampela, P., Nevanlinna, A., Säynäjäkangas, O., & Keistinen, T. (2013). High hospital burden in overlap syndrome of asthma and COPD. *Clinical Respiratory Journal*, *7*(4). https://doi.org/10.1111/crj.12013

Andersson, M., Modig, L., Hedman, L., Forsberg, B., & Rönmark, E. (2011). Heavy vehicle traffic is related to wheeze among schoolchildren: A population-based study in an area with low traffic flows. *Environmental Health: A Global Access Science Source*, *10*(1). https://doi.org/10.1186/1476-069X-10-91

Annunziato, F., Romagnani, C., & Romagnani, S. (2015). The 3 major types of innate and adaptive cell-mediated effector immunity. In *Journal of Allergy and Clinical Immunology* (Vol. 135, Issue 3). https://doi.org/10.1016/j.jaci.2014.11.001

Asarnoj, A., Hamsten, C., Wadén, K., Lupinek, C., Andersson, N., Kull, I., Curin, M., Anto, J., Bousquet, J., Valenta, R., Wickman, M., & van Hage, M. (2016). Sensitization to cat and dog allergen molecules in childhood and prediction of symptoms of cat and dog allergy in adolescence: A BAMSE/MeDALL study. *Journal of Allergy and Clinical Immunology*, *137*(3). https://doi.org/10.1016/j.jaci.2015.09.052

Axelsson, M., Ilmarinen, P., Backman, H., Ekerljung, L., Hedman, L., Langhammer, A., Lindberg, A., Lindqvist, A., Nwaru, B. I., Pallasaho, P., Sovijärvi, A., Vähätalo, I., Kankaanranta, H., Hisinger-Mölkänen, H., Piirilä, P., & Rönmark, E. (2020). Differences in diagnostic patterns of obstructive airway disease between areas and sex in Sweden and Finland - the Nordic EpiLung study. *Journal of Asthma*. https://doi.org/10.1080/02770903.2020.1776727

Axelsson, M., Lindberg, A., Kainu, A., Rönmark, E., & Jansson, S.-A. (2016). Respiratory symptoms increase health care consumption and affect everyday life – a cross-sectional population-based study from Finland, Estonia, and Sweden. *European Clinical Respiratory Journal*, *3*(1). https://doi.org/10.3402/ecrj.v3.31024

Azim, A., Freeman, A., Lavenu, A., Mistry, H., Haitchi, H. M., Newell, C., Cheng, Y., Thirlwall, Y., Harvey, M., Barber, C., Pontoppidan, K., Dennison, P., Arshad, S. H., Djukanovic, R., Howarth, P., & Kurukulaaratchy, R. J. (2020). New Perspectives on Difficult Asthma; Sex and Age of Asthma-Onset Based Phenotypes. *Journal of Allergy and Clinical Immunology: In Practice*, *8*(10). https://doi.org/10.1016/j.jaip.2020.05.053

Backman, H., Bhatta, L., Hedman, L., Brumpton, B., Vähätalo, I., Lassman-Klee, P. G., Nwaru, B., Mai, X.-M., Vikjord, S. A., Lindberg, A., Lundbäck, B., Rönmark, E., & Langhammer, A. (2020). *Respiratory symptoms as risk factors for mortality – the Nordic EpiLung Study*. https://doi.org/10.1183/13993003.congress-2020.1423

Backman, H., Räisänen, P., Hedman, L., Stridsman, C., Andersson, M., Lindberg, A., Lundbäck, B., & Rönmark, E. (2017). Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016—results from three population surveys. *Clinical and Experimental Allergy*, *47*(11). https://doi.org/10.1111/cea.12963

Baptist, A. P., Ross, J. A., & Clark, N. M. (2013). Older adults with asthma: Does age of asthma onset make a difference? *Journal of Asthma*, *50*(8). https://doi.org/10.3109/02770903.2013.816967

Barczyk, A., Maskey-Warzęchowska, M., Górska, K., Barczyk, M., Kuziemski, K., Śliwiński, P., Batura-Gabryel, H., Mróz, R., Kania, A., Obojski, A., Tażbirek, M., Celejewska-Wójcik, N., Guziejko, K., Brajer-Luftmann, B., Korzybski, D., Damps-Kostańska, I., & Krenke, R. (2019). Asthma-COPD Overlap—A Discordance Between Patient Populations Defined by Different Diagnostic Criteria. *Journal of Allergy and Clinical Immunology: In Practice*, *7*(7). https://doi.org/10.1016/j.jaip.2019.04.022

Barnes, P. J. (2006). Against the Dutch hypothesis: asthma and chronic obstructive pulmonary disease are distinct diseases. In *American journal of respiratory and critical care medicine* (Vol. 174, Issue 3). https://doi.org/10.1164/rccm.2604008

Barnes, P. J., & Celli, B. R. (2009). Systemic manifestations and comorbidities of COPD. In *European Respiratory Journal* (Vol. 33, Issue 5). https://doi.org/10.1183/09031936.00128008

Barnett, K., Mercer, S. W., Norbury, M., Watt, G., Wyke, S., & Guthrie, B. (2012). Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *The Lancet*, *380*(9836). https://doi.org/10.1016/S0140-6736(12)60240-2

Barros, R., Moreira, A., Fonseca, J., Ferraz De Oliveira, J., Delgado, L., Castel-Branco, M. G., Haahtela, T., Lopes, C., & Moreira, P. (2008). Adherence to the Mediterranean diet and fresh fruit intake are associated with improved asthma control. *Allergy: European Journal of Allergy and Clinical Immunology*, *63*(7). https://doi.org/10.1111/j.1398-9995.2008.01665.x

Bavbek, S., Yilmaz, I., Çelik, G., Aydin, O., Erkekol, F. O., Orman, A., Kurt, E., Ediger, D., Dursun, B., Abadoğlu, O., Özşeker, F., Akkaya, E., Karakiş, G. P., Canbakan, S., Yüksel, S., & Misirligil, Z. (2012). Prevalence of aspirin-exacerbated respiratory disease in patients with asthma in Turkey: A cross-sectional survey. *Allergologia et Immunopathologia*, *40*(4), 225–230. https://doi.org/10.1016/j.aller.2011.05.015

Becklake, M. R., & Kauffmann, F. (1999). Gender differences in airway behaviour over the human life span. In *Thorax* (Vol. 54, Issue 12). https://doi.org/10.1136/thx.54.12.1119

Bergqvist, J., Andersson, A., Schiöler, L., Olin, A. C., Murgia, N., Bove, M., Janson, C., Abramson, M. J., Leynaert, B., Nowak, D., Franklin, K. A., Pin, I., Storaas, T., Schlünssen, V., Heinrich, J., & Hellgren, J. (2020). Non-infectious rhinitis is more strongly associated with early—rather than late—onset of COPD: data from the European Community Respiratory Health Survey (ECRHS). *European Archives of Oto-Rhino-Laryngology*, *277*(5). https://doi.org/10.1007/s00405-020-05837-8

Bhatt, S. P., Balte, P. P., Schwartz, J. E., Cassano, P. A., Couper, D., Jacobs, D. R., Kalhan, R., O'Connor, G. T., Yende, S., Sanders, J. L., Umans, J. G., Dransfield, M. T., Chaves, P. H., White, W. B., & Oelsner, E. C. (2019). Discriminative Accuracy of FEV1:FVC Thresholds for COPD-Related Hospitalization and Mortality. *JAMA - Journal of the American Medical Association*, *321*(24). https://doi.org/10.1001/jama.2019.7233

Bhatta, D. N., & Glantz, S. A. (2020). Association of E-Cigarette Use With Respiratory Disease Among Adults: A Longitudinal Analysis. *American Journal of Preventive Medicine*, *58*(2). https://doi.org/10.1016/j.amepre.2019.07.028

Birzele, L. T., Depner, M., Ege, M. J., Engel, M., Kublik, S., Bernau, C., Loss, G. J., Genuneit, J., Horak, E., Schloter, M., Braun-Fahrländer, C., Danielewicz, H., Heederik, D., von Mutius, E., & Legatzki, A. (2017). Environmental and mucosal microbiota and their role in childhood asthma. *Allergy: European Journal of Allergy and Clinical Immunology*, *72*(1). https://doi.org/10.1111/all.13002

Blanc, P. D., Iribarren, C., Trupin, L., Earnest, G., Katz, P. P., Balmes, J., Sidney, S., & Eisner, M. D. (2009). Occupational exposures and the risk of COPD: Dusty trades revisited. *Thorax*, *64*(1). https://doi.org/10.1136/thx.2008.099390

Blöndal, V., Malinovschi, A., Sundbom, F., James, A., Middelveld, R., Franklin, K. A., Lundbäck, B., & Janson, C. (2021). Multimorbidity in asthma, association with allergy, inflammatory markers and symptom burden, results from the Swedish GA2LEN study. *Clinical and Experimental Allergy*, *51*(2). https://doi.org/10.1111/cea.13759

Borna, E., Nwaru, B. I., Bjerg, A., Mincheva, R., Rådinger, M., Lundbäck, B., & Ekerljung, L. (2019). Changes in the prevalence of asthma and respiratory symptoms in western Sweden between 2008 and 2016. *Allergy: European Journal of Allergy and Clinical Immunology*, *74*(9). https://doi.org/10.1111/all.13840

Boulet, L. P., & Boulay, M. È. (2011). Asthma-related comorbidities. In *Expert Review of Respiratory Medicine* (Vol. 5, Issue 3). https://doi.org/10.1586/ers.11.34

Bowatte, G., Lodge, C. J., Knibbs, L. D., Lowe, A. J., Erbas, B., Dennekamp, M., Marks, G. B., Giles, G., Morrison, S., Thompson, B., Thomas, P. S., Hui, J., Perret, J. L., Abramson, M. J., Walters, H., Matheson, M. C., & Dharmage, S. C. (2017). Traffic-related air pollution exposure is associated with allergic sensitization, asthma, and poor lung function in middle age. *Journal of Allergy and Clinical Immunology*, *139*(1). https://doi.org/10.1016/j.jaci.2016.05.008

Brusselle, G., Germinaro, M., Weiss, S., & Zangrilli, J. (2017). Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. *Pulmonary Pharmacology and Therapeutics*, *43*. https://doi.org/10.1016/j.pupt.2017.01.011

Brussino, L., Solidoro, P., & Rolla, G. (2018). Is it severe asthma or asthma with severe comorbidities? In *Journal of Asthma and Allergy* (Vol. 10, pp. 303–305). Dove Medical Press Ltd. https://doi.org/10.2147/JAA.S150462

Bull, F. C., Al-Ansari, S. S., Biddle, S., Borodulin, K., Buman, M. P., Cardon, G., Carty, C., Chaput, J. P., Chastin, S., Chou, R., Dempsey, P. C., Dipietro, L., Ekelund, U., Firth, J., Friedenreich, C. M., Garcia, L., Gichu, M., Jago, R., Katzmarzyk, P. T., … Willumsen, J. F. (2020). World Health Organization 2020 guidelines on physical activity and sedentary behaviour. In *British Journal of Sports Medicine* (Vol. 54, Issue 24). https://doi.org/10.1136/bjsports-2020-102955

Burbank, A. J., Sood, A. K., Kesic, M. J., Peden, D. B., & Hernandez, M. L. (2017). Environmental determinants of allergy and asthma in early life. In *Journal of Allergy and Clinical Immunology* (Vol. 140, Issue 1). https://doi.org/10.1016/j.jaci.2017.05.010

Burgel, P. R., Paillasseur, J. L., Janssens, W., Piquet, J., ter Riet, G., Garcia-Aymerich, J., Cosio, B., Bakke, P., Puhan, M. A., Langhammer, A., Alfageme, I., Almagro, P., Ancochea, J., Celli, B. R., Casanova, C., De-Torres, J. P., Decramer, M., Echazarreta, A., Esteban, C., … Roche, N. (2017). A simple algorithm for the identification of clinical COPD phenotypes. *European Respiratory Journal*, *50*(5). https://doi.org/10.1183/13993003.01034-2017

Burke, H., Leonardi-Bee, J., Hashim, A., Pine-Abata, H., Chen, Y., Cook, D. G., Britton, J. R., & McKeever, T. M. (2012). Prenatal and passive smoke exposure and incidence of asthma and wheeze: Systematic review and meta-analysis. In *Pediatrics* (Vol. 129, Issue 4). https://doi.org/10.1542/peds.2011-2196

Caldwell, J. T., Ford, C. L., Wallace, S. P., Wang, M. C., & Takahashi, L. M. (2017). Racial and ethnic residential segregation and access to health care in rural areas. *Health and Place*, *43*. https://doi.org/10.1016/j.healthplace.2016.11.015

Canadian Medical Association. (2013). Health equity and the social determinants of health: A role for the medical profession. *CMA Policy*.

Carlsten, C., Blomberg, A., Pui, M., Sandstrom, T., Wong, S. W., Alexis, N., & Hirota, J. (2016). Diesel exhaust augments allergen-induced lower airway inflammation in allergic individuals: A controlled human exposure study. *Thorax*, *71*(1). https://doi.org/10.1136/thoraxjnl-2015-207399

Casanova, C., Marin, J. M., Martinez-Gonzalez, C., de Lucas-Ramos, P., Mir-Viladrich, I., Cosio, B., Peces-Barba, G., Solanes-García, I., Agüero, R., Feu-Collado, N., Calle-Rubio, M., Alfageme, I., de Diego-Damia, A., Irigaray, R., Marín, M., Balcells, E., Llunell, A., Galdiz, J. B., Golpe, R., … De-Torres, J. P. (2015). Differential effect of modified Medical Research Council Dyspnea, COPD Assessment Test, and Clinical COPD Questionnaire for symptoms evaluation within the new GOLD staging and mortality in COPD. *Chest*, *148*(1). https://doi.org/10.1378/chest.14-2449

Cassell, A., Edwards, D., Harshfield, A., Rhodes, K., Brimicombe, J., Payne, R., & Griffin, S. (2018). The epidemiology of multimorbidity in primary care: A retrospective cohort study. *British Journal of General Practice*, *68*(669). https://doi.org/10.3399/bjgp18X695465

Chalitsios, C. v., McKeever, T. M., & Shaw, D. E. (2021). Incidence of osteoporosis and fragility fractures in asthma: A UK population-based matched cohort study. *European Respiratory Journal*, *57*(1). https://doi.org/10.1183/13993003.01251-2020

Chang, J. E., Ding, D., Martin-Lazaro, J., White, A., & Stevenson, D. D. (2012). Smoking, environmental tobacco smoke, and aspirin-exacerbated respiratory disease. *Annals of Allergy, Asthma and Immunology*, *108*(1), 14–19. https://doi.org/10.1016/j.anai.2011.09.022

Chanoine, S., Sanchez, M., Pin, I., Temam, S., Moual, N. le, Fournier, A., Pison, C., Bousquet, J., Bedouch, P., Boutron-Ruault, M. C., Varraso, R., & Siroux, V. (2018). Multimorbidity medications and poor asthma prognosis. *European Respiratory Journal*, *51*(4). https://doi.org/10.1183/13993003.02114-2017

Chatkin, J., Correa, L., & Santos, U. (2021). External Environmental Pollution as a Risk Factor for Asthma. In *Clinical Reviews in Allergy and Immunology*. https://doi.org/10.1007/s12016-020-08830-5

Chaudhuri, R., McSharry, C., Heaney, L. G., Niven, R., Brightling, C. E., Menzies-Gow, A. N., Bucknall, C., Mansur, A. H., Lee, W., Shepherd, M., Spears, M., Cowan, D. C., Husi, H., & Thomson, N. C. (2016). Effects of older age and age of asthma onset on clinical and inflammatory variables in severe refractory asthma. *Respiratory Medicine*, *118*. https://doi.org/10.1016/j.rmed.2016.07.005

Cheng, S. L., Lin, C. H., Wang, C. C., Chan, M. C., Hsu, J. Y., Hang, L. W., Perng, D. W., Yu, C. J., & Wang, H. C. (2019). Comparison between COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnea scores for evaluation of clinical symptoms, comorbidities and medical resources utilization in COPD patients. *Journal of the Formosan Medical Association*, *118*(1P3). https://doi.org/10.1016/j.jfma.2018.06.018

Christenson, S. A., Steiling, K., van den Berge, M., Hijazi, K., Hiemstra, P. S., Postma, D. S., Lenburg, M. E., Spira, A., & Woodruff, P. G. (2015). Asthma-COPD overlap: Clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *191*(7). https://doi.org/10.1164/rccm.201408-1458OC

Chua, K. P., Schuster, M. A., & McWilliams, J. M. (2013). Differences in health care access and utilization between adolescents and young adults with asthma. *Pediatrics*, *131*(5). https://doi.org/10.1542/peds.2012-2881

Chung, K. F., Wenzel, S. E., Brozek, J. L., Bush, A., Castro, M., Sterk, P. J., Adcock, I. M., Bateman, E. D., Bel, E. H., Bleecker, E. R., Boulet, L. P., Brightling, C., Chanez, P., Dahlen, S. E., Djukanovic, R., Frey, U., Gaga, M., Gibson, P., Hamid, Q., … Teague, W. G. (2014). International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *European Respiratory Journal*, *43*(2). https://doi.org/10.1183/09031936.00202013

CIBA. (1959). Terminology, Definitions, and Classification of Chronic Pulmonary Emphysema and Related Conditions: A Report of the conclusions of a CIBA guest symposium. *Thorax*, *14*(4), 286-undefined. https://doi.org/10.1136/thx.14.4.286

Collins, F. S., & Varmus, H. (2015). A New Initiative on Precision Medicine. *New England Journal of Medicine*, *372(*9). https://doi.org/10.1056/nejmp1500523

Colonna, M. (2018). Innate Lymphoid Cells: Diversity, Plasticity, and Unique Functions in Immunity. In *Immunity* (Vol. 48, Issue 6). https://doi.org/10.1016/j.immuni.2018.05.013

Contreras, Z. A., Chen, Z., Roumeliotaki, T., Annesi-Maesano, I., Baïz, N., von Berg, A., Bergström, A., Crozier, S., Duijts, L., Ekström, S., Eller, E., Fantini, M. P., Kjaer, H. F., Forastiere, F., Gerhard, B., Gori, D., Harskamp-Van Ginkel, M.

W., Heinrich, J., Iñiguez, C., … Chatzi, L. (2018). Does early onset asthma increase childhood obesity risk? A pooled analysis of 16 European cohorts. *European Respiratory Journal*, *52*(3). https://doi.org/10.1183/13993003.00504-2018

Coogan, P. F., Castro-Webb, N., Yu, J., O'Connor, G. T., Palmer, J. R., & Rosenberg, L. (2015). Active and passive smoking and the incidence of asthma in the Black Women's Health Study. *American Journal of Respiratory and Critical Care Medicine*, *191*(2). https://doi.org/10.1164/rccm.201406-1108OC

Coumou, H., Westerhof, G. A., de Nijs, S. B., Amelink, M., & Bel, E. H. (2019). New-Onset Asthma in Adults: What Does the Trigger History Tell Us? *Journal of Allergy and Clinical Immunology: In Practice*, *7*(3). https://doi.org/10.1016/j.jaip.2018.09.007

Coverstone, A. M., Seibold, M. A., & Peters, M. C. (2020). Diagnosis and Management of T2-High Asthma. *Journal of Allergy and Clinical Immunology: In Practice*, *8*(2). https://doi.org/10.1016/j.jaip.2019.11.020

Croft, J. B., Wheaton, A. G., Liu, Y., Xu, F., Lu, H., Matthews, K. A., Cunningham, T. J., Wang, Y., & Holt, J. B. (2018). Urban-Rural County and State Differences in Chronic Obstructive Pulmonary Disease — United States, 2015. *MMWR. Morbidity and Mortality Weekly Report*, *67*(7). https://doi.org/10.15585/mmwr.mm6707a1

Dahlgren, G., & Whitehead, M. (1991). Policies and strategies to promote social equity in health. . *Stockholm, Institute of Future Studies*. .

Dahlgren, G., & Whitehead, M. (2006). *European strategies for tackling social inequities in health: Levelling up Part 2. Available: www.who.int / Date last accessed June 7th 2021.*

Dahlin, A., & Weiss, S. T. (2016). Genetic and Epigenetic Components of Aspirin-Exacerbated Respiratory Disease. *Immunology and Allergy Clinics of North America*, *36*(4), 765–789. https://doi.org/10.1016/j.iac.2016.06.010

de Groot, V., Beckerman, H., Lankhorst, G. J., & Bouter, L. M. (2003). How to measure comorbidity: A critical review of available methods. *Journal of Clinical Epidemiology*, *56*(3). https://doi.org/10.1016/S0895-4356(02)00585-1

de Oliveira Figueiredo, R. A., Viljakainen, J., Viljakainen, H., Roos, E., Rounge, T. B., & Weiderpass, E. (2019). Identifying eating habits in Finnish children: A cross-sectional study. *BMC Public Health*, *19*(1). https://doi.org/10.1186/s12889-019-6603-x

Divo, M. J., Casanova, C., Marin, J. M., Pinto-Plata, V. M., De-Torres, J. P., Zulueta, J. J., Cabrera, C., Zagaceta, J., Sanchez-Salcedo, P., Berto, J., Davila, R. B., Alcaide, A. B., Cote, C., & Celli, B. R. (2015). COPD comorbidities network. *European Respiratory Journal*, *46*(3). https://doi.org/10.1183/09031936.00171614

Dixon, A. E., & Peters, U. (2018). The effect of obesity on lung function. In *Expert Review of Respiratory Medicine* (Vol. 12, Issue 9). https://doi.org/10.1080/17476348.2018.1506331

Do, A. N., Chun, Y., Grishina, G., Grishin, A., Rogers, A. J., Raby, B. A., Weiss, S. T., Vicencio, A., Schadt, E. E., & Bunyavanich, S. (2021). Network study of nasal transcriptome profiles reveals master regulator genes of asthma. *Journal of Allergy and Clinical Immunology*, *147*(3). https://doi.org/10.1016/j.jaci.2020.07.006

Doll, R., Peto, R., Boreham, J., & Sutherland, I. (2004). Mortality in relation to smoking: 50 Years' observations on male British doctors. *British Medical Journal*, *328*(7455). https://doi.org/10.1136/bmj.38142.554479.ae

Doll, R., Peto, R., Wheatley, K., Gray, R., & Sutherland, I. (1994). Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ*, *309*(6959). https://doi.org/10.1136/bmj.309.6959.901

Doña, I., Barrionuevo, E., Salas, M., Laguna, J. J., Agúndez, J., García-Martín, E., Bogas, G., Perkins, J. R., Cornejo-García, J. A., & Torres, M. J. (2018). NSAIDs-hypersensitivity often induces a blended reaction pattern involving multiple organs. *Scientific Reports*, *16710*. https://doi.org/10.1038/s41598-018-34668-1

Donkin, A., Goldblatt, P., Allen, J., Nathanson, V., & Marmot, M. (2018). Global action on the social determinants of health. *BMJ Global Health*, *3*. https://doi.org/10.1136/bmjgh-2017-000603

Dornhorst, A. (1955). Respiratory insufficiency. *Lancet*, *268*, 1185–1187.

Douthit, N., Kiv, S., Dwolatzky, T., & Biswas, S. (2015). Exposing some important barriers to health care access in the rural USA. In *Public Health* (Vol. 129, Issue 6). https://doi.org/10.1016/j.puhe.2015.04.001

Douwes, J., Gibson, P., Pekkanen, J., & Pearce, N. (2002). Non-eosinophilic asthma: Importance and possible mechanisms. In *Thorax* (Vol. 57, Issue 7). https://doi.org/10.1136/thorax.57.7.643

Douwes, J., Travier, N., Huang, K., Cheng, S., McKenzie, J., le Gros, G., von Mutius, E., & Pearce, N. (2007). Lifelong farm exposure may strongly reduce the risk of asthma in adults. *Allergy: European Journal of Allergy and Clinical Immunology*, *62*(10). https://doi.org/10.1111/j.1398-9995.2007.01490.x

Duijts, L., Reiss, I. K., Brusselle, G., & de Jongste, J. C. (2014). Early origins of chronic obstructive lung diseases across the life course. In *European Journal of Epidemiology* (Vol. 29, Issue 12). https://doi.org/10.1007/s10654-014-9981-5

Eagan, T. M. L., Gulsvik, A., Eide, G. E., & Bakke, P. S. (2004). The effect of educational level on the incidence of asthma and respiratory symptoms. *Respiratory Medicine*, *98*(8). https://doi.org/10.1016/j.rmed.2004.02.008

Eastman, J. J., Cavagnero, K. J., Deconde, A. S., Kim, A. S., Karta, M. R., Broide, D. H., Zuraw, B. L., White, A. A., Christiansen, S. C., & Doherty, T. A. (2017). Group 2 innate lymphoid cells are recruited to the nasal mucosa in patients with aspirin-exacerbated respiratory disease. *Journal of Allergy and Clinical Immunology*, *140*(1), 101. https://doi.org/10.1016/j.jaci.2016.11.023

Eduard, W., Douwes, J., Omenaas, E., & Heederik, D. (2004). Do farming exposures cause or prevent asthma? Results from a study of adult Norwegian farmers. *Thorax*, *59*(5). https://doi.org/10.1136/thx.2004.013326

Eduard, W., Pearce, N., & Douwes, J. (2009). Chronic bronchitis, COPD, and lung function in farmers: The role of biological agents. *Chest*, *136*(3). https://doi.org/10.1378/chest.08-2192

Ege, M. J., Frei, R., Bieli, C., Schram-Bijkerk, D., Waser, M., Benz, M. R., Weiss, G., Nyberg, F., van Hage, M., Pershagen, G., Brunekreef, B., Riedler, J., Lauener, R., Braun-Fahrländer, C., & von Mutius, E. (2007). Not all farming environments protect against the development of asthma and wheeze in children. *Journal of Allergy and Clinical Immunology*, *119*(5). https://doi.org/10.1016/j.jaci.2007.01.037

Ege, M. J., Mayer, M., Normand, A.-C., Genuneit, J., Cookson, W. O. C. M., Braun-Fahrländer, C., Heederik, D., Piarroux, R., & von Mutius, E. (2011). Exposure to Environmental Microorganisms and Childhood Asthma. *New England Journal of Medicine*, *364*(8). https://doi.org/10.1056/nejmoa1007302

Egger, G., Liang, G., Aparicio, A., & Jones, P. A. (2004). Epigenetics in human disease and prospects for epigenetic therapy. In *Nature* (Vol. 429, Issue 6990). https://doi.org/10.1038/nature02625

Eisner, M. D., Blanc, P. D., Omachi, T. A., Yelin, E. H., Sidney, S., Katz, P. P., Ackerson, L. M., Sanchez, G., Tolstykh, I., & Iribarren, C. (2011). Socioeconomic status, race and COPD health outcomes. *Journal of Epidemiology and Community Health*, *65*(1). https://doi.org/10.1136/jech.2009.089722

Ekerljung, L., Rönmark, E., Lötvall, J., Wennergren, G., Torén, K., & Lundbäck, B. (2013). Questionnaire layout and wording influence prevalence and risk estimates of respiratory symptoms in a population cohort. *Clinical Respiratory Journal*, *7*(1). https://doi.org/10.1111/j.1752-699X.2012.00281.x

Ellison-Loschmann, L., Sunyer, J., Plana, E., Pearce, N., Zock, J. P., Jarvis, D., Janson, C., Antó, J. M., & Kogevinas, M. (2007). Socioeconomic status, asthma and chronic bronchitis in a large community-based study. *European Respiratory Journal*, *29*(5). https://doi.org/10.1183/09031936.00101606

Enright, P. L., McClelland, R. L., Buist, A. S., Burke, G. L., Jackson, S., Elster, A., Furberg, C. D., Heiss, G., Kitzman, D., Lamb, M., Lefkowitz, D. S., Lyles, M. F., Nunn, C., Riley, W., Chen, J., Tucker, B., Rautaharju, F., Rautaharju, P., Bonekat, W., … Smith, P. (2001). Correlates of peak expiratory flow lability in elderly persons. *Chest*, *120*(6). https://doi.org/10.1378/chest.120.6.1861

Eriksson, J., Ekerljung, L., Bossios, A., Bjerg, A., Wennergren, G., Rönmark, E., Torén, K., Lötvall, J., & Lundbäck, B. (2015). Aspirin-intolerant asthma in the population: Prevalence and important determinants. *Clinical and Experimental Allergy*, *45*(1), 211–219. https://doi.org/10.1111/cea.12359

Fall, T., Lundholm, C., Örtqvist, A. K., Fall, K., Fang, F., Hedhammar, Å., Kämpe, O., Ingelsson, E., & Almqvist, C. (2015). Early exposure to dogs and farm animals and the risk of childhood asthma. *JAMA Pediatrics*, *169*(11). https://doi.org/10.1001/jamapediatrics.2015.3219

Ferreira, M. A. R., Mathur, R., Vonk, J. M., Szwajda, A., Brumpton, B., Granell, R., Brew, B. K., Ullemar, V., Lu, Y., Jiang, Y., Magnusson, P. K. E., Karlsson, R., Hinds, D. A., Paternoster, L., Koppelman, G. H., & Almqvist, C. (2019). Genetic Architectures of Childhood- and Adult-Onset Asthma Are Partly Distinct. *American Journal of Human Genetics*, *104*(4). https://doi.org/10.1016/j.ajhg.2019.02.022

Fletcher, C. M., Elmes, P. C., Fairbairn, A. S., & Wood, C. H. (1959). The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *British Medical Journal*, *2*(5147). https://doi.org/10.1136/bmj.2.5147.257

Fokkens, W. J., Lund, V. J., Hopkins, C., Hellings, P. W., Kern, R., Reitsma, S., Toppila-salmi, S., Bernal-sprekelsen, M., Mullol, J., Alobid, I., Anselmo-lima, W. T., Baroody, F., Cervin, A., Constantinidis, J., Gabory, L. De, Desrosiers, M., Diamant, Z., Douglas, R. G., Gevaert, P. H., … Zwetsloot, C. P. (2020a). European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology*, *20*(5), 1–464.

Fokkens, W. J., Lund, V. J., Hopkins, C., Hellings, P. W., Kern, R., Reitsma, S., Toppila-Salmi, S., Bernal-Sprekelsen, M., Mullol, J., Alobid, I., Terezinha Anselmo-Lima, W., Bachert, C., Baroody, F., von Buchwald, C., Cervin, A., Cohen, N., Constantinidis, J., de Gabory, L., Desrosiers, M., … Zwetsloot, C. P. (2020b). European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology*, *58*. https://doi.org/10.4193/Rhin20.600

Forman, D. E., Maurer, M. S., Boyd, C., Brindis, R., Salive, M. E., Horne, F. M. F., Bell, S. P., Fulmer, T., Reuben, D. B., Zieman, S., & Rich, M. W. (2018). Multimorbidity in Older Adults With Cardiovascular Disease. In *Journal of the American College of Cardiology* (Vol. 71, Issue 19). https://doi.org/10.1016/j.jacc.2018.03.022

Forte, G. C., da Silva, D. T. R., Hennemann, M. L., Sarmento, R. A., Almeida, J. C., & de Tarso Roth Dalcin, P. (2018). Diet effects in the asthma treatment: A systematic review. *Critical Reviews in Food Science and Nutrition*, *58*(11). https://doi.org/10.1080/10408398.2017.1289893

Fortin, M., Lapointe, L., Hudon, C., Vanasse, A., Ntetu, A. L., & Maltais, D. (2004). Multimorbidity and quality of life in primary care: A systematic review. In *Health and Quality of Life Outcomes* (Vol. 2). https://doi.org/10.1186/1477-7525-2-51

Freisling, H., Viallon, V., Lennon, H., Bagnardi, V., Ricci, C., Butterworth, A. S., Sweeting, M., Muller, D., Romieu, I., Bazelle, P., Kvaskoff, M., Arveux, P., Severi, G., Bamia, C., Kühn, T., Kaaks, R., Bergmann, M., Boeing, H., Tjønneland, A., … Ferrari, P. (2020). Lifestyle factors and risk of multimorbidity of cancer and cardiometabolic diseases: A multinational cohort study. *BMC Medicine*, *18*(1). https://doi.org/10.1186/s12916-019-1474-7

Freitas, P. D., Xavier, R. F., McDonald, V. M., Gibson, P. G., Cordova-Rivera, L., Furlanetto, K. C., de Oliveira, J. M., Carvalho-Pinto, R. M., Cukier, A., Stelmach, R., & Carvalho, C. R. F. (2021). Identification of asthma phenotypes based on extrapulmonary treatable traits. *European Respiratory Journal*, *57*(1). https://doi.org/10.1183/13993003.00240-2020

Gaffney, A. W., Hawks, L., Bor, D., White, A. C., Woolhandler, S., McCormick, D., & Himmelstein, D. U. (2021). National Trends and Disparities in Health-Care Access and Coverage Among Adults With Asthma and COPD. *Chest*. https://doi.org/10.1016/j.chest.2021.01.035

Gaffney, A. W., Hawks, L., White, A. C., Woolhandler, S., Himmelstein, D., Christiani, D. C., & McCormick, D. (2020). Health Care Disparities Across the Urban-Rural Divide: A National Study of Individuals with COPD. *Journal of Rural Health*. https://doi.org/10.1111/jrh.12525

Garin, N., Olaya, B., Perales, J., Moneta, M. V., Miret, M., Ayuso-Mateos, J. L., & Haro, J. M. (2014). Multimorbidity patterns in a national representative sample of the Spanish adult population. *PLoS ONE*, *9*(1). https://doi.org/10.1371/journal.pone.0084794

Gergen, P. J., Mitchell, H. E., Calatroni, A., Sever, M. L., Cohn, R. D., Salo, P. M., Thorne, P. S., & Zeldin, D. C. (2018). Sensitization and Exposure to Pets: The Effect on Asthma Morbidity in the US Population. *Journal of Allergy and Clinical Immunology: In Practice*, *6*(1). https://doi.org/10.1016/j.jaip.2017.05.019

Gershon, A. S., Thiruchelvam, D., Aaron, S., Stanbrook, M., Vozoris, N., Tan, W. C., Cho, E., & To, T. (2019). Socioeconomic status (SES) and 30-day hospital readmissions for chronic obstructive pulmonary (COPD) disease: A

population-based cohort study. *PLoS ONE*, *14*(5). https://doi.org/10.1371/journal.pone.0216741

Ghobadi, H., Ahari, S. S., Kameli, A., & Lari, S. M. (2012). The relationship between COPD assessment test (CAT) scores and severity of airflow obstruction in stable COPD Patients. *Tanaffos*, *11*(2).

Gibson, P. G., McDonald, V. M., & Marks, G. B. (2010). Asthma in older adults. *The Lancet*, *376*(9743), 803–813. https://doi.org/10.1016/S0140-6736(10)61087-2

GINA. (2021). *Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Available from: www.ginasthma.org/ Date last accessed: May 14th 2021.*

GINA, & GOLD. (2017). *Global Initiative for Asthma and Global Initiative for Chronic Obstructive Lung Disease. Diagnosis and Initial Treatment of Asthma, COPD and Asthma- COPD Overlap 2017. Available from www.ginasthma.org/ Date last accessed: May 14th 2021.*

GOLD. (2021). *Global Initiative for Chronic Obstructive Lung Disease, report 2021. Available from: www.goldcopd.org/ Date last accessed: May 14th 2021.*

Greene, C. C., Bradley, K. A., Bryson, C. L., Blough, D. K., Evans, L. E., Udris, E. M., & Au, D. H. (2008). The association between alcohol consumption and risk of COPD exacerbation in a veteran population. *Chest*, *134*(4). https://doi.org/10.1378/chest.07-3081

Grigsby, M., Siddharthan, T., Chowdhury, M. A. H., Siddiquee, A., Rubinstein, A., Sobrino, E., Miranda, J. J., Bernabe-Ortiz, A., Alam, D., & Checkley, W. (2016). Socioeconomic status and COPD among low-and middle-income countries. *International Journal of COPD*, *11*(1). https://doi.org/10.2147/COPD.S111145

Guillemin, F., Bombardier, C., & Beaton, D. (1993). Cross-cultural adaptation of health-related quality of life measures: Literature review and proposed guidelines. *Journal of Clinical Epidemiology*, *46*(12). https://doi.org/10.1016/0895-4356(93)90142-N

Guilleminault, L., Williams, E. J., Scott, H. A., Berthon, B. S., Jensen, M., & Wood, L. G. (2017). Diet and asthma: Is it time to adapt our message? In *Nutrients* (Vol. 9, Issue 11). https://doi.org/10.3390/nu9111227

Guthold, R., Stevens, G. A., Riley, L. M., & Bull, F. C. (2018). Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1·9 million participants. *The Lancet Global Health*, *6*(10). https://doi.org/10.1016/S2214-109X(18)30357-7

Haahtela, T. (2019). A biodiversity hypothesis. In *Allergy: European Journal of Allergy and Clinical Immunology* (Vol. 74, Issue 8). https://doi.org/10.1111/all.13763

Haahtela, T., Valovirta, E., Saarinen, K., Jantunen, J., Lindström, I., Kauppi, P., Laatikainen, T., Pelkonen, A., Salava, A., Tommila, E., Bousquet, J., Vasankari, T., & Mäkelä, M. J. (2021). The Finnish Allergy Program 2008-2018: Society-wide proactive program for change of management to mitigate allergy burden. In *Journal of Allergy and Clinical Immunology*. https://doi.org/10.1016/j.jaci.2021.03.037

Häggblom, J., Kettunen, K., Karjalainen, J., Heliövaara, M., Jousilahti, P., & Saarelainen, S. (2015). Prevalence of PI*Z and PI*S alleles of alpha-1-antitrypsin deficiency in Finland. *European Clinical Respiratory Journal*, *2*(1). https://doi.org/10.3402/ecrj.v2.28829

Han, Y. Y., Zhang, X., Wang, J., Wang, G., Oliver, B. G., Zhang, H. P., Kang, D. Y., Wang, L., Qiu, Z. X., & Li, W. M. (2021). Multidimensional Assessment of

Asthma Identifies Clinically Relevant Phenotype Overlap: A Cross-Sectional Study. *Journal of Allergy and Clinical Immunology: In Practice*, *9*(1). https://doi.org/10.1016/j.jaip.2020.07.048

Hanlon, P., Nicholl, B. I., Jani, B. D., McQueenie, R., Lee, D., Gallacher, K. I., & Mair, F. S. (2018). Examining patterns of multimorbidity, polypharmacy and risk of adverse drug reactions in chronic obstructive pulmonary disease: A cross-sectional UK Biobank study. *BMJ Open*, *8*(1). https://doi.org/10.1136/bmjopen-2017-018404

Hanski, I., von Hertzen, L., Fyhrquist, N., Koskinen, K., Torppa, K., Laatikainen, T., Karisola, P., Auvinen, P., Paulin, L., Mäkelä, M. J., Vartiainen, E., Kosunen, T. U., Alenius, H., & Haahtela, T. (2012). Environmental biodiversity, human microbiota, and allergy are interrelated. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(21). https://doi.org/10.1073/pnas.1205624109

Hanson, C., Rutten, E. P., Wouters, E. F. M., & Rennard, S. (2014). Influence of diet and obesity on COPD development and outcomes. In *International Journal of COPD* (Vol. 9). https://doi.org/10.2147/COPD.S50111

Hardin, M., Cho, M., McDonald, M. L., Beaty, T., Ramsdell, J., Bhatt, S., van Beek, E. J. R., Make, B. J., Crapo, J. D., Silverman, E. K., & Hersh, C. P. (2014). The clinical and genetic features of COPD-asthma overlap syndrome. *European Respiratory Journal*, *44*(2). https://doi.org/10.1183/09031936.00216013

Harrison, S., Davies, A. R., Dickson, M., Tyrrell, J., Green, M. J., Katikireddi, S. V., Campbell, D., Munafò, M., Dixon, P., Jones, H. E., Rice, F., Davies, N. M., & Howe, L. D. (2020). The causal effects of health conditions and risk factors on social and socioeconomic outcomes: Mendelian randomization in UK Biobank. *International Journal of Epidemiology*, *49*(5). https://doi.org/10.1093/ije/dyaa114

Hedman, J., Kaprio, J., Poussa, T., & Nieminen, M. M. (1999). Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *International Journal of Epidemiology*, *28*(4). https://doi.org/10.1093/ije/28.4.717

Hedman, L., Backman, H., Stridsman, C., Bosson, J. A., Lundbäck, M., Lindberg, A., Rönmark, E., & Ekerljung, L. (2018). Association of Electronic Cigarette Use With Smoking Habits, Demographic Factors, and Respiratory Symptoms. *JAMA Network Open*, *1*(3). https://doi.org/10.1001/jamanetworkopen.2018.0789

Heinonen, N., Tynkkynen, L. K., & Keskimäki, I. (2019). The transposition of the Patients' Rights Directive in Finland—Difficulties encountered. *Health Policy*, *123*(6). https://doi.org/10.1016/j.healthpol.2019.02.008

Hisinger-Mölkänen, H., Pallasaho, P., Haahtela, T., Lindqvist, A., Sovijärvi, A., & Piirilä, P. (2019). The increase of asthma prevalence has levelled off and symptoms decreased in adults during 20 years from 1996 to 2016 in Helsinki, Finland. *Respiratory Medicine*, *155*. https://doi.org/10.1016/j.rmed.2019.07.014

Hisinger-Mölkänen, H., Piirilä, P., Haahtela, T., Sovijärvi, A., & Pallasaho, P. (2018). Smoking, environmental tobacco smoke and occupational irritants increase the risk of chronic rhinitis. *World Allergy Organization Journal*, *11*(1). https://doi.org/10.1186/s40413-018-0184-5

Holguin, F., Bleecker, E. R., Busse, W. W., Calhoun, W. J., Castro, M., Erzurum, S. C., Fitzpatrick, A. M., Gaston, B., Israel, E., Jarjour, N. N., Moore, W. C., Peters,

S. P., Yonas, M., Teague, W. G., & Wenzel, S. E. (2011). Obesity and asthma: An association modified by age of asthma onset. *Journal of Allergy and Clinical Immunology*, *127*(6). https://doi.org/10.1016/j.jaci.2011.03.036

Honkamäki, J., Hisinger-Mölkänen, H., Ilmarinen, P., Piirilä, P., Tuomisto, L. E., Andersén, H., Huhtala, H., Sovijärvi, A., Backman, H., Lundbäck, B., Rönmark, E., Lehtimäki, L., & Kankaanranta, H. (2019). Age- and gender-specific incidence of new asthma diagnosis from childhood to late adulthood. *Respiratory Medicine*, *154*. https://doi.org/10.1016/j.rmed.2019.06.003

Honkamäki, J., Piirilä, P., Hisinger-Mölkänen, H., Tuomisto, L. E., Andersen, H., Huhtala, H., Sovijärvi, A., Backman, H., Lundbäck, B., Rönmark, E., Lehtimäki, L., Pallasaho, P., Ilmarinen, P., & Kankaanranta, H. (2020). *Age at asthma diagnosis and probability of remission in a population-based study*. https://doi.org/10.1183/13993003.congress-2020.4641

Hosseini, M., Almasi-Hashiani, A., Sepidarkish, M., & Maroufizadeh, S. (2019). Global prevalence of asthma-COPD overlap (ACO) in the general population: A systematic review and meta-analysis. In *Respiratory Research* (Vol. 20, Issue 1). https://doi.org/10.1186/s12931-019-1198-4

Hudey, S. N., Ledford, D. K., & Cardet, J. C. (2020). Mechanisms of non-type 2 asthma. In *Current Opinion in Immunology* (Vol. 66). https://doi.org/10.1016/j.coi.2020.10.002

Hughes, M. J., McGettrick, H. M., & Sapey, E. (2020). Shared mechanisms of multimorbidity in copd, atherosclerosis and type-2 diabetes: The neutrophil as a potential inflammatory target. *European Respiratory Review*, *29*(155). https://doi.org/10.1183/16000617.0102-2019

Huntley, A. L., Johnson, R., Purdy, S., Valderas, J. M., & Salisbury, C. (2012). Measures of multimorbidity and morbidity burden for use in primary care and community settings: A systematic review and guide. In *Annals of Family Medicine* (Vol. 10, Issue 2). https://doi.org/10.1370/afm.1363

Huovinen, E., Kaprio, J., & Koskenvuo, M. (2003). Factors associated to lifestyle and risk of adult onset asthma. *Respiratory Medicine*, *97*(3). https://doi.org/10.1053/rmed.2003.1419

Hurst, J. R., Vestbo, J., Anzueto, A., Locantore, N., Müllerova, H., Tal-Singer, R., Miller, B., Lomas, D. A., Agusti, A., MacNee, W., Calverley, P., Rennard, S., Wouters, E. F. M., & Wedzicha, J. A. (2010). Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. *New England Journal of Medicine*, *363*(12). https://doi.org/10.1056/nejmoa0909883

Hyyppä, M. T., & Mäki, J. (2001). Why do Swedish-speaking Finns have longer active life? An area for social capital research. *Health Promotion International*, *16*(1). https://doi.org/10.1093/heapro/16.1.55

Illi, S., Depner, M., Genuneit, J., Horak, E., Loss, G., Strunz-Lehner, C., Büchele, G., Boznanski, A., Danielewicz, H., Cullinan, P., Heederik, D., Braun-Fahrländer, C., & von Mutius, E. (2012). Protection from childhood asthma and allergy in Alpine farm environments - The GABRIEL Advanced Studies. *Journal of Allergy and Clinical Immunology*, *129*(6). https://doi.org/10.1016/j.jaci.2012.03.013

Ilmarinen, P., Pardo, A., Tuomisto, L. E., Vähätalo, I., Niemelä, O., Nieminen, P., & Kankaanranta, H. (2021). Long-term prognosis of new adult-onset asthma in obese patients. *European Respiratory Journal*, *57*(4). https://doi.org/10.1183/13993003.01209-2020

Ilmarinen, P., Stridsman, C., Bashir, M., Tuomisto, L. E., Vähätalo, I., Goksör, E., Kankaanranta, H., Backman, H., Langhammer, A., Piirilä, P., Rönmark, E., Lundbäck, B., Nwaru, B. I., & Wennergren, G. (2021). Level of education and asthma control in adult-onset asthma. *Journal of Asthma*. https://doi.org/10.1080/02770903.2021.1871742

Ilmarinen, P., Tuomisto, L. E., Niemelä, O., Danielsson, J., Haanpää, J., Kankaanranta, T., & Kankaanranta, H. (2016). Comorbidities and elevated IL-6 associate with negative outcome in adult-onset asthma. *European Respiratory Journal*, *48*(4). https://doi.org/10.1183/13993003.02198-2015

Ilmarinen, P., Tuomisto, L. E., Niemelä, O., Tommola, M., Haanpää, J., & Kankaanranta, H. (2017). Cluster Analysis on Longitudinal Data of Patients with Adult-Onset Asthma. *Journal of Allergy and Clinical Immunology: In Practice*, *5*(4). https://doi.org/10.1016/j.jaip.2017.01.027

ILO. (2012). *International Standard Classification of Occupations, ISCO-08. Available www.ilo.org / Date last accessed: May 14th 2021*.

Jannus-Pruljan, L., Meren, M., Põlluste, J., Loit, H. M., Kiviloog, J., Baburin, A., & Lundbäck, B. (2004). Postal survey on asthma, chronic bronchitis and respiratory symptoms among adult Estonians and non-Estonians (FinEsS-study). In *European Journal of Public Health* (Vol. 14, Issue 2). https://doi.org/10.1093/eurpub/14.2.114

Jartti, T., & Gern, J. E. (2017). Role of viral infections in the development and exacerbation of asthma in children. In *Journal of Allergy and Clinical Immunology* (Vol. 140, Issue 4). https://doi.org/10.1016/j.jaci.2017.08.003

Ji, H., Biagini Myers, J. M., Brandt, E. B., Brokamp, C., Ryan, P. H., & Khurana Hershey, G. K. (2016). Air pollution, epigenetics, and asthma. In *Allergy, Asthma and Clinical Immunology* (Vol. 12, Issue 1). https://doi.org/10.1186/s13223-016-0159-4

Johansson, H., Norlander, K., Berglund, L., Janson, C., Malinovschi, A., Nordvall, L., Nordang, L., & Emtner, M. (2015). Prevalence of exercise-induced bronchoconstriction and exercise-induced laryngeal obstruction in a general adolescent population. *Thorax*, *70*(1). https://doi.org/10.1136/thoraxjnl-2014-205738

Joubert, B. R., Felix, J. F., Yousefi, P., Bakulski, K. M., Just, A. C., Breton, C., Reese, S. E., Markunas, C. A., Richmond, R. C., Xu, C. J., Küpers, L. K., Oh, S. S., Hoyo, C., Gruzieva, O., Söderhäll, C., Salas, L. A., Baïz, N., Zhang, H., Lepeule, J., … London, S. J. (2016). DNA Methylation in Newborns and Maternal Smoking in Pregnancy: Genome-wide Consortium Meta-analysis. *American Journal of Human Genetics*, *98*(4). https://doi.org/10.1016/j.ajhg.2016.02.019

Juniper, E. F., O'Byrne, P. M., Guyatt, G. H., Ferrie, P. J., & King, D. R. (1999). Development and validation of a questionnaire to measure asthma control. *European Respiratory Journal*, *14*(4). https://doi.org/10.1034/j.1399-3003.1999.14d29.x

Kainu, A., Pallasaho, P., & Pietinalho, A. (2016). No change in prevalence of symptoms of COPD between 1996 and 2006 in Finnish adults – a report from the FinEsS Helsinki Study. *European Clinical Respiratory Journal*, *3*(1). https://doi.org/10.3402/ecrj.v3.31780

Kankaanranta, H., Kauppi, P., Tuomisto, L. E., & Ilmarinen, P. (2016). Emerging Comorbidities in Adult Asthma: Risks, Clinical Associations, and Mechanisms. In *Mediators of Inflammation* (Vol. 2016). https://doi.org/10.1155/2016/3690628

Kankaanranta, H., Tuomisto, L. E., & Ilmarinen, P. (2017). Age-specific incidence of new asthma diagnoses in Finland. *Journal of Allergy and Clinical Immunology: In Practice*, *5*(1). https://doi.org/10.1016/j.jaip.2016.08.015

Katon, W. J., Richardson, L., Lozano, P., & McCauley, E. (2004). The relationship of asthma and anxiety disorders. In *Psychosomatic Medicine* (Vol. 66, Issue 3). https://doi.org/10.1097/01.psy.0000126202.89941.ea

Kauppi, P., Kupiainen, H., Lindqvist, A., Tammilehto, L., Kilpeläinen, M., Kinnula, V. L., Haahtela, T., & Laitinen, T. (2011). Overlap syndrome of asthma and COPD predicts low quality of life. *Journal of Asthma*, *48*(3). https://doi.org/10.3109/02770903.2011.555576

Kauppi, P., Linna, M., Jantunen, J., Martikainen, J. E., Haahtela, T., Pelkonen, A., & Mäkelä, M. (2015). Chronic comorbidities contribute to the burden and costs of persistent asthma. *Mediators of Inflammation*, *2015*. https://doi.org/10.1155/2015/819194

Kaur, R., & Chupp, G. (2019). Phenotypes and endotypes of adult asthma: Moving toward precision medicine. In *Journal of Allergy and Clinical Immunology* (Vol. 144, Issue 1). https://doi.org/10.1016/j.jaci.2019.05.031

Kelly, M. P. (2010). The axes of social differentiation and the evidence base on health equity. In *Journal of the Royal Society of Medicine* (Vol. 103, Issue 7). https://doi.org/10.1258/jrsm.2010.100005

Kerminen, S., Havulinna, A. S., Hellenthal, G., Martin, A. R., Sarin, A. P., Perola, M., Palotie, A., Salomaa, V., Daly, M. J., Ripatti, S., & Pirinen, M. (2017). Fine-scale genetic structure in Finland. *G3: Genes, Genomes, Genetics*, *7*(10). https://doi.org/10.1534/g3.117.300217

Kew, K. M., Malik, P., Aniruddhan, K., & Normansell, R. (2017). Shared decision-making for people with asthma. In *Cochrane Database of Systematic Reviews* (Vol. 2017, Issue 10). https://doi.org/10.1002/14651858.CD012330.pub2

Khreis, H., Kelly, C., Tate, J., Parslow, R., Lucas, K., & Nieuwenhuijsen, M. (2017). Exposure to traffic-related air pollution and risk of development of childhood asthma: A systematic review and meta-analysis. In *Environment International* (Vol. 100). https://doi.org/10.1016/j.envint.2016.11.012

Kirjavainen, P. v., Karvonen, A. M., Adams, R. I., Täubel, M., Roponen, M., Tuoresmäki, P., Loss, G., Jayaprakash, B., Depner, M., Ege, M. J., Renz, H., Pfefferle, P. I., Schaub, B., Lauener, R., Hyvärinen, A., Knight, R., Heederik, D. J. J., von Mutius, E., & Pekkanen, J. (2019). Farm-like indoor microbiota in non-farm homes protects children from asthma development. *Nature Medicine*, *25*(7). https://doi.org/10.1038/s41591-019-0469-4

Klepaker, G., Svendsen, M. V., Hertel, J. K., Holla, O. L., Henneberger, P. K., Kongerud, J., & Fell, A. K. M. (2019). Influence of Obesity on Work Ability, Respiratory Symptoms, and Lung Function in Adults with Asthma. *Respiration*, *98*(6). https://doi.org/10.1159/000502154

Koskela, H. O., Lätti, A. M., & Purokivi, M. K. (2017). Long-term prognosis of chronic cough: A prospective, observational cohort study. *BMC Pulmonary Medicine*, *17*(1). https://doi.org/10.1186/s12890-017-0496-1

Koskinen, S., & Martelin, T. (2003). Why is Mortality Low among the Swedish-Speaking Minority in Finland? *Finnish Yearbook of Population Research*. https://doi.org/10.23979/fypr.44982

Kotaniemi, J. T., Pallasaho, P., Sovijärvi, A., Laitinen, L., & Lundbäck, B. (2002). Respiratory symptoms and asthma in relation to cold climate, inhaled allergens, and irritants: A comparison between Northern and Southern Finland. *Journal of Asthma*, *39*(7). https://doi.org/10.1081/JAS-120014930

Kowalski, M. L., Agache, I., Bavbek, S., Bakirtas, A., Blanca, M., Bochenek, G., Bonini, M., Heffler, E., Klimek, L., Laidlaw, T. M., Mullol, J., Niżankowska-Mogilnicka, E., Park, H. S., Sanak, M., Sanchez-Borges, M., Sanchez-Garcia, S., Scadding, G., Taniguchi, M., Torres, M. J., … Wardzyńska, A. (2019a). Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)—a EAACI position paper. *Allergy: European Journal of Allergy and Clinical Immunology*, *74*(1). https://doi.org/10.1111/all.13599

Kowalski, M. L., Agache, I., Bavbek, S., Bakirtas, A., Blanca, M., Bochenek, G., Bonini, M., Heffler, E., Klimek, L., Laidlaw, T. M., Mullol, J., Niżankowska-Mogilnicka, E., Park, H. S., Sanak, M., Sanchez-Borges, M., Sanchez-Garcia, S., Scadding, G., Taniguchi, M., Torres, M. J., … Wardzyńska, A. (2019b). Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)—a EAACI position paper. *Allergy: European Journal of Allergy and Clinical Immunology*, *74*(1), 28–39. https://doi.org/10.1111/all.13599

Kulla, G., Sarvimäki, A., & Fagerström, L. (2006). Health resources and health strategies among older Swedish-speaking Finns - A hermeneutic study. *Scandinavian Journal of Caring Sciences*, *20*(1). https://doi.org/10.1111/j.1471-6712.2006.00379.x

Kurashima, K., Takaku, Y., Ohta, C., Takayanagi, N., Yanagisawa, T., & Sugita, Y. (2016). COPD assessment test and severity of airflow limitation in patients with asthma, COPD, and asthma–COPD overlap syndrome. *International Journal of COPD*, *11*(1). https://doi.org/10.2147/COPD.S97343

Laidlaw, T. M., Mullol, J., Woessner, K. M., Amin, N., & Mannent, L. P. (2021). Chronic Rhinosinusitis with Nasal Polyps and Asthma. *Journal of Allergy and Clinical Immunology: In Practice*, *9*(3). https://doi.org/10.1016/j.jaip.2020.09.063

Lajunen, T. K., Jaakkola, J. J. K., & Jaakkola, M. S. (2021). Different effects of smoking on atopic and non-atopic adult-onset asthma. *Clinical and Translational Allergy*, *11*(8). https://doi.org/10.1002/clt2.12072

Lambrecht, B. N., & Hammad, H. (2017). The immunology of the allergy epidemic and the hygiene hypothesis. In *Nature Immunology* (Vol. 18, Issue 10). https://doi.org/10.1038/ni.3829

Lamprecht, B., Vanfleteren, L. E., Studnicka, M., Allison, M., McBurnie, M. A., Vollmer, W. M., Tan, W. C., Nielsen, R., Nastalek, P., Gnatiuc, L., Kaiser, B., Janson, C., Wouters, E. F. M., Burney, P., & Buist, A. S. (2013). Sex-related differences in respiratory symptoms: Results from the BOLD Study. In *European Respiratory Journal* (Vol. 42, Issue 3). https://doi.org/10.1183/09031936.00047613

Lange, P., Marott, J. L., Vestbo, J., Ingebrigtsen, T. S., & Nordestgaard, B. G. (2014). Socioeconomic status and prognosis of COPD in Denmark. *COPD: Journal of*

Chronic Obstructive Pulmonary Disease, *11*(4). https://doi.org/10.3109/15412555.2013.869580

Langhammer, A., Krokstad, S., Romundstad, P., Heggland, J., & Holmen, J. (2012). The HUNT study: Participation is associated with survival and depends on socioeconomic status, diseases and symptoms. *BMC Medical Research Methodology*, *12*. https://doi.org/10.1186/1471-2288-12-143

Larsson, M. L., Loit, H. M., Meren, M., Põlluste, J., Magnusson, A., Larsson, K., & Lundbäck, B. (2003). Passive smoking and respiratory symptoms in the FinEsS study. *European Respiratory Journal*, *21*(4). https://doi.org/10.1183/09031936.03.00033702

Lätti, A. M., Pekkanen, J., & Koskela, H. O. (2018). Defining the risk factors for acute, subacute and chronic cough: A cross-sectional study in a Finnish adult employee population. *BMJ Open*, *8*(7). https://doi.org/10.1136/bmjopen-2018-022950

Lebowitz, M. O., & Burrows, B. (1976). Comparison of questionnaires: the BMRC and NHLI respiratory questionnaires and a new self completion questionnaire. *American Review of Respiratory Disease*, *113*(5). https://doi.org/10.1164/arrd.1976.113.5.627

Leivseth, L., Nilsen, T. I. L., Mai, X. M., Johnsen, R., & Langhammer, A. (2014). Lung function and respiratory symptoms in association with mortality: The HUNT study. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *11*(1). https://doi.org/10.3109/15412555.2013.781578

Lieberoth, S., Backer, V., Kyvik, K. O., Skadhauge, L. R., Tolstrup, J. S., Grønbæk, M., Linneberg, A., & Thomsen, S. F. (2012). Intake of alcohol and risk of adult-onset asthma. *Respiratory Medicine*, *106*(2). https://doi.org/10.1016/j.rmed.2011.11.004

Lietzén, R., Suominen, S., Sillanmäki, L., Virtanen, P., Virtanen, M., & Vahtera, J. (2021). Multiple adverse childhood experiences and asthma onset in adulthood: Role of adulthood risk factors as mediators. *Journal of Psychosomatic Research*, *143*. https://doi.org/10.1016/j.jpsychores.2021.110388

Lindberg, A., Bjerg-Bäcklund, A., Rönmark, E., Larsson, L. G., & Lundbäck, B. (2006). Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking: Report from the Obstructive Lung Disease in Northern Sweden Studies. *Respiratory Medicine*, *100*(2). https://doi.org/10.1016/j.rmed.2005.04.029

Lindberg, A., Jonsson, A. C., Rönmark, E., Lundgren, R., Larsson, L. G., & Lundbäck, B. (2005). Prevalence of chronic obstructive pulmonary disease according to BTS, ERS, GOLD and ATS criteria in relation to doctor's diagnosis, symptoms, age, gender, and smoking habits. *Respiration*, *72*(5). https://doi.org/10.1159/000087670

Lindström, B., & Eriksson, M. (2006). Contextualizing salutogenesis and Antonovsky in public health development. In *Health Promotion International* (Vol. 21, Issue 3). https://doi.org/10.1093/heapro/dal016

Lindström, M., Kotaniemi, J., Jönsson, E., & Lundbäck, B. (2001). Smoking, respiratory symptoms, and diseases: A comparative study between northern Sweden and northern Finland: Report from the FinEsS study. *Chest*, *119*(3). https://doi.org/10.1378/chest.119.3.852

Loponen, J., Ilmarinen, P., Tuomisto, L. E., Niemelä, O., Tommola, M., Nieminen, P., Lehtimäki, L., & Kankaanranta, H. (2018). Daily physical activity and lung function decline in adult-onset asthma: a 12-year follow-up study. *European Clinical Respiratory Journal*, *5*(1). https://doi.org/10.1080/20018525.2018.1533753

Lötvall, J., Ekerljung, L., & Lundbäck, B. (2010). Multi-symptom asthma is closely related to nasal blockage, rhinorrhea and symptoms of chronic rhinosinusitis-evidence from the West Sweden Asthma Study. *Respiratory Research*, *11*. https://doi.org/10.1186/1465-9921-11-163

Lowe, K. E., Make, B. J., Crapo, J. D., Kinney, G. L., Hokanson, J. E., Kim, V., Iyer, A. S., Bhatt, S. P., Hoth, K. F., Holm, K. E., Wise, R., DeMeo, D., Foreman, M. G., Stone, T. J., & Regan, E. A. (2018). Association of low income with pulmonary disease progression in smokers with and without chronic obstructive pulmonary disease. *ERJ Open Research*, *4*(4). https://doi.org/10.1183/23120541.00069-2018

Lundback, B., Nystrom, L., Rosenhall, L., & Stjernberg, N. (1991). Obstructive lung disease in northern Sweden: Respiratory symptoms assessed in a postal survey. *European Respiratory Journal*, *4*(3).

Lundbäck, B., Stjernberg, N., Rosenhall, L., Lindström, M., Jönsson, E., & Andersson, S. (1993). Methacholine reactivity and asthma: Report from the Northern Sweden Obstructive Lung Disease Project. *Allergy*, *48*(2). https://doi.org/10.1111/j.1398-9995.1993.tb00696.x

Lutter, J. I., Jörres, R. A., Welte, T., Watz, H., Waschki, B., Alter, P., Trudzinski, F. C., Ohlander, J., Behr, J., Bals, R., Studnicka, M., Holle, R., Vogelmeier, C. F., & Kahnert, K. (2020). Impact of education on copd severity and all-cause mortality in lifetime never-smokers and longtime ex-smokers: Results of the cosyconet cohort. *International Journal of COPD*, *15*. https://doi.org/10.2147/COPD.S273839

Machin, M., Amaral, A. F. S., Wielscher, M., Rezwan, F. I., Imboden, M., Jarvelin, M. R., Adcock, I. M., Probst-Hensch, N., Holloway, J. W., & Jarvis, D. L. (2017). Systematic review of lung function and COPD with peripheral blood DNA methylation in population based studies. *BMC Pulmonary Medicine*, *17*(1). https://doi.org/10.1186/s12890-017-0397-3

Makowska, J. S., Burney, P., Jarvis, D., Keil, T., Tomassen, P., Bislimovska, J., Brozek, G., Bachert, C., Baelum, J., Bindslev-Jensen, C., Bousquet, J., Bousquet, P. J., Kai-Håkon, C., Dahlen, S. E., Dahlen, B., Fokkens, W. J., Forsberg, B., Gjomarkaj, M., Howarth, P., … Kowalski, M. L. (2016). Respiratory hypersensitivity reactions to NSAIDs in Europe: the global allergy and asthma network (GA2LEN) survey. *Allergy: European Journal of Allergy and Clinical Immunology*, *71*, 1603–1611. https://doi.org/10.1111/all.12941

Mamane, A., Baldi, I., Tessier, J. F., Raherison, C., & Bouvier, G. (2015). Occupational exposure to pesticides and respiratory health. In *European Respiratory Review* (Vol. 24, Issue 136). https://doi.org/10.1183/16000617.00006014

Marengoni, A., Angleman, S., Melis, R., Mangialasche, F., Karp, A., Garmen, A., Meinow, B., & Fratiglioni, L. (2011). Aging with multimorbidity: A systematic review of the literature. In *Ageing Research Reviews* (Vol. 10, Issue 4). https://doi.org/10.1016/j.arr.2011.03.003

Marmot, M., Allen, J., Bell, R., Bloomer, E., & Goldblatt, P. (2012). WHO European review of social determinants of health and the health divide. In *The Lancet* (Vol. 380, Issue 9846). https://doi.org/10.1016/S0140-6736(12)61228-8

Martikainen, P., Sipilä, P., Blomgren, J., & van Lenthe, F. J. (2008). The effects of migration on the relationship between area socioeconomic structure and mortality. *Health and Place*, *14*(2). https://doi.org/10.1016/j.healthplace.2007.07.004

Mathers, C. D., & Loncar, D. (2006). Projections of Global Mortality and Burden of Disease from 2002 to 2030. In *PLoS Medicine | www* (Vol. 3, Issue 11). www.plosmedicine.org

Matsuse, H., Shimoda, T., Fukushima, C., Mitsuta, K., Kawano, T., Tomari Shinya, Y., Saeki, S., Kondoh, Y., Machida, I., Obase, Y., Asai, S., & Kohno, S. (2001). Screening for acetaldehyde dehydrogenase 2 genotype in alcohol-induced asthma by using the ethanol patch test. *Journal of Allergy and Clinical Immunology*, *108*(5). https://doi.org/10.1067/mai.2001.118791

Maurer, J., Rebbapragada, V., Borson, S., Goldstein, R., Kunik, M. E., Yohannes, A. M., & Hanania, N. A. (2008). Anxiety and depression in COPD: Current understanding, unanswered questions, and research needs. *Chest*, *134*(4 SUPPL.). https://doi.org/10.1378/chest.08-0342

McDonald, V. M., Hiles, S. A., Godbout, K., Harvey, E. S., Marks, G. B., Hew, M., Peters, M., Bardin, P. G., Reynolds, P. N., Upham, J. W., Baraket, M., Bhikoo, Z., Bowden, J., Brockway, B., Chung, L. P., Cochrane, B., Foxley, G., Garrett, J., Jayaram, L., … Gibson, P. G. (2019). Treatable traits can be identified in a severe asthma registry and predict future exacerbations. *Respirology*, *24*(1). https://doi.org/10.1111/resp.13389

McDonald, V. M., Osadnik, C. R., & Gibson, P. G. (2019). Treatable traits in acute exacerbations of chronic airway diseases. In *Chronic Respiratory Disease* (Vol. 16). https://doi.org/10.1177/1479973119867954

Meininger, I., Carrasco, A., Rao, A., Soini, T., Kokkinou, E., & Mjösberg, J. (2020). Tissue-Specific Features of Innate Lymphoid Cells. In *Trends in Immunology* (Vol. 41, Issue 10). https://doi.org/10.1016/j.it.2020.08.009

Menezes, A. M. B., de Oca, M. M., Pérez-Padilla, R., Nadeau, G., Wehrmeister, F. C., Lopez-Varela, M. V., Muiño, A., Jardim, J. R. B., Valdivia, G., & Tálamo, C. (2014). Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype : COPD-Asthma. *Chest*, *145*(2). https://doi.org/10.1378/chest.13-0622

Miravitlles, M., Dirksen, A., Ferrarotti, I., Koblizek, V., Lange, P., Mahadeva, R., McElvaney, N. G., Parr, D., Piitulainen, E., Roche, N., Stolk, J., Thabut, G., Turner, A., Vogelmeier, C., & Stockley, R. A. (2017). European Respiratory Society statement: Diagnosis and treatment of pulmonary disease in α1-antitrypsin deficiency. *European Respiratory Journal*, *50*(5). https://doi.org/10.1183/13993003.00610-2017

Miravitlles, M., Soler-Cataluña, J. J., Calle, M., & Soriano, J. B. (2013). Treatment of COPD by clinical phenotypes: Putting old evidence into clinical practice. In *European Respiratory Journal* (Vol. 41, Issue 6). https://doi.org/10.1183/09031936.00118912

Moffatt, M. F., Gut, I. G., Demenais, F., Strachan, D. P., Bouzigon, E., Heath, S., von Mutius, E., Farrall, M., Lathrop, M., & Cookson, W. O. C. M. (2010). A Large-Scale, Consortium-Based Genomewide Association Study of Asthma. *New England Journal of Medicine*, *363*(13). https://doi.org/10.1056/nejmoa0906312

Mounce, L. T. A., Campbell, J. L., Henley, W. E., Tejerina Arreal, M. C., Porter, I., & Valderas, J. M. (2018). Predicting incident multimorbidity. *Annals of Family Medicine*, *16*(4). https://doi.org/10.1370/afm.2271

Munari, A. B., Gulart, A. A., dos Santos, K., Venâncio, R. S., Karloh, M., & Mayer, A. F. (2018). Modified Medical Research Council Dyspnea Scale in GOLD Classification Better Reflects Physical Activities of Daily Living. *Respiratory Care*, *63*(1). https://doi.org/10.4187/respcare.05636

Murgu, S. D., & Colt, H. G. (2006). Tracheobronchomalacia and excessive dynamic airway collapse. In *Respirology* (Vol. 11, Issue 4). https://doi.org/10.1111/j.1440-1843.2006.00862.x

Murrison, L. B., Brandt, E. B., Myers, J. B., & Khurana Hershey, G. K. (2019). Environmental exposures and mechanisms in allergy and asthma development. In *Journal of Clinical Investigation* (Vol. 129, Issue 4). https://doi.org/10.1172/JCI124612

Nguyen, H., Manolova, G., Daskalopoulou, C., Vitoratou, S., Prince, M., & Prina, A. M. (2019). Prevalence of multimorbidity in community settings: A systematic review and meta-analysis of observational studies. *Journal of Comorbidity*, *9*. https://doi.org/10.1177/2235042x19870934

Ntontsi, P., Photiades, A., Zervas, E., Xanthou, G., & Samitas, K. (2021). Genetics and epigenetics in asthma. In *International Journal of Molecular Sciences* (Vol. 22, Issue 5). https://doi.org/10.3390/ijms22052412

Öberg, M., Jaakkola, M. S., Woodward, A., Peruga, A., & Prüss-Ustün, A. (2011). Worldwide burden of disease from exposure to second-hand smoke: A retrospective analysis of data from 192 countries. *The Lancet*, *377*(9760). https://doi.org/10.1016/S0140-6736(10)61388-8

Obućina, O., & Saarela, J. (2020). Intergenerational transmission of ethnic identity in mixed native couples in Finland. *Acta Sociologica (United Kingdom)*, *63*(1). https://doi.org/10.1177/0001699319847507

Olafsdottir, T. A., Theodors, F., Bjarnadottir, K., Bjornsdottir, U. S., Agustsdottir, A. B., Stefansson, O. A., Ivarsdottir, E. v., Sigurdsson, J. K., Benonisdottir, S., Eyjolfsson, G. I., Gislason, D., Gislason, T., Guðmundsdóttir, S., Gylfason, A., Halldorsson, B. v., Halldorsson, G. H., Juliusdottir, T., Kristinsdottir, A. M., Ludviksdottir, D., … Stefansson, K. (2020). Eighty-eight variants highlight the role of T cell regulation and airway remodeling in asthma pathogenesis. *Nature Communications*, *11*(1). https://doi.org/10.1038/s41467-019-14144-8

Omland, Ø., Hjort, C., Pedersen, O. F., Miller, M. R., & Sigsgaard, T. (2011). New-onset asthma and the effect of environment and occupation among farming and nonfarming rural subjects. *Journal of Allergy and Clinical Immunology*, *128*(4). https://doi.org/10.1016/j.jaci.2011.06.006

Pagiatakis, C., Musolino, E., Gornati, R., Bernardini, G., & Papait, R. (2021). Epigenetics of aging and disease: a brief overview. In *Aging Clinical and Experimental Research* (Vol. 33, Issue 4). https://doi.org/10.1007/s40520-019-01430-0

PAHO. (2018). *Just Societies: Health Equity and Dignified Lives. Report of the Commission of the Pan American Health Organization on Equity and Health Inequalities in the Americas. Washington, D.C.: PAHO; 2019. Available www.iris.paho.org / Date last accessed 8th June 2021.*

Pakkasela, J., Ilmarinen, P., Honkamäki, J., Tuomisto, L. E., Andersén, H., Piirilä, P., Hisinger-Mölkänen, H., Sovijärvi, A., Backman, H., Lundbäck, B., Rönmark, E., Kankaanranta, H., & Lehtimäki, L. (2020). Age-specific incidence of allergic and non-allergic asthma. *BMC Pulmonary Medicine*, *20*(1). https://doi.org/10.1186/s12890-019-1040-2

Paljärvi, T., Martikainen, P., Leinonen, T., Pensola, T., & Mäkelä, P. (2014). Non-employment histories of middle-aged men and women who died from alcohol-related causes: A longitudinal retrospective study. *PLoS ONE*, *9*(5). https://doi.org/10.1371/journal.pone.0098620

Pallasaho, P., Lindström, M., Põlluste, J., Loit, H. M., Sovijärvi, A., & Lundbäck, B. (2004). Low socio-economic status is a risk factor for respiratory symptoms: A comparison between Finland, Sweden and Estonia. In *International Journal of Tuberculosis and Lung Disease* (Vol. 8, Issue 11).

Pallasaho, P., Lundbäck, B., Meren, M., Kiviloog, J., Loit, H. M., Larsson, K., & Laitinen, L. A. (2002). Prevalence and risk factors for asthma and chronic bronchitis in the capitals Helsinki, Stockholm, and Tallinn. *Respiratory Medicine*, *96*(10). https://doi.org/10.1053/rmed.2002.1308

Pallasaho, P., Rönmark, E., Haahtela, T., Sovijärvi, A. R. A., & Lundbäck, B. (2006). Degree and clinical relevance of sensitization to common allergens among adults: A population study in Helsinki, Finland. *Clinical and Experimental Allergy*, *36*(4). https://doi.org/10.1111/j.1365-2222.2006.02460.x

Palomares, O., Akdis, M., Martín-Fontecha, M., & Akdis, C. A. (2017). Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells. In *Immunological Reviews* (Vol. 278, Issue 1). https://doi.org/10.1111/imr.12555

Pavilonis, B. T., Sanderson, W. T., & Merchant, J. A. (2013). Relative exposure to swine animal feeding operations and childhood asthma prevalence in an agricultural cohort. *Environmental Research*, *122*. https://doi.org/10.1016/j.envres.2012.12.008

Pavlidis, S., Takahashi, K., Kwong, F. N. K., Xie, J., Hoda, U., Sun, K., Elyasigomari, V., Agapow, P., Loza, M., Baribaud, F., Chanez, P., Fowler, S. J., Shaw, D. E., Fleming, L. J., Howarth, P. H., Sousa, A. R., Corfield, J., Auffray, C., de Meulder, B., … Chung, K. F. (2019). "T2-high" in severe asthma related to blood eosinophil, exhaled nitric oxide and serum periostin. *European Respiratory Journal*, *53*(1). https://doi.org/10.1183/13993003.00938-2018

Peters, M. C., Ringel, L., Dyjack, N., Herrin, R., Woodruff, P. G., Rios, C., O'Connor, B., Fahy, J. v., & Seibold, M. A. (2019). A transcriptomic method to determine airway immune dysfunction in T2-high and T2-low asthma. *American Journal of Respiratory and Critical Care Medicine*, *199*(4). https://doi.org/10.1164/rccm.201807-1291OC

Pividori, M., Schoettler, N., Nicolae, D. L., Ober, C., & Im, H. K. (2019). Shared and distinct genetic risk factors for childhood-onset and adult-onset asthma: genome-wide and transcriptome-wide studies. *The Lancet Respiratory Medicine*, *7*(6). https://doi.org/10.1016/S2213-2600(19)30055-4

Ponce-Gallegos, M. A., Ramírez-Venegas, A., Falfán-Valencia, R., & Ponce-, M. A. (2017). Th17 profile in COPD exacerbations Innate immunity. *International Journal of Chronic Obstructive Pulmonary Disease*, *12*.

Porsbjerg, C., Lange, P., & Ulrik, C. S. (2015). Lung function impairment increases with age of diagnosis in adult onset asthma. *Respiratory Medicine*, *109*(7). https://doi.org/10.1016/j.rmed.2015.04.012

Postma, D. S., Weiss, S. T., van den Berge, M., Kerstjens, H. A. M., & Koppelman, G. H. (2015). Revisiting the Dutch hypothesis. In *Journal of Allergy and Clinical Immunology* (Vol. 136, Issue 3). https://doi.org/10.1016/j.jaci.2015.06.018

Preteroti, M., Whitmore, G. A., Vandemheen, K. L., FitzGerald, J. M., Lemière, C., Boulet, L. P., Penz, E., Field, S. K., Gupta, S., McIvor, R. A., Mayers, I., Hernandez, P., Lougheed, D., Ainslie, M., Licskai, C., Azher, T., Fraser, I., Mahdavian, M., & Aaron, S. D. (2020). Population-based case-finding to identify subjects with undiagnosed asthma or COPD. *The European Respiratory Journal*, *55*(6). https://doi.org/10.1183/13993003.00024-2020

Price, D., Fletcher, M., & van der Molen, T. (2014). Asthma control and management in 8,000 European patients: The REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *Npj Primary Care Respiratory Medicine*, *24*. https://doi.org/10.1038/npjpcrm.2014.9

Radhakrishna, N., Tay, T. R., Hore-Lacy, F., Stirling, R., Hoy, R., Dabscheck, E., & Hew, M. (2017). Validated questionnaires heighten detection of difficult asthma comorbidities. *Journal of Asthma*, *54*(3). https://doi.org/10.1080/02770903.2016.1212369

Radhakrishnan, D. K., Dell, S. D., Guttmann, A., Shariff, S. Z., Liu, K., & To, T. (2014). Trends in the age of diagnosis of childhood asthma. *Journal of Allergy and Clinical Immunology*, *134*(5). https://doi.org/10.1016/j.jaci.2014.05.012

Räisänen, P., Hedman, L., Andersson, M., Stridsman, C., Lindberg, A., Lundbäck, B., Rönmark, E., & Backman, H. (2020). Non-response did not affect prevalence estimates of asthma and respiratory symptoms - results from a postal questionnaire survey of the general population. *Respiratory Medicine*, *173*. https://doi.org/10.1016/j.rmed.2020.106017

Rastogi, D. (2020). Pediatric obesity-related asthma: A prototype of pediatric severe non-T2 asthma. In *Pediatric Pulmonology* (Vol. 55, Issue 3). https://doi.org/10.1002/ppul.24600

Reini, K., & Nyqvist, F. (2017). Sense of mastery differences between working-age Swedish- and Finnish-speaking Finns: A population-based study. In *Scandinavian Journal of Public Health* (Vol. 45, Issue 4). https://doi.org/10.1177/1403494817696183

Rice, L., & Sara, R. (2019). Updating the determinants of health model in the Information Age. In *Health Promotion International* (Vol. 34, Issue 6). https://doi.org/10.1093/heapro/day064

Riedler, J., Braun-Fahrländer, C., Eder, W., Schreuer, M., Waser, M., Maisch, S., Carr, D., Schierl, R., Nowak, D., & von Mutius, E. (2001). Exposure to farming in early life and development of asthma and allergy: A cross-sectional survey. *Lancet*, *358*(9288). https://doi.org/10.1016/S0140-6736(01)06252-3

Rijavec, M., Krumpestar, T., Škrgat, S., Kern, I., & Korošec, P. (2021). T2-high asthma, classified by sputum mrna expression of il4, il5, and il13, is characterized by

eosinophilia and severe phenotype. *Life*, *11*(2). https://doi.org/10.3390/life11020092

Robson, B., Purdie, G., Cram, F., & Simmonds, S. (2007). Age standardisation - An indigenous standard? In *Emerging Themes in Epidemiology* (Vol. 4). https://doi.org/10.1186/1742-7622-4-3

Rogliani, P., Sforza, M., & Calzetta, L. (2020). The impact of comorbidities on severe asthma. In *Current opinion in pulmonary medicine* (Vol. 26, Issue 1). https://doi.org/10.1097/MCP.0000000000000640

Rönmark, E., Bjerg, A., Perzanowski, M., Platts-Mills, T., & Lundbäck, B. (2009). Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden. *Journal of Allergy and Clinical Immunology*, *124*(2). https://doi.org/10.1016/j.jaci.2009.05.011

Ruokolainen, L., Fyhrquist, N., Laatikainen, T., Auvinen, P., Fortino, V., Scala, G., Jousilahti, P., Karisola, P., Vendelin, J., Karkman, A., Markelova, O., Mäkelä, M. J., Lehtimäki, S., Ndika, J., Ottman, N., Paalanen, L., Paulin, L., Vartiainen, E., von Hertzen, L., … Alenius, H. (2020). Immune-microbiota interaction in Finnish and Russian Karelia young people with high and low allergy prevalence. *Clinical and Experimental Allergy*, *50*(10). https://doi.org/10.1111/cea.13728

Saarela, J., & Finnäs, F. (2011). Family origin and mortality: Prospective Finnish cohort study. *BMC Public Health*, *11*. https://doi.org/10.1186/1471-2458-11-385

Saarela, J., & Finnäs, F. (2013). The International Family Migration of Swedish-Speaking Finns: The Role of Spousal Education. *Journal of Ethnic and Migration Studies*, *39*(3). https://doi.org/10.1080/1369183X.2013.733860

Saarela, J. M., & Finnäs, F. S. A. (2004). The health of Swedish-speaking and Finnish-speaking schoolchidlren in Finland. *Child: Care, Health and Development*, *30*(1). https://doi.org/10.1111/j.1365-2214.2004.00385.x

Sakib, M. N., Shooshtari, S., St John, P., & Menec, V. (2019). The prevalence of multimorbidity and associations with lifestyle factors among middle-aged Canadians: An analysis of Canadian Longitudinal Study on Aging data. *BMC Public Health*, *19*(1). https://doi.org/10.1186/s12889-019-6567-x

Samter, M., & Beers, R. F. (1968). Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Annals of Internal Medicine*, *68*, 975–983. https://doi.org/10.7326/0003-4819-68-5-975

Scadding, J. G. (1959). Principles of definition in medicine with special reference to chronic bronchitis and emphysema. *The Lancet*, *273*(7068). https://doi.org/10.1016/S0140-6736(59)90308-3

Schneider, C., Lee, J., Koga, S., Ricardo-Gonzalez, R. R., Nussbaum, J. C., Smith, L. K., Villeda, S. A., Liang, H. E., & Locksley, R. M. (2019). Tissue-Resident Group 2 Innate Lymphoid Cells Differentiate by Layered Ontogeny and In Situ Perinatal Priming. *Immunity*, *50*(6). https://doi.org/10.1016/j.immuni.2019.04.019

Schyllert, C., Lindberg, A., Hedman, L., Stridsman, C., Andersson, M., Ilmarinen, P., Piirilä, P., Krokstad, S., Lundbäck, B., Rönmark, E., & Backman, H. (2020). Low socioeconomic status relates to asthma and wheeze, especially in women. *ERJ Open Research*, *6*(3). https://doi.org/10.1183/23120541.00258-2019

Schyllert, C., Rönmark, E., Andersson, M., Hedlund, U., Lundbäck, B., Hedman, L., & Lindberg, A. (2016). Occupational exposure to chemicals drives the increased risk of asthma and rhinitis observed for exposure to vapours, gas, dust and

fumes: A cross-sectional population-based study. *Occupational and Environmental Medicine*, *73*(10). https://doi.org/10.1136/oemed-2016-103595

Sharpe, R. A., Bearman, N., Thornton, C. R., Husk, K., & Osborne, N. J. (2015). Indoor fungal diversity and asthma: A meta-analysis and systematic review of risk factors. *Journal of Allergy and Clinical Immunology*, *135*(1). https://doi.org/10.1016/j.jaci.2014.07.002

Shimoda, T., Obase, Y., Matsuse, H., Asai, S., & Iwanaga, T. (2017). The Pathogenesis of Alcohol-Induced Airflow Limitation in Acetaldehyde Dehydrogenase 2-Deficient Mice. *International Archives of Allergy and Immunology*, *171*(3–4). https://doi.org/10.1159/000452709

Sin, D. D., Miravitlles, M., Mannino, D. M., Soriano, J. B., Price, D., Celli, B. R., Leung, J. M., Nakano, Y., Park, H. Y., Wark, P. A., & Wechsler, M. E. (2016). What is asthma?COPD overlap syndrome? Towards a consensus definition from a round table discussion. In *European Respiratory Journal* (Vol. 48, Issue 3). https://doi.org/10.1183/13993003.00436-2016

Singer, L., Green, M., Rowe, F., Ben-Shlomo, Y., & Morrissey, K. (2019). Social determinants of multimorbidity and multiple functional limitations among the ageing population of England, 2002–2015. *SSM - Population Health*, *8*. https://doi.org/10.1016/j.ssmph.2019.100413

Singhvi, D., & Bon, J. (2021). CT Imaging and Comorbidities in COPD: Beyond Lung Cancer Screening. In *Chest* (Vol. 159, Issue 1). https://doi.org/10.1016/j.chest.2020.08.2053

Sipilä, P., & Martikainen, P. (2009). Language-group mortality differentials in Finland in 1988-2004: Assessment of the contribution of cause of death, sex and age. *European Journal of Public Health*, *19*(5). https://doi.org/10.1093/eurpub/ckp074

Skaaby, T., Kilpeläinen, T. O., Taylor, A. E., Mahendran, Y., Wong, A., Ahluwalia, T. S., Paternoster, L., Trompet, S., Stott, D. J., Flexeder, C., Zhou, A., Brusselle, G., Sajjad, A., Lahousse, L., Tiemeier, H., Have, C. T., Thuesen, B. H., Kårhus, L. L., Møllehave, L. T., … Linneberg, A. (2019). Association of alcohol consumption with allergic disease and asthma: a multi-centre Mendelian randomization analysis. *Addiction*, *114*(2). https://doi.org/10.1111/add.14438

Sluiter, H. J., Koeter, G. H., de Monchy, J. G. R., Postma, D. S., de Vries, K., & Orie, N. G. M. (1991). The Dutch hypothesis (chronic non-specific lung disease) revisited. In *European Respiratory Journal* (Vol. 4, Issue 4).

Soh, W. T., Aglas, L., Mueller, G. A., Gilles, S., Weiss, R., Scheiblhofer, S., Huber, S., Scheidt, T., Thompson, P. M., Briza, P., London, R. E., Traidl-Hoffmann, C., Cabrele, C., Brandstetter, H., & Ferreira, F. (2019). Multiple roles of Bet v 1 ligands in allergen stabilization and modulation of endosomal protease activity. *Allergy: European Journal of Allergy and Clinical Immunology*, *74*(12). https://doi.org/10.1111/all.13948

Soriano, J. B., Abajobir, A. A., Abate, K. H., Abera, S. F., Agrawal, A., Ahmed, M. B., Aichour, A. N., Aichour, I., Eddine Aichour, M. T., Alam, K., Alam, N., Alkaabi, J. M., Al-Maskari, F., Alvis-Guzman, N., Amberbir, A., Amoako, Y. A., Ansha, M. G., Antó, J. M., Asayesh, H., … Vos, T. (2017). Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The*

Lancet Respiratory Medicine, *5*(9). https://doi.org/10.1016/S2213-2600(17)30293-X

Soriano, J. B., Kendrick, P. J., Paulson, K. R., Gupta, V., Abrams, E. M., Adedoyin, R. A., Adhikari, T. B., Advani, S. M., Agrawal, A., Ahmadian, E., Alahdab, F., Aljunid, S. M., Altirkawi, K. A., Alvis-Guzman, N., Anber, N. H., Andrei, C. L., Anjomshoa, M., Ansari, F., Antó, J. M., … Vos, T. (2020). Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Respiratory Medicine*, *8*(6). https://doi.org/10.1016/S2213-2600(20)30105-3

Soriano, J. B., Visick, G. T., Muellerova, H., Payvandi, N., & Hansell, A. L. (2005). Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest*, *128*(4). https://doi.org/10.1378/chest.128.4.2099

Spece, L. J., Epler, E. M., Donovan, L. M., Griffith, M. F., Collins, M. P., Feemster, L. C., & Au, D. H. (2018). Role of comorbidities in treatment and outcomes after chronic obstructive pulmonary disease exacerbations. *Annals of the American Thoracic Society*, *15*(9). https://doi.org/10.1513/AnnalsATS.201804-255OC

Stenius-Aarniala, B., Poussa, T., Kvarnström, J., Grönlund, E. L., Ylikahri, M., & Mustajoki, P. (2000). Immediate and long term effects of weight reduction in obese people with asthma: Randomised controlled study. *British Medical Journal*, *320*(7238). https://doi.org/10.1136/bmj.320.7238.827

Stevenson, D. D., & Szczeklik, A. (2006). Clinical and pathologic perspectives on aspirin sensitivity and asthma. *Journal of Allergy and Clinical Immunology*, *118*, 773–786. https://doi.org/10.1016/j.jaci.2006.07.024

Szczeklik, A., Nizankowska, E., & Duplaga, M. (2000). Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *The European Respiratory Journal*, *16*(3), 432.

Sze, E., Bhalla, A., & Nair, P. (2020). Mechanisms and therapeutic strategies for non-T2 asthma. In *Allergy: European Journal of Allergy and Clinical Immunology* (Vol. 75, Issue 2). https://doi.org/10.1111/all.13985

Tan, D. J., Walters, E. H., Perret, J. L., Lodge, C. J., Lowe, A. J., Matheson, M. C., & Dharmage, S. C. (2015). Age-of-asthma onset as a determinant of different asthma phenotypes in adults: A systematic review and meta-analysis of the literature. In *Expert Review of Respiratory Medicine* (Vol. 9, Issue 1). https://doi.org/10.1586/17476348.2015.1000311

Tanaka, A., Sato, H., Akimoto, K., Matsunaga, T., & Sagara, H. (2021). Spontaneous sputum discriminates inflammatory phenotypes in patients with asthma. *Annals of Allergy, Asthma and Immunology*, *126*(1). https://doi.org/10.1016/j.anai.2020.06.017

Tashkin, D. P., Celli, B., Decramer, M., Liu, D., Burkhart, D., Cassino, C., & Kesten, S. (2008). Bronchodilator responsiveness in patients with COPD. *European Respiratory Journal*, *31*(4). https://doi.org/10.1183/09031936.00129607

Thacher, J. D., Gruzieva, O., Pershagen, G., Melén, E., Lorentzen, J. C., Kull, I., & Bergström, A. (2017). Mold and dampness exposure and allergic outcomes from birth to adolescence: data from the BAMSE cohort. *Allergy: European Journal of Allergy and Clinical Immunology*, *72*(6). https://doi.org/10.1111/all.13102

Timm, S., Frydenberg, M., Abramson, M. J., Bertelsen, R. J., Bråbäck, L., Benediktsdottir, B., Gislason, T., Holm, M., Janson, C., Jogi, R., Johannessen,

A., Kim, J. L., Malinovschi, A., Mishra, G., Moratalla, J., Sigsgaard, T., Svanes, C., & Schlünssen, V. (2019). Asthma and selective migration from farming environments in a three-generation cohort study. *European Journal of Epidemiology*, *34*(6). https://doi.org/10.1007/s10654-019-00491-9

Tinetti, M. E., Fried, T. R., & Boyd, C. M. (2012). Designing health care for the most common chronic condition - Multimorbidity. In *JAMA - Journal of the American Medical Association* (Vol. 307, Issue 23). https://doi.org/10.1001/jama.2012.5265

Tiotiu, A. I., Novakova, P., Nedeva, D., Chong-Neto, H. J., Novakova, S., Steiropoulos, P., & Kowal, K. (2020). Impact of air pollution on asthma outcomes. In *International Journal of Environmental Research and Public Health* (Vol. 17, Issue 17). https://doi.org/10.3390/ijerph17176212

Toennesen, L. L., Meteran, H., Hostrup, M., Wium Geiker, N. R., Jensen, C. B., Porsbjerg, C., Astrup, A., Bangsbo, J., Parker, D., & Backer, V. (2018). Effects of Exercise and Diet in Nonobese Asthma Patients—A Randomized Controlled Trial. *Journal of Allergy and Clinical Immunology: In Practice*, *6*(3). https://doi.org/10.1016/j.jaip.2017.09.028

Tolvanen, E., Koskela, T. H., Mattila, K. J., & Kosunen, E. (2018). Analysis of factors associated with waiting times for GP appointments in Finnish health centres: A QUALICOPC study. *BMC Research Notes*, *11*(1). https://doi.org/10.1186/s13104-018-3316-7

Tommola, M., Ilmarinen, P., Tuomisto, L. E., & Kankaanranta, H. (2017). Concern of underdiagnosing asthma-COPD overlap syndrome if age limit of 40 years for asthma is used. In *European Respiratory Journal* (Vol. 50, Issue 2). https://doi.org/10.1183/13993003.00871-2017

Tommola, M., Ilmarinen, P., Tuomisto, L. E., Lehtimäki, L., Niemelä, O., Nieminen, P., & Kankaanranta, H. (2019). Cumulative effect of smoking on disease burden and multimorbidity in adult-onset asthma. In *European Respiratory Journal* (Vol. 54, Issue 3). https://doi.org/10.1183/13993003.01580-2018

Tommola, M., Won, H. K., Ilmarinen, P., Jung, H., Tuomisto, L. E., Lehtimäki, L., Niemelä, O., Kim, T. B., & Kankaanranta, H. (2020). Relationship between age and bronchodilator response at diagnosis in adult-onset asthma. *Respiratory Research*, *21*(1). https://doi.org/10.1186/s12931-020-01441-w

Torén, K., Palmqvist, M., Löwhagen, O., Balder, B., & Tunsäter, A. (2006). Self-reported asthma was biased in relation to disease severity while reported year of asthma onset was accurate. *Journal of Clinical Epidemiology*, *59*(1). https://doi.org/10.1016/j.jclinepi.2005.03.019

Torén, K., Schiöler, L., Lindberg, A., Andersson, A., Behndig, A. F., Bergström, G., Blomberg, A., Caidahl, K., Engvall, J. E., Eriksson, M. J., Hamrefors, V., Janson, C., Kylhammar, D., Lindberg, E., Lindén, A., Malinovschi, A., Lennart Persson, H., Sandelin, M., Eriksson Ström, J., … Sköld, C. M. (2021). The ratio FEV1/FVC and its association to respiratory symptoms—A Swedish general population study. *Clinical Physiology and Functional Imaging*, *41*(2). https://doi.org/10.1111/cpf.12684

Torén, K., Vikgren, J., Olin, A. C., Rosengren, A., Bergström, G., & Brandberg, J. (2017). Occupational exposure to vapor, gas, dust, or fumes and chronic airflow limitation, COPD, and emphysema: The swedish cardiopulmonary bioimage

study (SCAPIS pilot). *International Journal of COPD*, *12*. https://doi.org/10.2147/COPD.S144933

Tsiligianni, I. G., van der Molen, T., Moraitaki, D., Lopez, I., Kocks, J. W. H., Karagiannis, K., Siafakas, N., & Tzanakis, N. (2012). Assessing health status in COPD. A head-to-head comparison between the COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ). *BMC Pulmonary Medicine*, *12*. https://doi.org/10.1186/1471-2466-12-20

Tuomisto, L., Erhola, M., Kaila, M., Brander, P. E., Puolijoki, H., Kauppinen, R., & Koskela, K. (2004). Asthma Programme in Finland: High consensus between general practitioners and pulmonologists on the contents of an asthma referral letter. *Primary Care Respiratory Journal*, *13*(4). https://doi.org/10.1016/j.pcrj.2004.04.001

Vally, H., de Klerk, N., & Thompson, P. J. (2000). Alcoholic drinks: Important triggers for asthma. *Journal of Allergy and Clinical Immunology*, *105*(3). https://doi.org/10.1067/mai.2000.104548

van Dijk, B. C. P., Svedsater, H., Heddini, A., Nelsen, L., Balradj, J. S., & Alleman, C. (2020). Relationship between the Asthma Control Test (ACT) and other outcomes: A targeted literature review. In *BMC Pulmonary Medicine* (Vol. 20, Issue 1). https://doi.org/10.1186/s12890-020-1090-5

VanderWeele, T. J. (2020). Optimal approximate conversions of odds ratios and hazard ratios to risk ratios. *Biometrics*, *76*(3). https://doi.org/10.1111/biom.13197

Vanfleteren, L. E. G. W., Spruit, M. A., Groenen, M., Gaffron, S., van Empel, V. P. M., Bruijnzeel, P. L. B., Rutten, E. P. A., Roodt, J. O. t., Wouters, E. F. M., & Franssen, F. M. E. (2013). Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *187*(7). https://doi.org/10.1164/rccm.201209-1665OC

Vetrano, D. L., Palmer, K., Marengoni, A., Marzetti, E., Lattanzio, F., Roller-Wirnsberger, R., Samaniego, L. L., Rodríguez-Mañas, L., Bernabei, R., & Onder, G. (2019). Frailty and multimorbidity: A systematic review and meta-analysis. In *Journals of Gerontology - Series A Biological Sciences and Medical Sciences* (Vol. 74, Issue 5). https://doi.org/10.1093/gerona/gly110

Vincze, L., & Joyce, N. (2018). Online Contact, Face-to-Face Contact, and Multilingualism: Young Swedish-Speaking Finns Develop Trilingual Identities. *Communication Studies*, *69*(1). https://doi.org/10.1080/10510974.2017.1413410

Volanen, S. M., Suominen, S., Koskenvuo, M., Lahelma, E., & Silventoinen, K. (2006). Sense of coherence and its determinants: A comparative study of the Finnish-speaking majority and the Swedish-speaking minority in Finland. *Scandinavian Journal of Public Health*, *34*(5). https://doi.org/10.1080/14034940600585812

von Bülow, A., Backer, V., Bodtger, U., Søes-Petersen, N. U., Assing, K. D., Skjold, T., & Porsbjerg, C. (2017). The level of diagnostic assessment in severe asthma: A nationwide real-life study. *Respiratory Medicine*, *124*. https://doi.org/10.1016/j.rmed.2017.01.010

von Ehrenstein, O. S., von Mutius, E., Illi, S., Baumann, L., Böhm, O., & von Kries, R. (2000). Reduced risk of hay fever and asthma among children of farmers. *Clinical and Experimental Allergy*, *30*(2). https://doi.org/10.1046/j.1365-2222.2000.00801.x

von Gablenz, P., & Holube, I. (2017). Social inequalities in pure-tone hearing assessed using occupational stratification schemes. *International Journal of Audiology*, *56*(7). https://doi.org/10.1080/14992027.2017.1294767

von Hertzen, L., & Haahtela, T. (2006). Disconnection of man and the soil: Reason for the asthma and atopy epidemic? In *Journal of Allergy and Clinical Immunology* (Vol. 117, Issue 2). https://doi.org/10.1016/j.jaci.2005.11.013

Wardlaw, A. J., Rick, E. M., Ozyigit, L. P., Scadding, A., Gaillard, E. A., & Pashley, C. H. (2021). New perspectives in the diagnosis and management of allergic fungal airway disease. In *Journal of Asthma and Allergy* (Vol. 14). https://doi.org/10.2147/JAA.S251709

Weaver, C. T., Elson, C. O., Fouser, L. A., & Kolls, J. K. (2013). The Th17 pathway and inflammatory diseases of the intestines, lungs, and skin. In *Annual Review of Pathology: Mechanisms of Disease* (Vol. 8). https://doi.org/10.1146/annurev-pathol-011110-130318

Wells, A. D., Poole, J. A., & Romberger, D. J. (2014). Influence of farming exposure on the development of asthma and asthma-like symptoms. In *International Immunopharmacology* (Vol. 23, Issue 1). https://doi.org/10.1016/j.intimp.2014.07.014

Wenzel, S. E. (2012). Asthma phenotypes: The evolution from clinical to molecular approaches. In *Nature Medicine* (Vol. 18, Issue 5). https://doi.org/10.1038/nm.2678

Whitehead, M., & Dahlgren, G. (1991). What can be done about inequalities in health? *The Lancet*, *338*(8774). https://doi.org/10.1016/0140-6736(91)91911-D

Whittaker, H. R., Bloom, C., Morgan, A., Jarvis, D., Kiddle, S. J., & Quint, J. K. (2021). Accelerated FEV1 decline and risk of cardiovascular disease and mortality in a primary care population of COPD patients. *European Respiratory Journal*, *57*(3). https://doi.org/10.1183/13993003.00918-2020

WHO. (1948). *The Constitution of the World Health Organization. Available: www.who.int / Date last accessed June 7th 2021.*

WHO. (2008). *Commission on Social Determinants of Health. (2008). Closing the gap in a generation : health equity through action on the social determinants of health : final report : executive summary. World Health Organization. https://apps.who.int/iris/handle/10665/69832 / Date last accessed: June 7th 2021.*

WHO. (2013). *Review of social determinants and the health divide in the WHO European Region: final report. Avaivable www.euro.who.int /Date last accessed 8th June 2021.*

WHO. (2018). *Medicines Reimbursement Policies in Europe, 2018. Available from: www.who.int/Date last accessed: June 7th 2021.*

WHO. (2020a). *World Health Organization. Global recommendations on physical activity for health. Geneva: World Health Organization, 2010. Available www.who.int / Data last assecced Jene 13th 2021.*

WHO. (2020b). *Assessing national capacity for the prevention and control of noncommunicable diseases 2019. Available www.who.int / Date last accessed: May 15th 2021.*

Wlasiuk, G., & Vercelli, D. (2012). The farm effect, or: When, what and how a farming environment protects from asthma and allergic disease. In *Current Opinion in Allergy and Clinical Immunology* (Vol. 12, Issue 5). https://doi.org/10.1097/ACI.0b013e328357a3bc

Wöhrl, S. (2018). NSAID hypersensitivity – recommendations for diagnostic work up and patient management. *Allergo Journal International*, *27*, 114–121. https://doi.org/10.1007/s40629-018-0064-0

Wu, W., Bleecker, E., Moore, W., Busse, W. W., Castro, M., Chung, K. F., Calhoun, W. J., Erzurum, S., Gaston, B., Israel, E., Curran-Everett, D., & Wenzel, S. E. (2014). Unsupervised phenotyping of Severe Asthma Research Program participants using expanded lung data. *Journal of Allergy and Clinical Immunology*, *133*(5). https://doi.org/10.1016/j.jaci.2013.11.042

Wu, X., Huang, Q., Javed, R., Zhong, J., Gao, H., & Liang, H. (2019). Effect of tobacco smoking on the epigenetic age of human respiratory organs. *Clinical Epigenetics*, *11*(1). https://doi.org/10.1186/s13148-019-0777-z

Xie, M., Liu, X., Cao, X., Guo, M., & Li, X. (2020). Trends in prevalence and incidence of chronic respiratory diseases from 1990 to 2017. *Respiratory Research*, *21*(1). https://doi.org/10.1186/s12931-020-1291-8

Yasui, H., Inui, N., Karayama, M., Mori, K., Hozumi, H., Suzuki, Y., Furuhashi, K., Enomoto, N., Fujisawa, T., Nakamura, Y., Watanabe, H., & Suda, T. (2019). Correlation of the modified Medical Research Council dyspnea scale with airway structure assessed by three-dimensional CT in patients with chronic obstructive pulmonary disease. *Respiratory Medicine*, *146*. https://doi.org/10.1016/j.rmed.2018.11.020

Yusuf, P. S., Hawken, S., Ôunpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J., & Lisheng, L. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet*, *364*(9438). https://doi.org/10.1016/S0140-6736(04)17018-9

Zhang, L., Valizadeh, H., Alipourfard, I., Bidares, R., Aghebati-Maleki, L., & Ahmadi, M. (2020). Epigenetic Modifications and Therapy in Chronic Obstructive Pulmonary Disease (COPD): An Update Review. In *COPD: Journal of Chronic Obstructive Pulmonary Disease* (Vol. 17, Issue 3). https://doi.org/10.1080/15412555.2020.1780576

Zhu, Z., Guo, Y., Shi, H., Liu, C. L., Panganiban, R. A., Chung, W., O'Connor, L. J., Himes, B. E., Gazal, S., Hasegawa, K., Camargo, C. A., Qi, L., Moffatt, M. F., Hu, F. B., Lu, Q., Cookson, W. O. C., & Liang, L. (2020). Shared genetic and experimental links between obesity-related traits and asthma subtypes in UK Biobank. *Journal of Allergy and Clinical Immunology*, *145*(2). https://doi.org/10.1016/j.jaci.2019.09.035

Zhu, Z., Zhu, X., Liu, C. L., Shi, H., Shen, S., Yang, Y., Hasegawa, K., Camargo, C. A., & Liang, L. (2019). Shared genetics of asthma and mental health disorders: A large-scale genome-wide cross-trait analysis. *European Respiratory Journal*, *54*(6). https://doi.org/10.1183/13993003.01507-2019

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PUBLICATIONS

PUBLICATION I

Dyspnea has an Association with Lifestyle: Differences Between Swedish and Finnish Speaking Persons in Western Finland

Heidi Andersén, Pinja Ilmarinen, Jasmin Honkamäki, Leena E Tuomisto, Päivi Piirilä, Hanna Hisinger-Mölkänen, Anssi Sovijärvi, Helana Backman, Bo Lundbäck, Eva Rönmark, Lauri Lehtimäki, Hannu Kankaanranta

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Dyspnea has an association with lifestyle: differences between Swedish and Finnish speaking persons in Western Finland

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ABSTRACT

Background Difference in dyspnea mMRC ≥2 between Finnish speaking and Swedish-speaking populations in Finland has not been previously studied.

Methods In February 2016, a respiratory questionnaire was sent to 8000 randomly selected subjects aged 20–69 years in western Finland with a response rate of 52.3%. The registered native language of each subject determined whether questionnaire in Finnish or Swedish was applied. Multiple logistic regression was performed to calculate Odds Ratios (OR) with 95% CI for the simultaneous effects of independent variables on dyspnea mMRC ≥2.

Results Of all participants, 2780 (71.9%) were Finnish speakers and 1084 (28.1%) were Swedish speakers. Finnish speakers had a higher prevalence of dyspnea mMRC ≥2 (11.1% vs 6.5% $p < 0.001$) when compared to Swedish speakers. Finnish speakers smoked more often, had higher BMI, spent less time moving during the day, had more often occupational exposure to vapours, gases, dusts or fumes (VGDF), and had lower socioeconomic status based on occupation. Significant risk factors for dyspnea mMRC ≥2 were COPD (OR = 10.94), BMI >35 (OR = 9.74), asthma (OR = 4.78), female gender (OR = 2.38), older age (OR = 2.20), current smoking (OR = 1.59), and occupational exposure to VGDF (OR = 1.47).

Conclusions Swedish speakers had less dyspnea mMRC ≥2 which is explained by a healthier lifestyle. Smoking, obesity, and occupational exposures should be in focus to improve respiratory health.

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Asthma; COPD; dyspnea; obesity; smoking; physical activity

Introduction

Significant differences in respiratory health have been described in different populations, e.g., between urban and rural populations [1] and between different countries. For example, a major difference in the prevalence of asthma and allergies has been described between Finnish and Russian Karelia [2]. However, the conclusions related to respiratory health and risk factors may be hampered by the fact that populations in these studies often are genetically different, people live in different areas and/or are being served by different health-care provider systems.

Finland is a bilingual country with 5.5 million habitants with Finnish and Swedish as the two official languages. Swedish speakers are a minority, less than 6% of the population, living mostly in coastal regions in southern and western Finland and having a tight protective community. There are several studies comparing health and socioeconomic, demographic and geographical circumstances between Swedish and Finnish-speaking Finns. Swedish-speaking school children are healthier in terms of objective measures of health [3]. The Swedish speakers have a less harmful drinking pattern [4] and lower rates of sickness allowance receipt and early retirement [5,6]. There is also a correlation between family origin and mortality [7]: the relative death risk compared to Finnish speakers born in western Finland was 1.13 for Finnish speakers born in eastern Finland and only 0.60 for Swedish speakers [8]. The language-group-related differences in mortality are highest for deaths related to alcohol, suicide, and other external causes [9].

To our knowledge, no previous studies have compared respiratory symptoms between Swedish and Finnish

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speakers in Finland. The present study cohort can give further insights into factors behind respiratory symptoms in a unique study population living in the same geographical area, being genetically similar and being served by the same social and health-care services. The main objective of this population-based study is to estimate and compare the prevalence of dyspnea mMRC ≥2 between Finnish and Swedish-speaking persons in Western Finland and to define risk factors for dyspnea.

Materials and methods

The present study population is a part of the latest FinEsS survey (Finland-Estonia-Sweden) conducted in Western Finland in February 2016. Respiratory questionnaires were sent to 8,000 randomly selected recipients aged 20–69 years in the Western Finland hospital districts of South Ostrobothnia and Vaasa. The sample was identified from the Finnish Population Register and reflected the language, age, and sex distribution of the population in the study area. Two reminders were sent to those not responding. The two main official languages of Finland are Finnish and Swedish and the registered native language was obtained from the Finnish Population Register. The registered native language of each subject determined whether questionnaire in Finnish or Swedish was applied. The basic characteristics of the cohort and the non-responder analysis have been published elsewhere [10]. Non-responders were more often males (47.4% vs. 55.5%, $p < 0.001$) and younger (50 vs 42 years, $p < 0.001$) than responders.

The current study was approved by the ethical committee of Helsinki University Hospital. Concurrently with this study a similar FinEsS-study was conducted in Helsinki with an identical questionnaire and corresponding protocols.

Questionnaire and definitions

The Finnish FinEsS questionnaire contains features from the ATS and Tucson questionnaires [11,12] and is developed from the OLIN questionnaire [13]. The questionnaire consists of questions on symptoms, respiratory diseases, medication and comorbidities, risk factors, and occupational factors considered relevant to respiratory epidemiology like exposure to vapours, gases, dusts or fumes (VGDF) [14] and occupations. Occupations were classified according to the International Standard Classification of Occupations 2008 (ISCO-08) that provides a system for classifying and aggregating occupational information in a four-level hierarchically structured classification where ISCO-08 skill level 1 is the primary level of education and level 4 is usually obtained as a result of higher education [15]. Median Body Mass Index (BMI) categories for analysis were normal weight <24.9 kg/m^2, overweight 25.0–29.9 kg /m^2, obesity category I 30.0–34.9 kg/m^2 and obesity category II >35.0 kg/m^2.

Dyspnea mMRC ≥2 was defined by an answer 'yes' to the question 'Do you have to walk slower than other people of your age on level ground because of breathlessness?' This question is comparable to the Modified Medical Research Council Dyspnea (mMRC) scale grade 2 and higher dyspnea [16] that shows a limitation in daily life due to exercise-induced dyspnea.

Attacks of breathlessness were defined by an answer 'yes' to the question 'Have you had intermittent breathlessness or attacks of breathlessness, with or without simultaneously appearing cough or wheezing during the last 12 months?'

Wheeze was defined by an answer 'yes' to the question "Have you had wheezing or whistling in your chest at any time during the last 12 months?"

Longstanding cough was defined by an answer 'yes' to the question "Have you had longstanding cough during the last 12 months?"

Translation process

Independent translation of the questionnaire from Swedish to Finnish was produced by a bilingual translator that was aware of the objective of the study and had an expertise in the study topic. Back-translations were done by two independent bilingual translators, one of them was Finnish, and the other was Swedish. A committee of professionals consisting of seven physicians, four of them bilinguals, compared translated versions and corrected errors in the first translations and improved cross-cultural adaptation. The quality and limitations of the final translation were estimated by an expert translator blinded to objectives of the study. The translation and cross-cultural adaptation process was performed according to guidelines [17].

Statistical analysis

Statistical analyses were performed using SPSS software version 24 (IBM SPSS, Armonk, NY, USA). Mann–Whitney U-test was used for continuous and Pearson chi-square – test for categorical variables. A p-value <0.05 was considered significant and 95% confidence intervals (CI) were calculated. Multiple logistic regression was performed to calculate Odds Ratios (OR) with 95% CI for the simultaneous effects of independent variables on different respiratory symptoms.

Results

Characteristics of the study subjects

The corrected sample size was 7942 subjects after exclusion of subjects with unsuccessful postal delivery of the questionnaire or non-analysable data as shown in Figure 1. In total, 4173 subjects of the 8000 invited responded yielding a participation rate of 52.3%. Of the responders, 206 were excluded because of missing data on smoking and 103 were excluded from the present study because of native language being other than Finnish or Swedish. Altogether 3864 subjects (48.3%) were included in the present study population, of which 2780 (71.9%) were Finnish speaking and 1084 (28.1%) were Swedish speaking (Figure 1). The participation rate for Finnish speakers was 51.4% (2932 out of 5704) and 60.0% (1132 out of 1886) for Swedish speakers. The median age of responders was 54 years for Finnish speakers and 50 years for Swedish speakers ($p < 0.001$) and a slight dominance of women over men was observed in both groups (Table 1). BMI based on self-reported height and weight were 26.3 for Finnish speakers and 25.4 for Swedish speakers ($p < 0.001$).

Respiratory symptoms

A higher proportion of Finnish speakers (11.1%) had dyspnea mMRC ≥2 as compared with Swedish speakers (6.5%, $p < 0.001$) (Figure 2). In addition, 16.5% of the Finnish speakers and 11.6% of the Swedish speakers had attacks of breathlessness during the last 12 months ($p < 0.001$). There was no difference between Finnish and Swedish speakers in the prevalence of longstanding cough (14.2% vs. 12.2% $p = 0.106$) or wheeze during the last 12 months (17.0% vs. 19.4% $p = 0.082$).

Respiratory diagnoses

There were no significant differences in the prevalence of allergies or physician-diagnosed asthma between Finnish and Swedish speakers (Table 1). However, physician-diagnosed chronic bronchitis, COPD, and emphysema were more prevalent (3.0%) in Finnish speakers than in Swedish speakers (1.3%, $p = 0.002$).

Life-style and socioeconomic factors

Smoking was more common in Finnish speakers, 23.5% vs 16.1% ($p < 0.001$), as well as heavy smoking (Table 2). On average, Finnish speakers spent 3 h and Swedish speakers 4 h moving during the day ($p < 0.001$); thus, Finnish speakers were more physically inactive than Swedish speakers. However, no difference in exercise ('sports') frequency was found between language groups. During the first 5 years of life, Finnish speakers had lived less often in a rural area ($p < 0.001$), but had more often families that were farmers ($p < 0.024$). There was a difference in exposure to VGDF in the working environment: 40.8% of the Finnish speakers and 27.8% of the Swedish speakers were exposed ($p < 0.001$). According to ISCO-08 skill level, Finnish speakers had lower socioeconomic status based on occupation than Swedish speakers ($p = 0.007$).

Risk factors for dyspnea

Multiple logistic regression analysis was performed to define Odd Ratios for risk factors of having dyspnea mMRC ≥2. Most significant risk factors were diagnosis of COPD (OR = 10.9, $p < 0.001$) and BMI >35 (OR = 9.7, $p < 0.001$). Other statistically significant

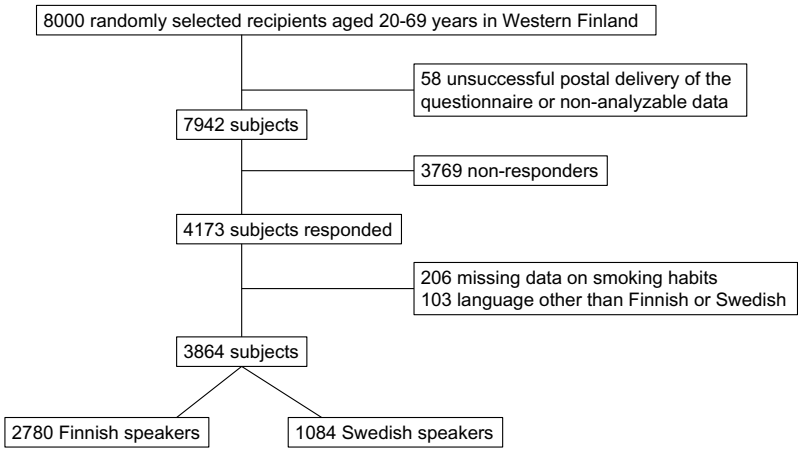

Figure 1. Flow chart of the study.

Table 1. Basic demographics of Finnish and Swedish-speaking responders.

	Finnish speakers n = 2780 (71.9%)	Swedish speakers n = 1084 (28.1%)	p-value
Males	1312 (47.2%)	535 (49.4%)	0.237
Age (yrs.)	54 (40–63)	50 (36–63)	<0.001
BMI (kg/m2)	26.3 (23.7–29.7)	25.4 (22.9–28.2)	<0.001
Physician diagnosed asthma	319 (11.5%)	125 (11.5%)	0.955
Allergy (allergic rhinitis to pollen or animals or allergic conjunctivitis)	604 (21.7%)	221 (20.4%)	0.382
Physician diagnosed chronic bronchitis, COPD or emphysema	83 (3.0%)	14 (1.3%)	0.002

Data is shown as n (%) or median (25–75 percentiles).

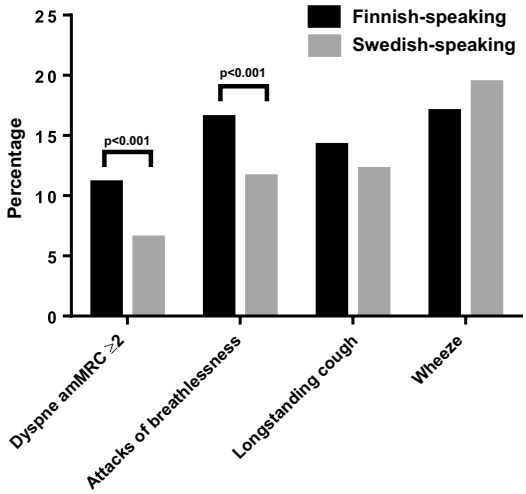

Figure 2. Respiratory symptoms in Finnish and Swedish-speaking responders.

Table 2. Social and lifestyle factors among Finnish and Swedish-speaking responders.

	Finnish speakers n = 2780 (71.9%)	Swedish speakers n = 1084 (28.1%)	p-value
Exercise ('sports') at least 2–3 times per week	2030 (73.7%)	763 (71.2%)	0.133
Physical activity, daily hours spent moving	3 (SD 3.2)	4 (SD 3.4)	<0.001
Current smokers	653 (23.5%)	175 (16.1%)	<0.001
If Current smoker, heavy smoker (smoking > 15 cigarettes)	217 (34.3%)	41 (24.3%)	0.016
Ex-smokers	792 (28.5%)	278 (25.6%)	0.078
Never smokers	1384 (49.8%)	636 (58.7%)	<0.001
Exposure to vapours, gases, dusts or fumes in working environment	1105 (40.8%)	290 (27.8%)	<0.001
Lived on rural area during first five years of life	1082 (69.3%)	811 (75%)	<0.001
Family was farmers during first five years of life	1191 (44.3%)	433 (40.2%)	0.024
ISCO-08 skill level	124 (5.3%)	34 (3.8%)	0.007
1 (lowest)	1415 (60.1%)	511 (57.0%)	
2	491 (20.9%)	189 (21.1%)	
3	323 (13.7%)	162 (18.1%)	
4 (highest)			

Data is shown as n (%), or median (SD).

risk factors were diagnosis of asthma, older age, female gender, smoking, occupational exposure to VGDF, overweight, and grade 1 obesity. Native language, skill level, time spent moving or sitting were not found to be significant risk factors (Table 3). The same risk factors were found to be associated with attacks of breathlessness during the last 12 months, except for age. Asthma (OR 19.9, $p < 0.001$) and COPD (OR 14.7, $p < 0.001$) were the most significant risk factors for attacks of breathlessness (Table 4).

Table 3. Multiple logistic regressions for dyspnea mMRC ≥2.

	OR	95% CI	p-value
Age groups (20–39 yrs. ref group)			
40–59 yrs.	1.39	0.91–2.14	0.131
60–69 yrs.	2.20	1.44–3.37	<0.001
Female gender	2.38	1.71–3.30	<0.001
Finnish-speaking	1.29	0.89–1.88	0.185
Smoking status (never smoker ref group)			
Current smoker	1.59	1.08–2.35	0.019
Ex-smoker	1.07	0.75–1.51	0.725
Occupational exposure to vapours, gases, dust or fumes	1.47	1.07–2.02	0.018
BMI (<25 ref group)			
Overweight (25–29.9)	1.57	1.06–2.33	0.026
Obesity grade I (30–34.99)	3.51	2.30–5.37	<0.001
Obesity grade II (35-)	9.74	6.01–15.81	<0.001
Time spent moving (continuous)	0.96	0.91–1.01	0.107
Time spent sitting (continuous)	1.04	0.92–1.17	0.522
ISCO-08 skill level (4-highest ref group)			
1 (lowest)	1.21	0.56–2.58	0.628
2	1.41	0.86–2.31	0.178
3	1.040	0.59–1.82	0.892
Physician-diagnosis of asthma	4.78	3.41–6.71	<0.001
Physician-diagnosis of COPD	10.94	5.91–20.26	<0.001

Table 4. Multiple logistic regressions for Attacks of breathlessness during the last 12 months.

	OR	95% CI	p-value
Age groups (60–70 yrs. ref group)			
20–39 yrs.	1.08	0.77–1.52	0.655
40–59 yrs.	1.32	0.98–1.77	0.066
Female gender	1.69	1.29–2.21	<0.001
Finnish-speaking	1.33	0.98–1.80	0.064
Smoking status (never smoker ref group)			
Current smoker	1.47	1.05–2.05	0.024
Ex-smoker	1.23	0.91–1.65	0.177
Occupational exposure	1.36	1.03–1.79	0.029
BMI (<25 ref group)			
Overweight (25–29.9)	1.47	1.09–1.99	0.011
Obesity grade I (30–34.99)	1.76	1.22–2.55	0.003
Obesity grade II (35-)	2.89	1.79–4.68	<0.001
Time spent moving (continuous)	1.02	0.98–1.06	0.398
Time spent sitting (continuous)	1.05	0.95–1.15	0.373
ISCO-08 skill level (4 -highest ref group)			
1 (lowest)	1.02	0.52–1.98	0.960
2	0.99	0.67–1.48	0.974
3	1.16	0.75–1.77	0.504
Physician-diagnosis of asthma	19.86	14.91–26.44	<0.001
Physician-diagnosis of COPD	14.66	7.47–28.78	<0.001

Discussion

In this study we report for the first time that prevalence of dyspnea mMRC ≥2 and attacks of breathlessness was higher in Finnish speakers when compared to Swedish speakers from the same population, the difference having significance for public health. Even though there was a clear difference in symptom prevalence between the language groups, belonging to a language population per se was not a risk factor for dyspnea or attacks of breathlessness. Differences in lifestyle was observed between Finnish and Swedish speakers and significant risk factors for these respiratory symptoms were COPD, asthma, obesity (especially grade II), current smoking, occupational exposure, and female gender.

Overall the prevalence of different respiratory symptoms found in this study was similar to what has been previously reported in comparable populations [18–21]. For example, the prevalence of dyspnea mMRC ≥2 was 11.1% for Finnish speakers and 6.5% for Swedish speakers in the present study. In a previous study, there was a considerable geographical variation in dyspnea in populations from 15 countries: the prevalence of dyspnea mMRC ≥2 was 13% in the combined cohort [18]. Prevalence of attacks of breathlessness has been reported to be approximately 14–15% in a previous study from Scandinavia [19], and in this study the prevalence of attacks of breathlessness was between 11.6% and 16.5%. Prevalence of longstanding cough has been reported to be

between 10% and 12% in Sweden [20], while in this study it was 14.2 vs 12.2% in Finnish and Swedish speakers, respectively. In previous study prevalence of wheeze has been around 23% in Nordic countries and Australia [19,22,23], but 13% in US population [21], and in this current study it was 17.0% for Finnish speakers and 19.4% Swedish speakers. Thus, the reported prevalence of respiratory symptoms in the present study falls into the previously reported range.

Differences in the prevalence of respiratory symptoms between Swedish and Finnish speakers are unlikely explained by the prevalence of asthma or allergy as there was no difference in the prevalence of these diseases between the two language groups. COPD was more common in Finnish speakers (3.0% versus 1.3%), but the prevalence of COPD was low, and explains the differences in symptom prevalence only partly. Although the symptoms were more frequent in the Finnish speakers, the spoken language was not an independent risk factor for respiratory symptoms in multiple logistic regression analysis. This suggests that the other culture-related factors affecting respiratory health may explain the differences in symptom prevalence between the language groups. In previous studies, Swedish speakers had a higher sense of mastery and the association was mediated by social support [24], and they possessed more structural and cognitive social capital [25], while the Finnish speakers were more often migrated, mistrusting and less active in community events [26]. These cultural differences might lead to healthier habits for the Swedish-speaking Finns. Interestingly, significant differences were found in many health-related habits between Finnish and Swedish speakers and these were also found to be independent risk factors for respiratory symptoms. In addition to diseases such as asthma and COPD or non-modifiable factors like age and sex, also clearly modifiable factors like high BMI, current smoking, and occupational exposure were significant risk factors for having respiratory symptoms. BMI >35 was associated with dyspnea mMRC ≥2 with OR 9.74 that was almost as high as the OR for COPD and 2 times higher than the OR for asthma. Overweight and obesity gr I were also risk factors for dyspnea and therefore, we consider that difference in BMI between the two language groups is an important factor explaining the higher prevalence of respiratory symptoms in Finnish speakers. Previous studies have suggested that dyspnea is very frequent in obese subjects and mMRC scale can be used in the assessment of dyspnea in obese patients [27,28]. The significant risk factors for dyspnea mMRC≥2 were similar to those for attacks of breathlessness, but dyspnea mMRC≥2 was more often associated with COPD, obesity, and old age, whereas attacks of breathlessness with asthma and not with age.

Current smoking and occupational exposures which are known risk factors for many respiratory symptoms [22,-29–34] were more common in the Finnish speakers. In a previous study in northern Sweden, there was a parallel trend of decreasing respiratory symptoms and a lower prevalence of smoking [20]. Association between respiratory symptoms and increasing age has been shown before [35] and was observed also in this study. In the present study, females reported more often dyspnea when compared to males and this finding is supported by results from previous studies [18,29]. In a previous study low socioeconomic status was a risk factor for respiratory symptoms [30]. In contrast, socioeconomic status based on occupation was not associated with respiratory symptoms in our study. The discrepancy between the previous study [30] and our study may be explained by the additional adjustment for lifestyle factors performed in our study. As these are associated with both low socioeconomic status and symptoms, they may explain the increased prevalence of respiratory symptoms in the studied Finnish-speaking population.

Significant disparities in respiratory health have been described in ethnically different populations and with uneven access to healthcare [1,2,36,37]. Most studies on ethnic minority-group inequalities are comparing genetically and socioeconomically different populations [38]. This study compared populations living in the same geographic area and having the same access to public healthcare public schools without fees in their respective native languages, using same shops, gyms, swimming halls, and sport clubs, but that still are prone to social gatherings within the language group. Populations in hospital districts of South Ostrobothnia and Vaasa are part of the same Finnish Western genetic subpopulation [39]. Swedish-speaking population and Finnish-speaking population show a high degree of admixture from Sweden which most probably occurred at an early period after immigration over a thousand years ago [40]. It is unclear how much saturation of genes has happened in language groups and therefore language was included in the regression analysis. Finnish and Swedish speakers have been later culturally divided by the language. Language and culture are even more tightly bound together than blood bonds and this makes a significant difference to daily habits and socioeconomic factors. In this study population, we can study how daily habits affect the risk for symptoms.

Major strengths of this study include the random sample reflecting the general population, large sample size, established structured questionnaire and validity of the translation. A limitation of this study is that the response rate could have been higher, but it corresponds well with similar recent surveys [41]. The participation

rate was lower for Finnish speakers, 51.4% compared to 60.0% for Swedish speakers. Still, both language groups are well represented. Further studies with clinical data, e.g., on the exercise capacity differences might strengthen the results found in this survey. Furthermore, it should be noted that that exercise and physical activity are two different concepts. Physical exercise is high or moderate-intensity movement conducted with a purpose for shorter periods of time (i.e., 'sports') whereas physical activity includes all human bodily movement [42].

The clinical implication of this study is that smoking, high BMI, and occupational exposures should be the main considerations for respiratory health in the general public. Association between dyspnea and obesity might be underestimated in clinical practice. In medicine, we strive to diagnose and treat diseases and often have limited resources and knowledge to treat obesity as a cause of dyspnea.

We found that in genetically similar populations with different languages and culture the Swedish speakers had less respiratory symptoms and lower prevalence of COPD as they smoked less, had lower BMI, and had less occupational exposures compared to the Finnish speakers from the same region. Further behavioural, clinical, and even genetic studies are needed in order to find differences in respiratory disease phenotypes due to habits in this worldwide unique population.

Authors contribution

HA conceptualized and designed the study, performed analyses together with PI, drafted the initial manuscript, and approved the final manuscript as submitted. PI, LL, HK conceptualized and designed the study, provided statistical input and critical revision of the manuscript, and approved the final manuscript as submitted; JH, LET, PP, HHM, AS, HB, BL, and ER conceptualized and designed the study, provided critical revision of the manuscript, and approved the final manuscript as submitted. We affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Disclosure statement

The authors declare no conflict of interest related to this study. Outside this study, HA reports personal fees from Boehringer Ingelheim, MSD and Roche. Outside this study, PI reports personal fees from MundiPharma, Orion, Astra Zeneca, and GlaxoSmithKline. LET reports non-financial support from Chiesi, non-financial support from Boehringer-Ingelheim, personal fees from Astra Zeneca, non-financial support from Orion Pharma, non-financial support from TEVA and other from Novartis, outside the submitted work. HB reports personal fees from Boehringer–Ingelheim and AstraZeneca outside the submitted work. HHM reports employment at GSK. LL reports personal fees from ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis, Orion Pharma, GSK, Teva, Mundipharma, SanofiGenzyme, outside the submitted work. HK report grants, personal fees, and non-financial support from AstraZeneca, personal fees from Chiesi Pharma AB, personal fees, and non-financial support from Boehringer-Ingelheim, personal fees from Novartis, personal fees from Mundipharma, personal fees from Roche, personal fees, and non-financial support from Orion Pharma, personal fees from Sanofi-Genzyme outside the submitted work.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the Department of Medicine of Helsinki University Central Hospital (199/13/03/00/15) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study. The general Data Protection Regulation (EU) 2016/679 was followed.

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References

[1] Von Ehrenstein OS, Von Mutius E, Illi S, et al. Reduced risk of hay fever and asthma among children of farmers. Clin Exp Allergy. 2000;30(2):187–193.
[2] Pekkarinen PT, Laatikainen T, Jousilahti P, et al. A disparity in the association of asthma, rhinitis, and eczema with allergen-specific IgE between Finnish and Russian Karelia. Allergy. 2007;62(3):281–287.
[3] Saarela J, Finnäs F. The health of Swedish-speaking and Finnish-speaking schoolchildren in Finland. Child Care, Heal Dev. 2004;30(1):51–58.
[4] Paljärvi T, Suominen S, Koskenvuo M, et al. The differences in drinking patterns between Finnish-speaking majority and Swedish-speaking minority in Finland. Eur J Public Health. 2009;19(3):278–284.
[5] Reini K, Saarela J. Differences in sickness allowance receipt between Swedish speakers and Finnish speakers in Finland. Finnish Yearb Popul Res. 2017;52:43–58.
[6] Saarela J, Finnäs F. Language-group differences in very early retirement in Finland. Demogr Res. 2002;7:49–66.
[7] Saarela J, Finnäs F. Mortality inequality in two native population groups. Popul Stud (NY). 2005;59(3):313–320.
[8] Saarela J, Finnäs F. Family origin and mortality: prospective Finnish cohort study. BMC Public Health. 2011;11(1):385.
[9] Sipilä P, Martikainen P. Language-group mortality differentials in Finland: the effects of local language composition. Health Place. 2010;16(3):446–451.
[10] Honkamäki J, Hisinger-Mölkänen H, Ilmarinen P, et al. Age- and gender-specific incidence of new asthma diagnosis from childhood to late adulthood. Respir Med. 2019;154:56–62.
[11] Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902–907.
[12] Lebowitz MD, Burrows B. Comparison of questionnaires: the BMRC and NHLI respiratory questionnaires and a new self-completion questionnaire. Am Rev Respir Dis. 1976;113(5):627–635.
[13] Lundbäck B, Nyström L, Rosenhall L, et al. Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey. Eur Respir J. 1991;4(3):257–266.
[14] Blanc PD, Eisner MD, Balmes JR, et al. Exposure to vapors, gas, dust, or fumes: assessment by a single survey item compared to a detailed exposure battery and a job exposure matrix. Am J Ind Med. 2005;48(4):110–117.
[15] International Labour Organization. Classification of Occupations. Int Labour Organ. 2012;1:1–420.
[16] Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest. 1988;93(3):580–586.
[17] Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. J Clin Epidemiol. 1993;46(12):1417–1432.
[18] Grønseth R, Vollmer WM, Hardie JA, et al. Predictors of dyspnoea prevalence: results from the BOLD study. Eur Respir J. 2014;43(6):1610–1620.
[19] Axelsson M, Lindberg A, Kainu A, et al. Respiratory symptoms increase health care consumption and affect everyday life – a cross-sectional population-based study from Finland, Estonia, and Sweden. Eur Clin Respir J. 2016;3(1):31024.

[20] Backman H, Hedman L, Jansson SA, et al. Prevalence trends in respiratory symptoms and asthma in relation to smoking - Two cross-sectional studies ten years apart among adults in northern Sweden. World Allergy Organ J. 2014;7:1.
[21] Wheaton AG, Ford ES, Thompson WW, et al. Pulmonary function, chronic respiratory symptoms, and health-related quality of life among adults in the USA–National Health and Nutrition Examination Survey 2007-2010. BMC Public Health. 2013;13(1):854.
[22] James AL, Knuiman MW, Divitini ML, et al. Risk factors for respiratory symptoms in adults: the Busselton Health Study. Respirology. 2013;18(8):1256–1260.
[23] Voll-Aanerud M, Eagan TML, Wentzel-Larsen T, et al. Respiratory symptoms, COPD severity, and health related quality of life in a general population sample. Respir Med. 2008;102(3):399–406.
[24] Reini K, Nyqvist F. Sense of mastery differences between working-age Swedish- and Finnish-speaking Finns: a population-based study. Scand J Public Health. 2017;45(4):404–410.
[25] Nyqvist F, Finnäs F, Jakobsson G, et al. The effect of social capital on health: the case of two language groups in Finland. Health Place. 2008;14(2):347–360.
[26] Hyyppä MT, Mäki J. Individual-level relationships between social capital and self-rated health in a bilingual community. Prev Med. 2001;32(2):148–155.
[27] Launois C, Barbe C, Bertin E, et al. The modified Medical Research Council scale for the assessment of dyspnea in daily living in obesity: a pilot study. BMC Pulm Med. 2012;1;12(61. DOI:10.1186/1471-2466-12-61.
[28] Sjöström L, Larsson B, Backman L, et al. Swedish obese subjects (SOS). Recruitment for an intervention study and a selected description of the obese state. Int J Obes Relat Metab Disord. 1992;16(6):465–479.
[29] Lundbäck B, Stjernberg N, Nyström L, et al. Epidemiology of respiratory symptoms, lung function and important determinants. Report from the Obstructive Lung Disease in Northern Sweden Project. Tuber Lung Dis. 1994;75 (2):116–126.
[30] Pallasaho P, Lindström M, Põlluste J, et al. Low socio-economic status is a risk factor for respiratory symptoms: a comparison between Finland, Sweden and Estonia. Int J Tuberc Lung Dis. 2004;8(11):1292–1300.
[31] Lindström M, Kotaniemi J, Jönsson E, et al. Smoking, respiratory symptoms, and diseases: a comparative study between northern Sweden and northern Finland: report from the FinEsS study. Chest. 2001;119(3):852–861.
[32] Kim J-L, Torén K, Lohman S, et al. Respiratory symptoms and respiratory-related absence from work among health care workers in Sweden. J Asthma. 2013;50(2):174–179.
[33] Khan AW, Moshammer HM, Kundi M. Industrial hygiene, occupational safety and respiratory symptoms in the Pakistani cotton industry. BMJ Open. 2015;5(4):e007266.
[34] Ghosh T, Gangopadhyay S, Das B. Prevalence of respiratory symptoms and disorders among rice mill workers in India. Environ Health Prev Med. 2014;19(3):226–233.
[35] Viegi G, Pedreschi M, Baldacci S, et al. Prevalence rates of respiratory symptoms and diseases in general population samples of North and Central Italy. Int J Tuberc Lung Dis. 1999;3(11):1034–1042.
[36] Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the USA, 2001-2010. NCHS Data Brief. 2012;94:1.
[37] Gillies TD, Tomlin AM, Dovey SM, et al. Ethnic disparities in asthma treatment and outcomes in children aged under 15 years in New Zealand: analysis of national databases. Prim Care Respir J. 2013;22(3):312–318.
[38] Jannus-Pruljan L, Meren M, Põlluste J, et al. Postal survey on asthma, chronic bronchitis and respiratory symptoms among adult Estonians and non-Estonians (FinEsS-study). Eur J Public Health. 2004;14(2):114–119. .
[39] Kerminen S, Havulinna AS, Hellenthal G, et al. Fine-scale genetic structure in Finland. G3 (Bethesda). 2017;7 (10):3459–3468.
[40] Virtaranta-Knowles K, Sistonen PNH. A population genetic study in Finland: comparison of the Finnish- and Swedish-speaking populations. Hum Hered. 1991;41(4):248–264.
[41] Tolonen H, Koponen P, Borodulin K, et al. Language as a determinant of participation rates in Finnish health examination surveys. Scand J Public Health. 2018;46 (2):240–243.
[42] Loponen J, Ilmarinen P, Tuomisto LE, et al. Daily physical activity and lung function decline in adult-onset asthma: a 12-year follow-up study. Eur Clin Respir J. 2018;5(1):1533753.

PUBLICATION II

Multimorbidity in Finnish and Swedish Speaking Finns; Association with Daily Habits and Socioeconomic Status-Nordic EpiLung Cross-Sectional Study

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Multimorbidity in Finnish and Swedish speaking Finns; association with daily habits and socioeconomic status – Nordic EpiLung cross-sectional study

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ABSTRACT

Multimorbidity is an emerging public health priority. This study aims to assess the role of lifestyle and socioeconomic status in the prevalence of multimorbidity and chronic diseases by using two language groups that are part of the same genetic subgroup but differ by daily habits. We conducted a cross-sectional survey in 2016 with randomly selected population sample with 4173 responders (52.3%) aged 20–69 years in Western Finland. We included 3864 Finnish participants with Swedish (28.1%) or Finnish (71.9%) as a native language. We used a questionnaire to assess participants' chronic diseases and lifestyle. We determined multimorbidity as a disease count ≥ 2.

Finnish speakers were more likely to have a diagnosis of COPD, heart failure, diabetes, reflux disease, chronic kidney failure, and painful conditions than Swedish speakers. The prevalence of multimorbidity was higher for Finnish speakers in the age group of 60–69 years (41.0% vs. 32.0%, $p = 0.018$) than Swedish speakers. A higher proportion of Finnish speakers smoked, were obese, inactive, and had lower socioeconomic status compared to Swedish speakers. All these factors, in addition to age and female sex, were significant risk factors for multimorbidity. Prevalence of multimorbidity was different in two language groups living in the same area and was associated with differences in lifestyle factors such as smoking, physical inactivity and obesity.

1. Introduction

Multimorbidity, defined as patients living with two or more chronic health conditions, is of paramount public health concern to any aging population as the prevalence of multimorbidity increases with age (Barnett et al., 2012). The prevalence of multimorbidity seems to be increasing, at least in western countries (Buttorff et al., 2017; Lebenbaum et al., 2018).

To understand multimorbidity in a broader context, not only the inter-correlation between different diseases or their medication but also factors related to the daily life need to be considered (Violan et al., 2014a). Many prevalence studies on multimorbidity are register-based

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with limited information on participants' lifestyle and BMI. One approach to overcome this problem is to compare multimorbidity between countries, in different nationalities or ethnic groups, known to have differing habits (Garin et al., 2016). However, this kind of analysis may be hampered by geographical factors, different political systems, healthcare organizations, and access to healthcare between ethnic groups.

Another way of solving this could be to study two genetically similar populations living in the same socio-cultural landscape. Western Finland is one of the most affluent areas in the country, which contributes to the health benefits in Western Finland when compared to the general population of Finland (Saarela and Finnäs, 2011). Finnish and Swedish speaking Finns are part of the same Finnish genetic subpopulation (Kerminen et al., 2017), living in the same geographical area sharing the same educational institutions and healthcare system but with differing daily habits.

Swedish speakers have less harmful drinking patterns (Paljarvi et al., 2009), lower rates of sickness allowance, less early retirement (Reini and Saarela, 2017; Saarela and Finnäs, 2002), and mortality (Saarela and Finnäs, 2011, 2005). The mortality difference between language-groups is highest in deaths related to alcohol, suicide, and other external causes (Sipilä and Martikainen, 2010).

Compared to existing studies on socioeconomic inequalities (Ahmadi et al., 2016; Mathur et al., 2011), FinEsS Western Finland study population provides a different aspect as inequalities concern the majority in a population sharing several determinants of health but differing in lifestyle. Also, habits were asked from the study participants, instead of making assumptions based on how the different language groups differ on average. The aim was to assess prevalence of multimorbidity in Swedish and Finnish speaking people in Western Finland and to evaluate lifestyle factors associated with multimorbidity.

2. Methods

2.1. Study design and participants

In collaboration with Nordic EpiLung, the latest FinEsS' (Finland-Estonia-Sweden) survey for Western Finland was conducted in February 2016. Health questionnaires were sent to 8,000 randomly selected recipients aged 20–69 years in hospital districts of South Ostrobothnia and Vaasa. We identified recipients' personal information from the Finnish Population Register, and the sample reflected the population in the study area. The official native language of a recipient determined whether we used a Finnish or Swedish questionnaire. We sent two reminders to those not responding.

2.2. Compliance with ethical standards

Ethics Committee of the Department of Medicine of Helsinki University Central Hospital approved the study (approval number 200/13/03/00/15). Informed written consent was obtained from all individual participants included in the study. We followed the General Data Protection Regulation (EU) 2016/679. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

2.3. Questionnaire

The FinEsS questionnaire comprises questions on respiratory symptoms, respiratory diseases, diseases and morbidity in general, risk factors, occupation, and use of medication, and have previously been used in many studies in several countries (Honkamäki et al., 2019; Larsson et al., 2003; Pallasaho et al., 2011).

2.4. Variables

The assessment of multimorbidity was based on self-reported diseases or medical conditions and defined as disease count ≥ 2 in any individual responder (Valderas et al., 2009). The rationale for diseases included was based on three independent sources: (1) previous publication (Barnett et al., 2012), (2) the most common comorbidities found in adult asthma in the same area (Ilmarinen et al., 2016), and (3) comorbidities reported to be associated with asthma (Kankaanranta et al., 2016).

The question asked on diseases was 'Has a doctor diagnosed you with any one of the following diseases: asthma, chronic obstructive pulmonary disease (COPD), hypertension, coronary heart disease, atrial fibrillation or another cardiac arrhythmia, heart failure, stroke or transient ischemic attack, diabetes, depression, panic attack or anxiety, treated dyspepsia/reflux disease, chronic kidney failure, sleep apnea, osteoporosis, and painful condition requiring daily analgesic medication?' with tick boxes yes/no for each of the diseases.

Participants were considered to be physically active if they were physically active at least three hours ($\geq$180 min) per day, which was answered by the question 'How many hours in a day do you spend moving/physically active?'. We divided participants into current smokers, ex-smokers (when the participants stopped smoking more than 12 months before), and never smokers (neither a current smoker nor an ex-smoker). Body Mass Index (BMI) was based on self-reported height and weight and was categorized as follows: under and normal weight $<$ 25 kg/m^2, overweight 25.0–29.9 kg/m^2, obesity grade I 30.0–34.9 kg/m^2 and obesity grade II $\geq$ 35.0 kg/m^2.

We asked each participant of their main occupation. Occupations were classified according to The International Standard Classification of Occupations 2008 (ISCO-08), providing a system for classifying professional skill levels in a four-level hierarchy. ISCO-08 skill level 1 is the primary level of education, and level 4 is higher education (Gaskin et al., 2014). Occupational exposure to vapors, gases, dust, or fumes (VGDF) was asked with a question. 'Are you now, or have you been heavily exposed to gases, dust, or fumes at work'?

2.5. Statistical analysis

Statistical analyses were performed by using IBM SPSS Statistics software version 26 (IBM SPSS, Armonk, NY, USA). Pearson chi-square –test was used for categorical variables. A p-value < 0.05 was considered significant.

Binary logistic regression models with multimorbidity as outcome were performed to calculate unadjusted Odds Ratios (OR) with 95% confidence intervals (CI) for age, sex, smoking status, BMI, physical activity, skill level, and native language. Multivariable binary logistic regression with multimorbidity as outcome was performed to calculate adjusted ORs with 95% CI including age, sex, smoking status, BMI, physical activity, skill level, and native language in the same model. Sensitivity analyses were performed with three different disease grouping models (see Appendix).

3. Results

3.1. Characteristics of the study participants

In total, 4173 participants of the 8000 invited responded, yielding a participation rate of 52.3%. Of the responders, 206 were excluded due to missing data on smoking, and 103 were excluded since their native language was not Finnish or Swedish. Altogether 3864 participants were included in the present study population (48.3%), of which 2780 (71.9%) were Finnish speaking, and 1084 (28.1%) were Swedish speaking. Fig. A1 shows a flow chart of the study.

The response rate was 51.4% (2932 out of 5704) for Finnish speakers and 60.0% (1132 out of 1886) for Swedish speakers. Non-responders

were more often males and younger than responders (Table A1). The Finnish speaking group aged 20–39 years is most underrepresented. The age group 60–69 years has response rate of 73.8% (72.1% for Finnish speakers and 78.8% for Swedish speakers). For those over 40 years, the response rate was 61.7%.

Table 1 shows characteristics of the study participants. We observed a slight dominance of women over men in both language groups. The proportion of participants in the youngest age group was higher among Swedish speakers than Finnish speakers. The prevalence of obesity, active smoking and ex-smoking were higher in Finnish speakers than Swedish speakers. The level of physical activity was lower in Finnish speakers than Swedish speakers. Also, the ISCO-08 skill level was lower in Finnish speakers compared to Swedish speakers, whereas occupational exposure to VGDF was higher in Finnish speakers than Swedish speakers. Prevalence of family history of chronic bronchitis, COPD, or emphysema was higher in Finnish speakers than Swedish speakers.

3.2. Multimorbidity

Finnish speakers were more likely multi-morbid compared to Swedish speakers, with 26.0% prevalence of multimorbidity for Finnish speakers and 22.3% for Swedish speakers ($p = 0.049$). At the level of single diseases, Finnish speakers had more frequently a diagnosis of COPD (3.0% vs 1.3%, $p = 0.002$), heart failure (1.7% vs 0.5%, $p = 0.002$), diabetes (8.1% vs 5.1%, $p = 0.001$), treated dyspepsia/reflux disease (7.2% vs 4.9%, $p = 0.008$), chronic kidney failure (0.9% vs 0.2%, $p = 0.016$) and painful conditions (9.8% vs 5.1%, $p < 0.001$) compared to Swedish speakers (Table 2).

Table 1
Characteristics of the study participants.

	Finnish speakers n = 2780	Swedish speakers n = 1084	p-value
Female	1468 (52.8%)	549 (50.6%)	0.227
Age groups			<0.001
20–44	866 (32.3%)	430 (41.3%)	
45–59	895 (33.4%)	293 (28.1%)	
60–69	918 (34.3%)	319 (30.6%)	
BMI < 25	1007 (37.0%)	499 (47.1%)	<0.001
BMI 25–29.99	1089 (40.0%)	392 (37.0%)	
BMI 30–34.99	447 (16.4%)	126 (11.9%)	
BMI ≥ 35	179 (6.6%)	43 (4.1%)	
Smoking status			<0.001
Ex-smoker	789 (28.4%)	277 (25.6%)	
Current smoker	605 (21.8%)	170 (15.7%)	
Non-smoker	1386 (49.9%)	637 (58.8%)	
ISCO-08 skill level			0.008
1	124 (5.3%)	34 (3.8%)	
2	1415 (60.1%)	511 (57.0%)	
3	489 (20.8%)	189 (21.1%)	
4	325 (13.8%)	162 (18.1%)	
Occupational exposure to VGDF	1105 (40.8%)	290 (29.4%)	<0.001
Family history of chronic bronchitis, COPD or emphysema	342 (12.3%)	71 (6.5%)	<0.001
Duration of daily physical activity ≥ 3 h	1309 (50.8%)	676 (67.6%)	<0.001

Data is shown as n (%). Abbreviations: BMI (Body Mass Index), ISCO (International Standard Classification of Occupations), VGDF (Vapors, gases, dust and fumes), and COPD (Chronic obstructive pulmonary disease). Missing cases BMI 82 (2%), physical activity 287 (7%), and skill level 615 (16%) of total 3864.

Table 2
Prevalence of chronic diseases for Finnish and Swedish speaking responders.

	Finnish speakers	Swedish speakers	p-value
Asthma	319 (11.5%)	125 (11.5%)	0.955
COPD	83 (3.0%)	14 (1.3%)	0.002
Hypertension	634 (22.8%)	253 (23.3%)	0.733
Coronary heart disease	84 (3.0%)	29 (2.7%)	0.597
Atrial fibrillation and other cardiac arrhythmias	215 (7.7%)	70 (6.5%)	0.193
Heart failure	47 (1.7%)	5 (0.5%)	0.002
Stroke and transient ischemic attack	61 (2.2%)	29 (2.7%)	0.406
Diabetes	224 (8.1%)	55 (5.1%)	0.001
Depression	278 (10%)	101 (9.3%)	0.548
Panic attack or anxiety	160 (5.8%)	69 (6.4%)	0.495
Treated dyspepsia, reflux disease	201 (7.2%)	53 (4.9%)	0.008
Chronic kidney failure	25 (0.9%)	2 (0.2%)	0.016
Sleep apnea	139 (5.0%)	50 (4.6%)	0.678
Osteoporosis	75 (2.7%)	24 (2.2%)	0.429
Painful condition	272 (9.8%)	55 (5.1%)	<0.001

Data is shown as n (%).

3.3. Multimorbidity in different age groups

There was no significant difference in multimorbidity between Finnish and Swedish speakers in age groups 20–39 years (8.9% vs. 12.1%, $p = 0.202$) or 40–59 years (22.6% vs. 20.4%, $p = 0.427$). However, in the age group 60–69 years, Finnish speakers were more often multimorbid (41.0% vs. 32.0%, $p = 0.018$) (Fig. A2).

In the whole study population, the percentage of persons suffering from at least 1, 2, 3, or 4 diseases, as well as the morbidity count, increased with age (Fig. 1a). The percentage of respondents with at least 1, 2, 3, or 4 diseases seemed to be higher in Finnish speakers than Swedish speakers in older age groups (Fig. 1b).

3.4. Risk factors for multimorbidity

Significant independent risk factors for multimorbidity in both unadjusted and adjusted analyses were age, current and ex-smoking and overweight and obesity (Table 3). Swedish language was a risk-reducing factor for multimorbidity only in unadjusted model. Lower skill levels 1 and 2 were risk factors for multimorbidity only in unadjusted model. Physical inactivity was significant risk factor in adjusted model. Age over 60 (OR = 5.91) and obesity grade II (OR = 5.62) were the most significant risk factors for multimorbidity.

3.5. Multimorbidity prevalence in association to smoking status, physical activity, and BMI

Since current and ex-smoking, overweight, obesity and physical inactivity were significant risk factors for multimorbidity, we calculated the prevalence of multimorbidity in association with smoking status, physical activity, and BMI.

Ex-smokers had the highest multimorbidity prevalence in all BMI groups (Table A2). Table A3 shows that among obese participants, the prevalence of multimorbidity was higher in the physically inactive group compared to the physically active group. We had all data on the four variables for 3525 out of 3864 participants. We divided participants into four groups: never smokers with daily physical activity ≥ 3 h (n = 968), never smokers with daily physical activity < 3 h (n = 916), current or ex-smokers with daily physical activity ≥ 3 h (n = 1017), and current or ex-smokers with daily physical activity < 3 h (n = 676) and calculated multimorbidity prevalence in BMI groups: under and normal weight < 25 kg/m2, overweight 25.0–29.9 kg/m2, obesity grade I 30.0–34.9 kg/m2 and obesity grade II ≥ 35.0 kg/m2. The results are shown in Table A4. In the group with BMI < 25 kg/m2, never smokers and physically active responders, the prevalence of multimorbidity was 12.2% and in the group with BMI ≥ 35.0 kg/m2, current or ex-smokers

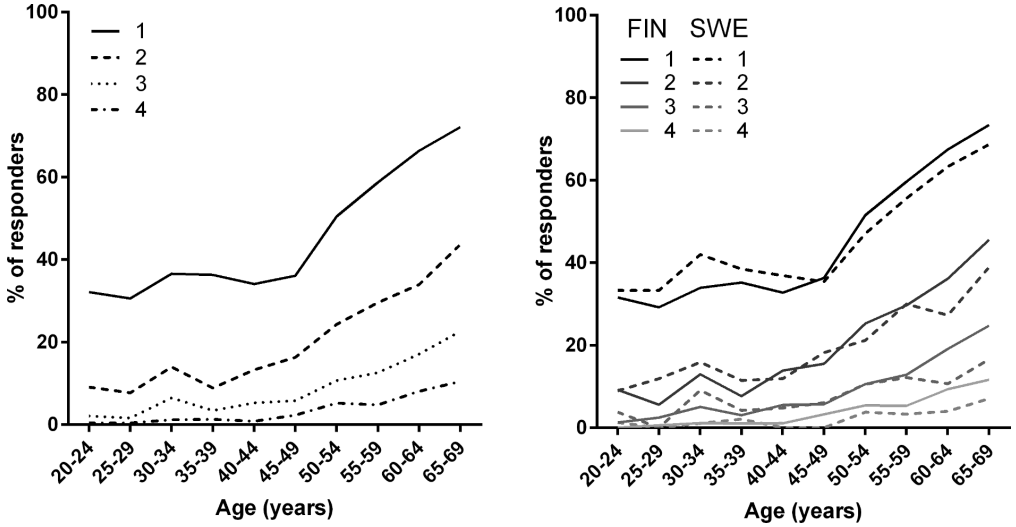

Fig. 1. Prevalence of participants with at least 1, 2, 3 or 4 diseases according to age in the whole study sample (A) and separately in Finnish and Swedish speakers (B).

Table 3
Factors associated with multimorbidity (morbidity count ≥ 2) in univariate and multivariate logistic regression analyses.

	Crude OR (95% CI)	*Adjusted OR (95% CI)
Age groups (20–39 yrs. ref group)		
40–59 yrs.	2.55 (2.01–3.24)	2.35 (1.74–3.16)
60–69 yrs.	5.85 (4.65–7.37)	5.91 (4.40–7.93)
Female	1.03 (0.89–1.19)	1.32 (1.09–1.60)
Swedish-speaking	0.82 (0.69–0.96)	1.13 (0.92–1.40)
Smoking status (never smoker ref group)		
Current smoker	1.55 (1.28–1.88)	1.85 (1.43–2.38)
Ex-smoker	2.09 (1.77–2.48)	1.82 (1.47–2.25)
BMI (<25 ref group)		
Overweight (25–29.9)	1.90 (1.58–2.29)	1.53 (1.23–1.91)
Obesity grade I (30–34.99)	3.55 (2.85–4.42)	2.73 (2.09–3.56)
Obesity grade II (≥35-)	7.20 (5.33–9.73)	5.62 (3.88–8.15)
Duration of daily physical activity < 3 h	1.15 (0.99–1.35)	1.23 (1.01–1.49)
ISCO-08 Skill level (4 ref group)		
1	1.94 (1.29–2.90)	1.58 (1.00–2.51)
2	1.59 (1.24–2.04)	1.24 (0.93–1.65)
3	0.94 (0.75–1.36)	0.98 (0.71–1.36)

* Adjusted for age, sex, native language, smoking status, BMI, physical activity, and skill level. Bold indicates $p < 0.05$. Abbreviations: BMI (Body Mass Index) and ISCO (International Standard Classification of Occupations).

and physically inactive participants the prevalence of multimorbidity was 57.4%. Results modified for patient education are shown in the multimorbidity risk assessment chart in Fig. 2.

3.6. Sensitivity analyses

We constructed disease groups to take into account the possible interrelationships between diseases. The three models composed are described in Appendix. The difference in multimorbidity prevalence between language groups remained after accounting one disease group as one disease (Table A5). In multivariable binary logistic regression analysis, results remained similar, except physical inactivity lost significance (Table A6).

4. Discussion

In this study, we found that multimorbidity was more prevalent in Finnish speakers compared to Swedish speakers in Western Finland. Finnish speakers had a higher BMI, they smoked more often, had a lower social status based on occupation, and were physically less active when compared to Swedish speakers. These lifestyle-related and socioeconomic aspects were associated with multimorbidity and might explain the difference between the two language groups. Finnish speakers had significantly more often 6 out of 16 self-reported diagnoses, and they had more often a diagnosis of COPD, heart failure, diabetes, treated dyspepsia/reflux disease, chronic kidney failure, and painful condition.

The disease count ≥ 2 is a simple and widely accepted concept to define multimorbidity, but it has limitations; it does not consider disease severity or inter-relationships. For example, hypertension, and diabetes interrelate to cardiovascular disease along with lifestyle-associated factors (Straus et al., 2002; Yusuf et al., 2004). Risk factors can be associated, or there may be true causality, both options lead to disease clusters. Therefore, causal models of multimorbidity should be interpreted with high caution (Valderas et al., 2009). Considering the possible disease interrelations, we carried out three sensitivity analyses with disease grouping based on disease co-occurrence in our cohort and the difference between langue groups remained.

The prevalence of multimorbidity in this study was 26% for Finnish speakers and 22% for Swedish speakers, similar to the prevalence in the UK (23%) (Barnett et al., 2012), but lower than overall pooled multimorbidity prevalence (33%) in a recent literature review (Nguyen et al., 2019). In Sweden, 38% were multimorbid in the age group 60–74 years (Marengoni et al., 2016), compared to 41% vs. 32% in our Finnish and Swedish speaking Finns in the age group 60–69 years.

In a previous study, multimorbidity occurred in deprived areas 10–15 years earlier than in the most affluent areas (Mercer and Watt, 2007). In our study, low socioeconomic status had a relationship with multimorbidity consistent with current evidence (Donovan et al., 1996; Marmot, 2005; Salisbury et al., 2011; Van den Akker et al., 1998; Violan et al., 2014b; Walker, 2007). According to our results, Finnish speakers with lower socioeconomic status might have poorer health and health behaviors. Earlier studies showed that better psychosocial living conditions in childhood and working conditions in adulthood among

Multimorbidity risk assessment chart

The prevalence of multimorbidity (morbidity count ≥2) is in percentage. Multimorbidity has an association with smoking status, physical activity, and Body Mass Index (BMI) based on data of 3525 participants aged 20-69 years in Western Finland.

	BMI <25	BMI 25-29.99	BMI 30-34.99	BMI ≥35
Never smoker physically active	12.2	18.0	30.0	43.2
Never smoker physically inactive	11.1	20.3	33.1	56.5
Current or ex-smoker physically active	17.8	28.0	34.1	55.0
Current or ex-smoker physically inactive	19.5	30.2	53.6	57.4

Variables: multimorbidity=morbidity count ≥2, physically active=daily physical activity ≥3h, physically inactive=daily physical activity <3h, current smokers=active smokers or stopped less than 12 months before, ex-smokers=stopped smoking more than 12 months before, never smokers=neither a current smoker nor an ex-smoker, BMI groups: under and normal weight < 25kg/m2, overweight 25.0–29.9kg/m2, obesity grade I 30.0–34.9kg/m2 and obesity grade II ≥35.0kg/m2.

Fig. 2. Multimorbidity risk assessment chart.

Swedish speakers facilitates advanced individual's sense of coherence (Volanen et al., 2006). Sense of coherence is an individual's capacity to manage stress and sustain healthy habits and is related to health in general (Eriksson and Lindström, 2005) which may contribute to the difference seen in multimorbidity between Swedish and Finnish speakers. Social participation is considered to be related to good self-rated health and social capita among Swedish speaking Finns (Hyyppä and Mäki, 2001, 2003).

Few previous studies have shown a higher prevalence of multimorbidity among minority ethnic populations in East London and Iran (Ahmadi et al., 2016; Mathur et al., 2011). However, we describe these health disparities in the majority population and with fewer confounding factors, like ethnicity, access to education or healthcare, than in previous studies.

We found that multimorbidity is positively associated with obesity. Previously in a longitudinal study in Canada, the most considerable increase in multimorbidity was found among seniors living with obesity (Lebenbaum et al., 2018). Multimorbidity was highly associated with increasing BMI and OR 2.73 for obesity grade I was higher than previously reported OR 1.65–2.20 (Agborsangaya et al., 2012; Booth et al., 2014). In our study, obesity grade II (OR 5.62) and age of 60–69 years (OR 5.91) were equal risk factors for multimorbidity. Therefore, obesity is the most influential treatable risk factor for multimorbidity.

Our study shows that physical inactivity defined as daily activity/movement less than three hours a day is a risk factor for multimorbidity. The association between physical inactivity was in line with existing evidence (Ahmadi et al., 2016; Keats et al., 2017; Wikström et al., 2015), although the definition of physical inactivity varies between studies. In the Iranian cohort (Ahmadi et al., 2016), physical activity was defined only based on occupational activity. The Finnish FINRISK study (Wikström et al., 2015) used a complex Physical Activity Questionnaire combined with a smaller cohort with activity measurements. A previous study used a cut-point of four hours daily to evaluate the association between physical inactivity and lung function decline in adult-onset asthma (Loponen et al., 2018). Paradoxically, Finnish speaking school-children aged 14–15 showed more leisure-time exercise despite higher amount of alcohol consumption, smoking, and physician-diagnosed diseases than Swedish speakers in Western Finland (Saarela and

Finnäs, 2004). How regular exercise and physical activity relate to other health behaviors needs further studies.

COPD prevalence has been shown to be higher in minorities and among people with low socioeconomic status due to differences in health behaviors, mainly smoking, and differences in occupational exposure to inhalant toxins. Low socioeconomic status is also associated with worsened COPD health outcomes (Axelsson et al., 2018; Dransfield and Bailey, 2006; Holt et al., 2011; Pleasants et al., 2016; Tran et al., 2011). In our study, the Finnish speaking majority had lower socioeconomic status and, hence, more smoking and occupational exposure to VGDF. Finnish speakers had two times as frequently diagnosis of COPD compared to Swedish speakers. A family history of COPD was more common among Finnish speakers than Swedish speakers, presumably due to family's habits and occupation.

We identified ex-smokers as having a higher probability for multimorbidity than current smokers, similar to a study in the UK (Booth et al., 2014). In contrast to our study, an Australian study showed that current smokers had a higher probability for multimorbidity; in subanalyses in the age group >60 years, however, ex-smoking was a higher risk for multimorbidity than current smoking (Taylor et al., 2010). By the age of 60 years, diseases associated with smoking are possible, and hence people stop smoking. In a cohort of adult-onset asthma, multimorbidity increased dose-dependently with smoked pack-years (Tommola et al., 2019), and in that study, the risk for multimorbidity was rather associated with pack-years than with current smoking status. We do not have information on smoked pack-years for the responders, and we do not know if ex-smokers had more pack-years than current smokers. Also, other possible explanations exist. Firstly, healthcare integrates interventions to stop smoking into care, and there is contact with healthcare at the time of diagnosis. Secondly, smoking cessation is associated with weight gain, and paradoxically might worsen glycemic control and increase the risk for diabetes, even though smoking is a risk factor for diabetes (Bush et al., 2016). Regardless of smoking cessation being associated with short-term risk of type 2 diabetes, there is still a benefit on cardiovascular and all-cause mortality (Hu et al., 2018).

Overall, studies on multimorbidity combining information on obesity, smoking status, and physical activity are rare, and therefore findings of our study provide further evidence on the association between obesity and multimorbidity. The prevalence of multimorbidity was 12% in physically active, never smoking participants with normal weight and 57% in physically inactive, smoking participants with BMI $\geq$ 35.0 kg/m2. Our results demonstrate the phenomenon in a motivating way, and the multimorbidity risk assessment chart might be important for patient education within smoking cessation, diabetes, and weight reduction.

The major strengths of this study are; random sample, a large sample size, and established structured questionnaire. This study was based on self-report data, which could be considered as a limitation of this study. Another limitation is the lack of knowledge on the disease severity. However, the FinEsS questionnaire has been validated in several previous Nordic studies, and as a large-scale questionnaire, it has several benefits compared to register-based data. The self-reported data is valuable as it combines information like smoking, exercise, and BMI not readily available in register-based data. As another limitation of the study, nutritional factors and alcohol consumption were not included in the questionnaire. However, we can assume Swedish speakers have a healthier diet and more moderate alcohol consumption based on two earlier studies (De Oliveira Figueiredo et al., 2019; Paljarvi et al., 2009).

Disease count did not include information on malignancies and HIV, thus the Charlson Comorbidity Index or the ACG System measures could not be calculated. Finland is a low HIV prevalence country. Disease counts perform as well as sophisticated measures in predicting the outcome (Huntley et al., 2012). Due to the lack of standardization of diseases included in multimorbidity studies, comparison between studies is challenging (Garin et al., 2016; Marengoni et al., 2011).

The response rate was moderate in the present study. In our study, non-responders were younger and more often males compared to responders, consistent with previous findings (Rönmark et al., 2009). The participation rate was higher for Swedish speakers, similar to the FINRISK Study 2012 (Tolonen et al., 2018). However, to minimize bias, we used age groups in statistical analysis. We conclude that this study might have included some non-responder bias that mainly affects younger and males; still, as the main difference in multimorbidity was found in older age groups and their response rate was higher, we consider the main results to be reliable.

Taken together, we have shown that smoking, overweight, obesity, and physical inactivity were associated with multimorbidity. To reduce the disease-burden the general population as well as the specific target groups need more information about these findings. Therefore, we provided a multimorbidity risk assessment chart for patient education. This study gives population-based insight that it might be possible to reduce multimorbidity and thus, the general disease burden at older age with smoking cessation, weight reduction, and increased physical activity although other determinants of health may also play a role.

4.1. Conclusion

In this study we found that Finnish speakers were more multimorbid than Swedish speakers, and COPD and diabetes were among diseases more common in Finnish speakers. Lifestyle-associated risk factors for multimorbidity smoking, overweight, obesity, and physical inactivity should be targeted in health interventions.

5. Ethics approval

The study was approved by the Ethics Committee of the Department of Medicine of Helsinki University Central Hospital (approval number 200/13/03/00/15).

6. Data statement section

All data generated or analyzed during this study are included in this published article (and its Supplementary Information File). According to ethical permission and data-protection laws of Finland, single person data cannot be made available.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2021.101338.

References

Agborsangaya, C.B., Lau, D., Lahtinen, M., Cooke, T., Johnson, J.A., 2012. Multimorbidity prevalence and patterns across socioeconomic determinants: a cross-sectional survey. BMC Public Health 12 (1). https://doi.org/10.1186/1471-2458-12-201.

Ahmadi, B., Alimohammadian, M., Yaseri, M., Majidi, A., Boreiri, M., Islami, F., Poustchi, H., Derakhshan, M.H., Feizesani, A., Pourshams, A., Abnet, C.C., Brennan, P., Dawsey, S.M., Kamangar, F., Boffetta, P., Sadjadi, A., Malekzadeh, R., 2016. Multimorbidity: Epidemiology and risk factors in the golestan cohort study, Iran a cross-sectional analysis. Med. (United States) 95 (7), e2756. https://doi.org/10.1097/MD.0000000000002756.

Axelsson, S., Mulinari, S., Wemrell, M., Leckie, G., Perez, R., Merlo, J., 2018. SSM - Population Health Chronic Obstructive Pulmonary Disease in Sweden: an intersectional multilevel analysis of individual heterogeneity and discriminatory accuracy. SSM - Popul. Heal. 4, 334–346. https://doi.org/10.1016/j.ssmph.2018.03.005.

Barnett, K., Mercer, S.W., Norbury, M., Watt, G., Wyke, S., Guthrie, B., 2012. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 380 (9836), 37–43. https://doi.org/10.1016/S0140-6736(12)60240-2.

Booth, H.P., Prevost, A.T., Gulliford, M.C., 2014. Impact of body mass index on prevalence of multimorbidity in primary care: Cohort study. Fam. Pract. 31 (1), 38–43. https://doi.org/10.1093/fampra/cmt061.

Bush, T., Lovejoy, J.C., Deprey, M., Carpenter, K.M., 2016. The effect of tobacco cessation on weight gain, obesity, and diabetes risk. Obesity 24 (9), 1834–1841. https://doi.org/10.1002/oby.21582.

Buttorff, C., Ruder, T., Bauman, M., 2017. Multiple Chronic Conditions in the United States, Multiple Chronic Conditions in the United States. https://doi.org/10.7249/tl221.

De Oliveira Figueiredo, R.A., Viljakainen, J., Viljakainen, H., Roos, E., Rounge, T.B., Weiderpass, E., 2019. Identifying eating habits in Finnish children: A cross-sectional study. BMC Public Health 19 (1), 312. https://doi.org/10.1186/s12889-019-6603-x.

Eachus, J., Williams, M., Chan, P., Smith, G.D., Grainge, M., Donovan, J., Frankel, S., 1996. Deprivation and cause specific morbidity: evidence from the Somerset and Avon survey of health. BMJ 312 (7026), 287–292. https://doi.org/10.1136/bmj.312.7026.287.

Dransfield, M.T., Bailey, W.C., 2006. COPD: racial disparities in susceptibility, treatment, and outcomes. Clin. Chest Med. 27 (3), 463–471. https://doi.org/10.1016/j.ccm.2006.04.005.

Eriksson, M., Lindström, B., 2005. Validity of Antonovsky's sense of coherence scale: a systematic review. J. Epidemiol. Community Health 60, 376–381. https://doi.org/10.1136/jech.2003.018085.

Garin, N., Koyanagi, A., Chatterji, S., Tyrovolas, S., Olaya, B., Leonardi, M., Lara, E., Koskinen, S., Tobiasz-Adamczyk, B., Ayuso-Mateos, J.L., Haro, J.M., 2016. Global Multimorbidity Patterns: A Cross-Sectional, Population-Based, Multi-Country Study. Journals Gerontol. - Ser. A Biol. Sci. Med. Sci. 71 (2), 205–214. https://doi.org/10.1093/gerona/glv128.

Gaskin, D.J., Thorpe, R.J., McGinty, E.E., Bower, K., Rohde, C., Young, J.H., LaVeist, T. A., Dubay, L., 2014. Disparities in diabetes: the nexus of race, poverty, and place. Am. J. Public Health 104 (11), 2147–2155. https://doi.org/10.2105/AJPH.2013.301420.

Holt, J.B., Zhang, X., Presley-Cantrell, L., Croft, J.B., 2011. Geographic disparities in chronic obstructive pulmonary disease (COPD) hospitalization among Medicare beneficiaries in the United States. Int. J. COPD 6, 321–328. https://doi.org/10.2147/COPD.S19945.

Honkamäki, J., Hisinger-Mölkänen, H., Ilmarinen, P., Piirilä, P., Tuomisto, L.E., Andersén, H., Huhtala, H., Sovijärvi, A., Backman, H., Lundbäck, B., Rönmark, E., Lehtimäki, L., Kankaanranta, H., 2019. Age- and gender-specific incidence of new asthma diagnosis from childhood to late adulthood. Respir. Med. 154, 56–62. https://doi.org/10.1016/j.rmed.2019.06.003.

Hu, Y., Zong, G., Liu, G., Wang, M., Rosner, B., Pan, A.n., Willett, W.C., Manson, J.E., Hu, F.B., Sun, Q.i., 2018. Smoking cessation, weight change, type 2 diabetes, and mortality. N. Engl. J. Med. 379 (7), 623–632. https://doi.org/10.1056/NEJMoa1803626.

Huntley, A.L., Johnson, R., Purdy, S., Valderas, J.M., Salisbury, C., 2012. Measures of multimorbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. Ann. Fam. Med. 10 (2), 134–141. https://doi.org/10.1370/afm.1363.

Hyyppä, M.T., Mäki, J., 2001. Individual-level relationships between social capital and self-rated health in a bilingual community. Prev. Med. (Baltim) 32 (2), 148–155. https://doi.org/10.1006/pmed.2000.0782.

Hyyppä, M.T., Mäki, J., 2003. Social participation and health in a community rich in stock of social capital. Health Educ. Res. 18 (6), 770–779. https://doi.org/10.1093/her/cyf044.

Ilmarinen, P., Tuomisto, L.E., Niemelä, O., Danielsson, J., Haanpää, J., Kankaanranta, T., Kankaanranta, H., 2016. Comorbidities and elevated IL-6 associate with negative outcome in adult-onset asthma. Eur. Respir. J. 48 (4), 1052–1062. https://doi.org/10.1183/13993003.02198-2015.

Kankaanranta, H., Kauppi, P., Tuomisto, L.E., Ilmarinen, P., 2016. Emerging comorbidities in adult asthma: risks, clinical associations, and mechanisms. Mediators Inflamm. 2016, 1–23. https://doi.org/10.1155/2016/3690628.

Keats, M.R., Cui, Y., DeClercq, V., Dummer, T.J.B., Forbes, C., Grandy, S.A., Hicks, J., Sweeney, E., Yu, Z.M., Parker, L., 2017. Multimorbidity in Atlantic Canada and association with low levels of physical activity. Prev. Med. (Baltim) 105, 326–331. https://doi.org/10.1016/j.ypmed.2017.10.013.

Kerminen, S., Havulinna, A.S., Hellenthal, G., Martin, A.R., Sarin, A.-P., Perola, M., Palotie, A., Salomaa, V., Daly, M.J., Ripatti, S., Pirinen, M., 2017. Fine-Scale Genetic Structure in Finland. G3 (Bethesda) 7 (10), 3459–3468. https://doi.org/10.1534/g3.117.300217.

Larsson, M.L., Loit, H-M., Meren, M., Pölluste, J., Magnusson, A., Larsson, K., Lundbäck, B., 2003. Passive smoking and respiratory symptoms in the FinEsS study. Eur. Respir. J. 21 (4), 672–676. https://doi.org/10.1183/09031936.03.00033702.

Lebenbaum, M., Zaric, G.S., Thind, A., Sarma, S., 2018. Trends in obesity and multimorbidity in Canada. Prev. Med. (Baltim) 116, 173–179. https://doi.org/10.1016/j.ypmed.2018.08.025.

Loponen, J., Ilmarinen, P., Tuomisto, L.E., Niemelä, O., Tommola, M., Nieminen, P., Lehtimäki, L., Kankaanranta, H., 2018. Daily physical activity and lung function decline in adult-onset asthma: a 12-year follow-up study. Eur. Clin. Respir. J. 5 (1), 1533753. https://doi.org/10.1080/20018525.2018.1533753.

Marengoni, A., Angleman, S., Meinow, B., Santoni, G., Mangialasche, F., Rizzuto, D., Fastbom, J., Melis, R., Parker, M., Johnell, K., Fratiglioni, L., 2016. Coexisting chronic conditions in the older population: variation by health indicators. Eur. J. Intern. Med. 31, 29–34. https://doi.org/10.1016/j.ejim.2016.02.014.

Marengoni, A., Angleman, S., Melis, R., Mangialasche, F., Karp, A., Garmen, A., Meinow, B., Fratiglioni, L., 2011. Aging with multimorbidity: a systematic review of the literature. Ageing Res. Rev. 10 (4), 430–439. https://doi.org/10.1016/j.arr.2011.03.003.

Marmot, M., 2005. Social determinants of health inequalities. Lancet 365 (9464), 1099–1104. https://doi.org/10.1016/S0140-6736(05)71146-6.

Mathur, R., Hull, S.A., Badrick, E., Robson, J., 2011. Cardiovascular multimorbidity: the effect of ethnicity on prevalence and risk factor management. Br. J. Gen. Pract. 61 (586), e262–e270. https://doi.org/10.3399/bjgp11X572454.

Mercer, S.W., Watt, G.C.M., 2007. The inverse care law: clinical primary care encounters in deprived and affluent areas of Scotland. Ann. Fam. Med. 5 (6), 503–510. https://doi.org/10.1370/afm.778.

Nguyen, H., Manolova, G., Daskalopoulou, C., Vitoratou, S., Prince, M., Prina, A.M., 2019. Prevalence of multimorbidity in community settings: a systematic review and meta-analysis of observational studies, 2235042X1987093 J. Comorbidity 9. https://doi.org/10.1177/2235042X19870934.

Paljarvi, T., Suominen, S., Koskenvuo, M., Winter, T., Kauhanen, J., 2009. The differences in drinking patterns between Finnish-speaking majority and Swedish-speaking minority in Finland. Eur. J. Public Health 19 (3), 278–284. https://doi.org/10.1093/eurpub/ckp007.

Pallasaho, P., Juusela, M., Lindqvist, A., Sovijärvi, A., Lundbäck, B., Rönmark, E., 2011. Allergic rhinoconjunctivitis doubles the risk for incident asthma - results from a population study in Helsinki, Finland. Respir. Med. 105 (10), 1449–1456. https://doi.org/10.1016/j.rmed.2011.04.013.

Pleasants, R.A., Riley, I.L., Mannino, D.M., 2016. Defining and targeting health disparities in chronic obstructive pulmonary disease. Int. J. COPD 11, 2475–2496. https://doi.org/10.2147/COPD.S79077.

Reini, K., Saarela, J., 2017. Differences in sickness allowance receipt between Swedish speakers and Finnish Speakers in Finland. Finnish Yearb. Popul. Res. 52, 43–58. https://doi.org/10.23979/fypr.66598.

Rönmark, E.P., Ekerljung, L., Lötvall, J., Torén, K., Rönmark, E., Lundbäck, B., 2009. Large scale questionnaire survey on respiratory health in Sweden: Effects of late- and non-response. Respir. Med. 103 (1807) https://doi.org/10.1016/j.rmed.2009.07.014.

Saarela, J., Finnäs, F., 2011. Family origin and mortality: prospective Finnish cohort study. BMC Public Health 11, 385. https://doi.org/10.1186/1471-2458-11-385.

Saarela, J., Finnäs, F., 2004. The health of Swedish-speaking and Finnish-speaking schoolchildren in Finland. Child Care Health Dev. 30 (1), 51–58. https://doi.org/10.1111/j.1365-2214.2004.00385.x.

Saarela, J., Finnäs, F., 2005. Mortality inequality in two native population groups. Popul. Stud. (NY) 59 (3), 313–320. https://doi.org/10.1080/00324720500249372.

Saarela, J., Finnäs, F., 2002. Language-group differences in very early retirement in Finland. Demogr. Res. 7, 49–66. https://doi.org/10.4054/DemRes.2002.7.3.

Salisbury, C., Johnson, L., Purdy, S., Valderas, J.M., Montgomery, A.A., 2011. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. Br. J. Gen. Pract. 61 (582), e12–e21. https://doi.org/10.3399/bjgp11X548929.

Sipilä, P., Martikainen, P., 2010. Language-group mortality differentials in Finland: the effects of local language composition. Heal. Place 16 (3), 446–451. https://doi.org/10.1016/j.healthplace:2009.11.014.

Straus, S.E., Majumdar, S.R., McAlister, F.A., 2002. New evidence for stroke prevention: scientific review. J. Am. Med. Assoc. 288, 1388–1395. https://doi.org/10.1001/jama.288.11.1388.

Taylor, A.W., Price, K., Gill, T.K., Adams, R., Pilkington, R., Carrangis, N., Shi, Z., Wilson, D., 2010. Multimorbidity - not just an older person's issue. Results from an Australian biomedical study. BMC Public Health 10, 718. https://doi.org/10.1186/1471-2458-10-718.

Tolonen, H., Koponen, P., Borodulin, K., Männistö, S., Peltonen, M., Vartiainen, E., 2018. Language as a determinant of participation rates in Finnish health examination surveys. Scand. J. Public Health 46, 240–243. https://doi.org/10.1177/1403494817725243.

Tommola, M., Ilmarinen, P., Tuomisto, L.E., Lehtimäki, L., Niemelä, O., Nieminen, P., Kankaanranta, H., 2019. Cumulative effect of smoking on disease burden and multimorbidity in adult-onset asthma. Eur. Respir. J. 54 (3), 1801580. https://doi.org/10.1183/13993003.01580-201810.1183/13993003.01580-2018.Shareable1.

Tran, H.N., Siu, S., Iribarren, C., Udaltsova, N., Klatsky, A.L., 2011. Ethnicity and risk of hospitalization for Asthma and chronic obstructive pulmonary disease. Ann. Epidemiol. 21 (8), 615–622. https://doi.org/10.1016/j.annepidem.2010.10.015.

Valderas, J.M., Starfield, B., Sibbald, B., Salisbury, C., Roland, M., 2009. Defining comorbidity: Implications for understanding health and health services. Ann. Fam. Med. 7 (4), 357–363. https://doi.org/10.1370/afm.983.

van den Akker, M., Buntinx, F., Metsemakers, J.F.M., Roos, S., Knottnerus, J.A., 1998. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. J. Clin. Epidemiol. 51 (5), 367–375. https://doi.org/10.1016/S0895-4356(97)00306-5.

Violan, C., Foguet-Boreu, Q., Flores-Mateo, G., Salisbury, C., Blom, J., Freitag, M., Glynn, L., Muth, C., Valderas, J.M., Scuteri, A., 2014. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PLoS One 9 (7), e102149. https://doi.org/10.1371/journal.pone.0102149.

Volanen, S.-M., Suominen, S., Lahelma, E., Koskenvuo, M., Silventoinen, K., 2006. Sense of coherence and its determinants: a comparative study of the Finnish-speaking majority and the Swedish-speaking minority in Finland. Scand. J. Public Health 34 (5), 515–525. https://doi.org/10.1080/14034940600585812.

Walker, A.E., 2007. Multiple chronic diseases and quality of life: patterns emerging from a large national sample, Australia. Chronic Illn. 3 (3), 202–218. https://doi.org/10.1177/1742395307081504.

Wikström, K., Lindström, J., Harald, K., Peltonen, M., Laatikainen, T., 2015. Clinical and lifestyle-related risk factors for incident multimorbidity: 10-year follow-up of Finnish population-based cohorts 1982–2012. Eur. J. Intern. Med. 26 (3), 211–216. https://doi.org/10.1016/j.ejim.2015.02.012.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J., Lisheng, L., 2004. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet 364 (9438), 937–952. https://doi.org/10.1016/S0140-6736(04)17018-9.

PUBLICATION III

Influence of Childhood Exposure to a Farming Environment on Age at Asthma Diagnosis in a Population-Based Study

Heidi Andersén, Pinja Ilmarinen, Jasmin Honkamäki, Leena E Tuomisto, Hanna Hisinger-Mölkänen, Helena Backman, Bo Lundbäck, Eva Rönmark, Lauri Lehtimäki, Anssi Sovijärvi, Päivi Piirilä, Hannu Kankaanranta

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ORIGINAL RESEARCH

Influence of Childhood Exposure to a Farming Environment on Age at Asthma Diagnosis in a Population-Based Study

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Video abstract

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Purpose: Asthma is a heterogeneous disease, and factors associated with different asthma phenotypes are poorly understood. Given the higher prevalence of farming exposure and late diagnosis of asthma in more rural Western Finland as compared with the capital of Helsinki, we investigated the relationship between childhood farming environment and age at asthma diagnosis.

Methods: A cross-sectional population-based study was carried out with subjects aged 20–69 years in Western Finland. The response rate was 52.5%. We included 3864 participants, 416 of whom had physician-diagnosed asthma at a known age and with data on the childhood environment. The main finding was confirmed in a similar sample from Helsinki. Participants were classified as follows with respect to asthma diagnosis: early diagnosis (0–11 years), intermediate diagnosis (12–39 years), and late diagnosis (40–69 years).

Results: The prevalence of asthma was similar both without and with childhood exposure to a farming environment (11.7% vs 11.3%). Allergic rhinitis, family history of asthma, ex-smoker, occupational exposure, and BMI $\geq$ 30 kg/m^2 were associated with a higher likelihood of asthma. Childhood exposure to a farming environment did not increase the odds of having asthma (aOR, 1.10; 95% CI, 0.87–1.40). It did increase the odds of late diagnosis (aOR, 2.30; 95% CI, 1.12–4.69), but the odds were lower for early (aOR, 0.49; 95% CI, 0.30–0.80) and intermediate diagnosis of asthma (aOR, 0.75; 95% CI, 0.47–1.18).

Conclusion: Odds were lower for early diagnosis of asthma and higher for late diagnosis of asthma in a childhood farming environment. This suggests a new hypothesis concerning the etiology of asthma when it is diagnosed late.

Keywords: agriculture, early-diagnosed asthma, intermediate-diagnosed asthma, late-diagnosed asthma, risk factors, phenotypes

Summary

- Late-onset asthma incidence was higher in agricultural Western Finland than in urban Southern Finland in a recent EpiLung study. Our study tries to find a reason for this difference.
- Childhood exposure to a farming environment and its microbiota has been shown to reduce the likelihood of allergic, often early-onset asthma. In contrast, data from the Finnish EpiLung study show that growing up in a farming environment increased the odds of asthma after age 40.
- This result suggests a new hypothesis concerning the etiology of late-diagnosed asthma. Therefore, based on the premise, children should be

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protected from harmful exposures but be exposed to diverse microbiota for good respiratory health.

Introduction

Asthma is a disease with several distinct phenotypes and endotypes. Age at asthma diagnosis is one way to divide asthma patients into phenotypes.[1,2] We categorized participants into three groups: early- (0–11 years), intermediate- (12–39 years), and late-diagnosed (40–69 years) asthma. Respiratory viral infections are important triggers of asthma exacerbations at all ages. Nonetheless, it is unclear whether rhinovirus or respiratory syncytial virus are causally related to later atopic or nonatopic asthma.[3]

Early-diagnosed asthma patients are more often atopic and have a family history of atopy or asthma, thus having Type 2-predominant immunity (T2), responsiveness to glucocorticoids, and a good prognosis.[4,5] For early-diagnosed asthma, reported risk factors include male sex,[10] early abnormalities in lung function,[11] atopy,[7] air pollution,[12] prenatal and household tobacco smoke,[13] and obesity.[14] Early- and intermediate-diagnosed asthma have partly shared, but somewhat distinct, genetic risk factors, and genetics may play a more prominent role in young persons.[15] Patients with intermediate- or late-diagnosed asthma are more often females with worse prognoses and low disease remission rates[6]. In addition, they more often have persistent airflow limitation with either nonallergic T2 high- or non-T2 immunity.[7–9] For intermediate- and late-diagnosed asthma, known risk factors include female sex, smoking, occupational exposures, rhinitis, obesity, and early puberty.[8,16] Although the risk factors for early-diagnosed asthma are well documented, there is still a lack of understanding of asthma risk factors in terms of the age at asthma onset, particularly risk factors associated with late-diagnosed asthma. Early- and late-diagnosed asthma may have different (eg, sex) or similar (eg, smoking, air impurities) risk factors.

Childhood exposure to farming environment reduces the risk for allergies and allergic asthma. However, most studies are based on a population <50 years of age, and thus, conclusions on the association of a childhood farming environment with late-diagnosed asthma cannot be drawn.[17,18] High microbial diversity in the environment has been associated with lower asthma risk among children exposed to agricultural settings.[18–20] Protective factors in the farming milieu are related to higher expression levels of innate immunity genes that contribute to the development of the immune system.[21,22] Early- and late-diagnosed asthma are different in terms of driving immunity.[2,8] Therefore, we hypothesized that the childhood environment might modify asthma risk differently for early-onset and late-onset asthma.

Objectives

This study aimed to compare factors associated with early-, intermediate-, and late-diagnosed asthma in a genetically homogenous population[23] living in Western Finland, consisting of rural and suburban residents sharing the same social and healthcare services. The results were confirmed in a more urban and heterogeneous Helsinki cohort. Although there are several previous studies on asthma, this study is the first to date to evaluate both early-diagnosed and late-diagnosed phenotypes of asthma in the same setting, focusing on the role of childhood living conditions.

Methods

The study included a cross-sectional random sample of the population aged 20–69 years in February 2016 in Seinäjoki and Vaasa in Western Finland and Helsinki in Southern Finland as part of FinEsS (Finland–Estonia–Sweden) and EpiLung study. Nonresponders were often under 40 years and males.[24,25]

In Western Finland, 4173 participants responded in a postal survey, yielding a participation rate of 52.5% (Figure 1). To maintain a more homogenous population and childhood environment, we excluded 103 subjects with a primary language other than Finnish or Swedish, since they were likely to be immigrants. Altogether, 3864 subjects were included in the analyses.

The definition of late-diagnosed asthma varies among studies, from 12 years of age to ≥65 years of age.[26,27] As stated above, participants were categorized into three groups: early- (0–11 years), intermediate- (12–39 years), and late-diagnosed (40–69 years) asthma. We decided not to use the term "age of onset," which might be different than the age at diagnosis and is seldom known. We used the presence and absence of allergic rhinitis to indicate asthma as allergic or nonallergic.[28] We analyzed the main results in Western Finland, a rural and farming region with a low migration rate, and validated the main result with the Helsinki cohort.[25]

Definitions

Physician-diagnosed asthma: Affirmative answer to "Has a doctor diagnosed you as having asthma?"

The age at asthma diagnosis: "What age were you when a doctor diagnosed you as having asthma?"

Childhood exposure to a farming environment: "Did you live on a farm during your first 5 years?" Because of urbanization, many aged 60 to 70 years grew up on a farm but had

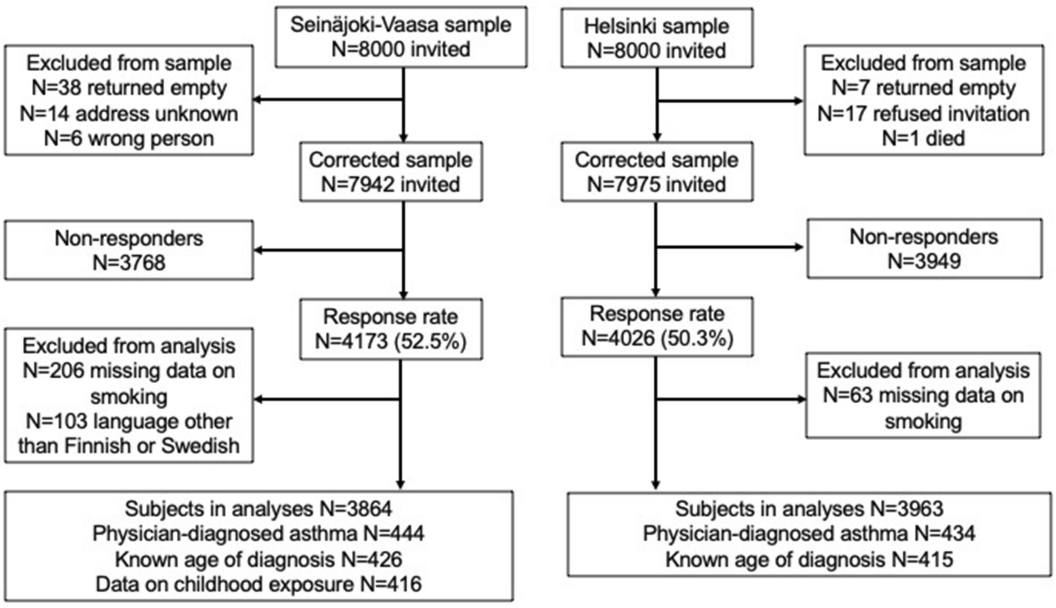

Figure 1 Flowchart depicting the study enrollment. The Seinäjoki-Vaasa sample was the main cohort, and Helsinki was the validation cohort.

different occupations later in life within the area. The farms used to be small and family-owned. Childhood exposure to farming, cattle, or hay work often continued during the entire childhood and occasionally even after the children moved away from the farm.

Physician-diagnosed Chronic Obstructive Pulmonary Disease (COPD): "Has a doctor diagnosed you as having chronic bronchitis, COPD, or emphysema?"

Family history of asthma: "Do you have a family history of asthma?"

Family history of allergic rhinitis: "Do you have a family history of allergic rhinitis?"

Occupational exposure to VGDF (vapors, gases, dust, or fumes): "Are you now being, or have you been, heavily exposed to gases, dust, or fumes at work?"

Physician-diagnosed allergic rhinitis: "Has a doctor diagnosed you as having allergic rhinitis caused by pollen (eg, birch, grass, mugwort)?" or "Has a doctor diagnosed you as having allergic rhinitis caused by dander, such as from a cat or dog?"

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software version 26 (IBM SPSS, Armonk, NY, USA). The Kruskal–Wallis test was used to compare continuous variables with a nonnormal distribution between the three groups, and ANOVA was used to compare means. Pearson's chi-square test was used to compare categorical variables. A p-value <0.05 was considered significant.

Cox time to event analyses were done for age at asthma diagnosis for those with and without childhood exposure to farming environments with a comparison of hazard ratio (log rank). A null hypothesis was that the environment did not play a role in age at diagnosis.

Multivariable binary logistic regression analyses were performed to calculate odds ratios (ORs) with 95% confidence intervals (CI) by using the dependent and independent variables described below.

Physician-diagnosed asthma: Independent variables were age, sex, allergic rhinitis, living on a farm during the first 5 years of life, family history of asthma, family history of allergy, smoking status, occupational exposure to VGDF, and current BMI.

Early-diagnosed asthma (age at diagnosis < 12 years): Independent variables were sex, physician-diagnosed allergy, living on a farm during the first 5 years of life, family history of asthma, and family history of allergy.

Intermediate-onset asthma (age at diagnosis of 12–39 years) and late-onset asthma (age at diagnosis ≥40): Independent variables in intermediate- and late-onset models were sex, allergic rhinitis, living on a farm during the first 5 years of life, family histories of asthma, family histories of allergy, smoking status, occupational exposure to VGDF, and current BMI.

Results

Demographics of those with and without childhood exposure to farming are shown in Table 1. Those with childhood exposure to a farming environment were older, had higher BMI, lower social status based on occupation, smoked less, had more occupational exposure, and exercised more than those without childhood exposure.

Table 1 Demographics of the 3767 Participants in Western Finland with Known Childhood Environment

	Childhood Non-Farming Environment n=2143 (56.9%)	**Childhood Farming Environment n=1624 (43.1%)**	**p**
Female gender	1161 (54.2%)	805 (49.6%)	0.005
Mean age (SD) Median age	46 (14.7) 48	55 (12.9) 59	<0.001
Mean BMI (SD) Median BMI	26.5 (4.9) 25.8	27.1 (4.7) 26.3	<0.001
Family history of allergy	742 (34.6%)	431 (26.5%)	<0.001
Family history of asthma	550 (25.7%)	421 (25.9%)	0.857
Current farmers	25 (1.4%)	179 (12.6%)	<0.001
Low socioeconomic status	1033 (58.1%)	1003 (71.1%)	<0.001
Physical activity more than 3 hours daily	1036 (51.6%)	914 (61.1%)	<0.001
Physical exercise more than 2–3 times a week	1525 (71.7%)	1208 (75.0%)	0.023
Occupational exposure to VGDF	670 (31.8%)	697 (44.3%)	<0.001
Smoking status Never smokers Ex-smokers Current smokers	 1073 (50.1%) 580 (27.1%) 490 (22.9%)	 911 (56.1%) 449 (27.6%) 264 (16.3%)	<0.001
Physician diagnosed asthma	250 (11.7%)	184 (11.3%)	0.749
Age group 20–39 yrs 40–59 yrs 60–69 yrs	 109 (14.2%) 82 (9.8%) 59 (10.9%)	 35 (14.1%) 58 (9.7%) 91 (11.7%)	
Current asthma medication	250 (11.7%)	194 (11.9%)	0.792
Allergic rhinitis	442 (20.6%)	240 (14.8%)	<0.001
Age group 20–39 yrs 40–59 yrs 60–69 yrs	 209 (27.1%) 170 (20.4%) 63 (11.7%)	 58 (23.4%) 102 (17.1%) 80 (10.3%)	
Physician diagnosed COPD	48 (2.2%)	46 (2.8%)	0.248
Age group 20–39 yrs 40–59 yrs 60–69 yrs	 3 (0.4%) 17 (2.0%) 28 (5.2%)	 1 (0.4%) 14 (2.3%) 31 (4.0%)	

Notes: We excluded 97 with missing information on childhood exposure to farming environment. Low socioeconomic status was based on occupation and skill level.

However, the prevalence of asthma was the same for both those exposed and not exposed to a childhood farming environment. The characteristics of the participants with asthma compared to those without asthma are shown in Table E1.

We analyzed associated factors for asthma with logistic regression. These were allergic rhinitis, family history of asthma, being an ex-smoker, occupational exposure to VGDF, and obesity, but not childhood exposure to a farming environment (Table 2).

Early-, Intermediate- and Late-Diagnosed Asthma

Of the responders with physician-diagnosed asthma, 114 (26.8%) had early-diagnosed asthma, 173 (40.6%) had intermediate-diagnosed asthma, and 139 (32.6%) had late-diagnosed asthma.

Early-diagnosed asthma was more frequent among males, and late- and intermediate-diagnosed asthma was more frequent among females (Table E2). Allergic rhinitis was most frequent in the early-diagnosed asthma group and the least frequent in the late-diagnosed asthma group. Current obesity was almost two times more frequent in late-diagnosed asthma than in early-diagnosed asthma. Participants with late-diagnosed asthma more often had occupational exposure to VGDF, a smoking history, and COPD. Additionally, the proportions of patients with childhood exposure to a farming environment and a current occupation within agriculture were higher in late- than in early- or intermediate-diagnosed asthma. Childhood exposure to a farming environment and late-diagnosed asthma seemed to correlate, and therefore we did further analyses. Among 444 participants with physician-diagnosed asthma, the number of patients with a known age at asthma diagnosis and data on childhood exposure to farming was 416 (93.7%).

Table 2 Factors Associated with Asthma Assessed by Multivariable Logistic Regression Analyses

	Physician-Diagnosed Asthma (n=444)	
	*Adjusted	
	OR	95% CI
Age	1.00	0.99–1.01
Female sex	1.21	0.95–1.54
Physician-diagnosed allergic rhinitis	6.64	5.23–8.44
Childhood exposure to farming environment	1.10	0.87–1.40
Family history of asthma	2.38	1.88–3.02
Family history of allergy	0.90	0.70–1.16
Nonsmoker (ref.)		
Ex-smoker	1.54	1.19–1.99
Current smoker	1.21	0.89–1.64
Occupational exposure to VGDF	1.32	1.04–1.67
BMI <25 kg/m^2 (ref.)		
BMI 25–29.99 kg/m^2	0.87	0.67–1.14
BMI ≥30 kg/m^2	1.38	1.03–1.84

Notes: *The model was adjusted for all covariates shown in the table Study population n=3864.

Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ILC, innate lymphoid cells; OR, odds ratio; Th, helper T cells; VGDF, vapors, gases, dust, or fumes.

The Age at Asthma Diagnosis

These 416 patients were included in the following analyses to illustrate the connection between the childhood environment and age at asthma diagnosis. The mean ages of diagnosis were compared between those with and those without a childhood exposure to farming. The mean diagnosis age was higher for those with than for those without childhood exposure to farming environment (33.5 years vs 23.0 years; $p < 0.001$) (Figure 2A). Cox survival analyses show that 50% were given their asthma diagnosis by the age of 37 years if exposed to childhood farming, compared to by the age of 20 years if not exposed to farming childhood environment, hazard ratio 0.60 (0.50–0.73) (Figure 2B).

Factors Associated with Asthma Age at Diagnosis Groups

Marked differences were found in associated factors among different ages at asthma diagnosis in both the crude and adjusted analyses (Figure 3; Tables E3 and E4). Interestingly, those with childhood exposure to a farming environment had lower odds for early- and intermediate-diagnosed asthma but higher odds for late-diagnosed asthma. This main result was validated in the Helsinki data, and the result was similar, childhood exposure had lower odds for early-diagnosed and higher odds for late-diagnosed asthma (Figure 3B, Table E5).

Because younger subjects are less likely to grow up on a farm due to urbanization and of course cannot have late-onset asthma, we performed two additional analyses. OR of intermediate-diagnosed asthma was analyzed for those

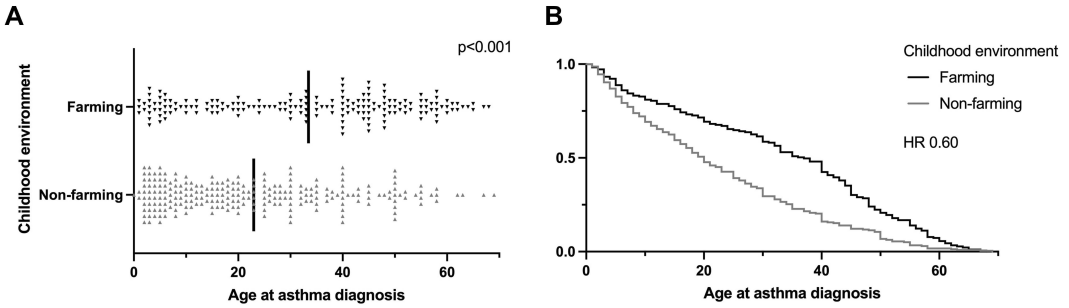

Figure 2 (**A**) Age at asthma diagnosis between subjects with farming and nonfarming childhood environments (n = 416) (ANOVA). Vertical lines indicate means (**B**). Cox survival analyses of age at asthma diagnosis and childhood exposure to farming and nonfarming environments (n = 416).

over 40 years of age (Figure 3C, Table E6) and OR of late-diagnosed asthma for those over 60 years and additionally adjusted for age (Figure 3C, Table E7).

Sensitivity Analyses for the Main Result

To exclude the possibility that data on subjects who were currently farming could affect our results, we performed a sensitivity analysis excluding participants who were currently or previously working within agriculture. Childhood exposure to a farming environment had higher odds of late-diagnosed asthma in this model (Figure 4, Table E8).

We performed a sensitivity analysis, excluding participants with coexisting physician-diagnosed COPD because asthma and COPD share some risk factors and a considerable proportion of participants with late-onset asthma have coexisting COPD. In this model, childhood exposure to a farming environment continued to have higher odds for late-diagnosed asthma (Figure 4, Table E9). In separate analyses for allergic and nonallergic subjects, childhood exposure to a farming environment remained a risk factor for late-diagnosed asthma (Figure 4, Table E10).

Discussion

The main result of this study was that the same factor, childhood exposure to a farming environment, affected the probability of early- and late-diagnosed asthma differently. This exposure was associated with lower odds for asthma diagnosed before the age of 40 years but higher odds for asthma diagnosed after the age of 40 years among both allergic and nonallergic responders. The results remained the same after excluding a previous or current farming occupation or COPD.

Other Associated Factors

Females had higher odds of intermediate- and late-diagnosed asthma, consistent with previous findings.[4,50] Similar to an earlier study, late-diagnosed asthma was more often nonallergic.[8] Ex-smoking and occupational exposures were associated with asthma, although they were not associated with age at asthma diagnosis. The previously reported attributable risk of occupational exposure ranges from 10% to 25% or more for adult asthma.[51,52]

Childhood Farming Exposure Association with Late-Diagnosed Asthma

Prevalence of asthma was similar with and without childhood exposure to farming in the age group 40–69 years. In contrast, there was some evidence linking childhood exposure to farming environment to late-diagnosed asthma. An earlier study showed a gradual increase in asthma diagnoses over time after farming exposures, supporting our finding.[18] A limitation of earlier studies is that their late-onset asthma populations were small; participants were adults aged 20–44 years or 25–49 years.[17,18] Asthma was associated with livestock in nonatopic farmers in Norway.[29] A significant dose–response correlation was found between the amount of dust, fungal spores, bacteria, endotoxin, or ammonia and the development of nonatopic asthma. Nevertheless, the presence of livestock was reported to reduce asthma risk among atopic farmers.[29] Adult farmers with respiratory disease more often have neutrophilic airway inflammation,[30] and neutrophilic inflammation may also indicate T2-low asthma in addition to COPD remodeling.[31] Occupational agricultural exposures are also associated with the development of chronic obstructive pulmonary disease.[32,33]

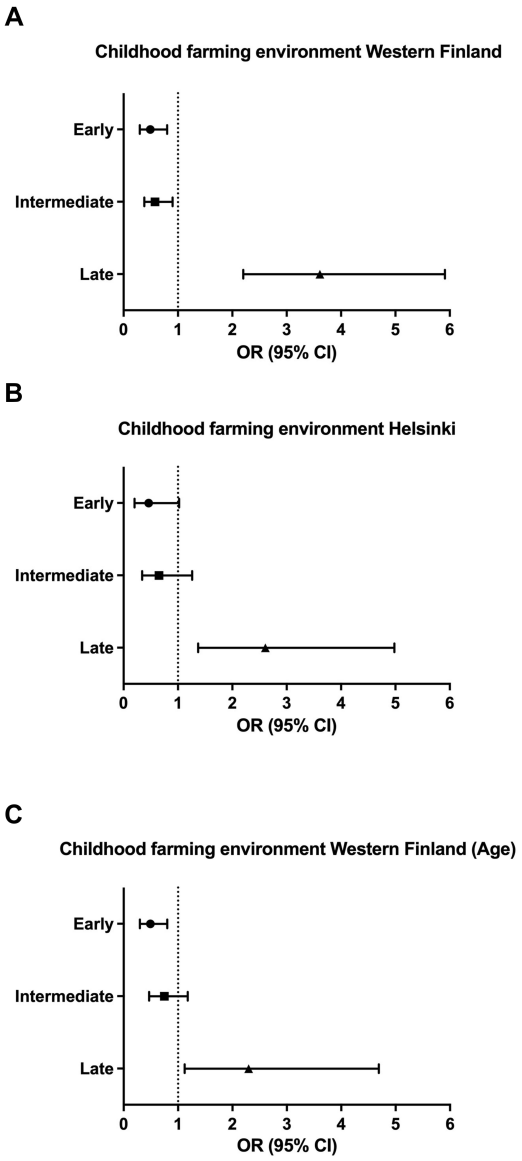

Figure 3 Association of age at asthma diagnosis with childhood exposure to a farming environment in Western Finland (**A**), validation in the Helsinki population (**B**) and adjusted for age in Western Finland (**C**). For Figure A logistic regression analyses are shown in.Table E4, for Figure B logistic regression analyses are shown in Table E5, and for Figure C in Tables E4, E6, and E7.

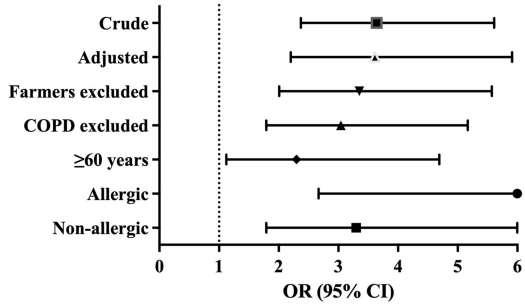

Figure 4 Association between childhood exposure to a farming environment of life and late-diagnosed asthma in all subjects and different subgroups in Western Finland. Models were adjusted for sex, allergic rhinitis, childhood exposure to a farming environment, family histories of asthma, family histories of allergy, smoking status, occupational exposure to vapors, gases, dust, or fumes, and current BMI. The crude results are shown in Table E3, and the adjusted models are presented in Tables E4, E7–E9, and E10. The result remained in the adjusted analyses after exclusion of farmers (Table E8), COPD (Table E9), and those < 60 years of age additionally adjusted for age (Table E7). Higher odds were seen for both allergic and nonallergic participants (Table E10).

Comparison with Earlier Childhood Farming Exposure Studies

In previous prospective studies, a childhood farming environment protected against early-onset asthma.[20,34,35] The OR of 0.49 in our study was similar in magnitude to that reported in studies from suburban Europe (OR 0.49) and alpine areas (OR 0.74).[36,37] The childhood farming environment is related to higher expression levels of innate immunity genes and protects against asthma development during childhood.[21] In an earlier study, long-term and early-life exposure to stables and farm milk was associated with the highest protective effect against asthma development in children.[38] In another study, farm-like indoor microbiota in nonfarm homes also protected children from asthma development.[39]

However, not all farming exposures protect against asthma in children.[21] Children with a larger relative environmental exposure to swine animal feeding operations had increased asthma risk (OR 1.51).[40] In young adults aged 16–26 years, asthma risk for those born and raised on a farm was reduced (OR 0.50), whereas childhood exposure to large-scale swine and dairy feeding operations increased asthma risk (OR 3.37).[41] Our finding is similar to those of studies that consider childhood exposure to farming as a protective factor against adult-onset asthma under 50 years of age.[17,18]

Interpretation of the Results

It has been proposed that the agricultural environment offers a rich microbial environment that reduces aberrant Th2 activation and reduces the risk of allergic asthma.[18–20] Growing up on a farm leads to a lifelong protective effect against allergic rhinitis.[42] In contrast, our study indicates that the protective effect on asthma might not be lifelong.

On the other hand, farming offers exposure to environmental factors, leading to repeated injury of the airway epithelium that enhances mucosal permeability of foreign substances and further leads to epithelial barrier fragility.[43] Thus, epithelial cytokines (eg, interleukin-25, interleukin-33, and thymic stromal lymphopoietin) released upon stimulation from environmental exposure can activate innate lymphoid cells (ILC2s) in an allergen-independent manner, leading to the development of nonallergic T2-high asthma.[44,45]

ILCs are predominantly tissue-resident cells, and the perinatal period is critical for the distribution of ILCs within developing organs, especially ILC2s.[46] It seems that the ILC pool residing in a given tissue is the result of waves of development from fetal to adult life (a phenomenon termed layered ontogeny) and may include different ILC subsets.[47] ILC plasticity has been demonstrated in humans, and the change from ILC3s and ILC2s into ILC1s requires inflammatory cytokines (eg, interleukin-15, interleukin-23, interleukin-12, and interleukin-1b).[48] This conversion is likely impacted by infections and other cytokine microenvironmental changes, such as in autoimmunity.[48] Late-onset asthma is often considered to be mainly T2-low asthma; activation of Th1 and Th17 cells (type 1 and type 3 immunity, respectively) leads to neutrophil activation, and both T2 and non-T2 inflammatory pathways lead to airway remodeling.[31,49]

We hypothesize that in addition to microbial biodiversity, the childhood farming environment presents early harmful exposure to irritants that tease the epithelium and lead to epithelial barrier fragility. Over time, possibly the presence of cumulative exposure to various irritants (eg, occupational exposure, smoking) leads to layered ontogeny or ILC plasticity and generates an adult cell pool composed of cells of different origins. Cumulative exposure may lead to airway inflammation not mediated by ILC2s and to the development of T2-low late-onset asthma.

Strengths and Limitations

The strengths of the study were its large general population-based random sample and use of a validated questionnaire. Asthma diagnoses are based on objective lung function measurements and are reliable in Finland because of reimbursement policies.[53] The age at asthma diagnosis corresponded with the asthma reimbursement data, in which 24.7% had early-diagnosed asthma, 28.3% had intermediate-diagnosed asthma, and 47.0% had late-diagnosed asthma when an age distribution similar to that in this study was applied.[49]

As a limitation of the present study, recall bias concerning the age at asthma diagnosis is possible, considering that the recall periods are long. However, the start date of reimbursement is stated on reimbursement cards and is similar to age at diagnosis, reducing the possibility of recall bias. Furthermore, the age at asthma diagnosis might differ from the age at asthma onset; a person can have symptoms as a child but obtain a diagnosis later in life. Nonetheless, a previous study showed that the self-reported age at asthma onset in adults is accurate.[54] Unfortunately in this kind of study, it is difficult to ascertain the connection between the timing of asthma diagnosis and timing of factors occurring later in life (eg, smoking, exposure to VGDF, and BMI), which may be a source of bias.

Another limitation was the response rate of 52.3%. Young age groups and males were underrepresented, and in a similar Swedish cohort, nonresponders did not affect prevalence estimates.[55] However, the response rate among those over 40 years of age was 61.7%. A methodological weakness is that younger subjects are less likely to grow up on a farm because of increasing urbanization. These younger subjects cannot have late-onset asthma because of their young age, which can introduce bias. Analyses in a population aged over 40 years and over 60 years adjusted for age were conducted to address this bias due to the cross-sectional design. Even in these analyses, the childhood farming environment had higher odds of late-diagnosed asthma. We performed sensitivity analyses to reduce the potential bias of misdiagnosis by excluding those with coexisting COPD or current farmers. In these analyses, the childhood farming environment still presented higher odds for late-diagnosis asthma.

Additionally, we validated the main finding in a more urban and heterogeneous Helsinki FinEsS survey. In Helsinki 434 subjects had physician-diagnosed asthma, and there were 415 responders for age at diagnosis. Of those, 131 (31.6%) had early-diagnosed asthma, 184 (44.3%) had intermediate-diagnosed asthma, and 100 (24.1%) had late-diagnosed asthma. Of those with physician-diagnosed asthma with a known age at diagnosis, 184 (42.4%) in Western Finland and 47 (11.5%) in Helsinki had childhood exposure to a farming environment.

Our study population in Western Finland is genetically homogenous,[23] but we cannot exclude genetic variations, such as in Toll-like receptor 6.[56] Because of selective

migration, children do not receive protection against early-onset asthma, because parents move away from the farming environment because of their asthma.[57] Use of physician-diagnosed allergic rhinitis as a marker for allergies has limitations, because the association between allergic sensitization and rhinitis is strongest among the youngest age groups.[58]

Clinical Implications

Asthma protection resulting from exposure to the farming environment might not be lifelong. A recent Finnish birth cohort study showed that a childhood farm environment protected from allergic sensitizations until middle age but it did not protect from new allergic sensitizations as an adult.[59] One way forward could be a study boosting immunity with farm-like microbiota in adults to see whether it reduces asthma risk for non-T2 late-onset asthma, similar to protection seen in early-onset asthma.[39] Consideration may be given to modifying adult immune and allergic responses by re-exposure of adults to farm environments without exposure to chemicals, gases, and fumes. Children should be protected from harmful exposures but be exposed to biodiversity, animals, and microbes for good respiratory health. Further studies are needed on which exact causative agents in the farming milieu are protective or harmful. Our study shows that a childhood farming environment is associated with late-diagnosed asthma, and this should be assessed when evaluating an older person for asthma.

Conclusion

We found that the asthma diagnosis age is essential for epidemiologic studies. The difference in median age at diagnosis was 17 years for those not exposed and exposed for childhood farming environment, however the prevalence of asthma as an adult was the similar in both groups. The childhood exposure to farming environment protected against asthma before the age of 40 years but had higher odds in late-onset asthma. Further prospective epidemiological and genetic studies are needed to resolve the risk factor heterogeneity among different age groups at asthma diagnosis.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article (and its Supplementary Information File). According to ethical permission and data-protection laws of Finland, single-person data cannot be made available.

Compliance with Ethical Standard

Informed written consent was obtained from all individual participants. The Ethics Committee of the Department of Medicine of Helsinki University Central Hospital approved this study (approval number 200/13/03/00/15). The study was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

HA, JH, ER, AS, LL, PP have nothing to disclose. Dr Ilmarinen is an employee of GlaxoSmithKline. Dr Ilmarinen reports personal fees from Astra Zeneca, GlaxoSmithKline, Mundipharma, and Novartis outside the submitted work. Dr Tuomisto reports personal fees and non-financial support from Boehringer-Ingelheim, personal fees from Astra Zeneca, outside the submitted work. Dr Hisinger-

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References

1. de Nijs SB, Venekamp LN, Bel EH. Adult-onset asthma: is it really different? *Eur Respir Rev*. 2013;22(127):44–52. doi:10.1183/09059180.00007112
2. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med*. 2012;18(5):716–725. doi:10.1038/nm.2678
3. Jartti T, Bønnelykke K, Elenius V, Feleszko W. Role of viruses in asthma. *Semin Immunopathol*. 2020;42:61–74. doi:10.1007/s00281-020-00781-5
4. Bisgaard H, Bonnelykke K. Long-term studies of the natural history of asthma in childhood. *J Allergy Clin Immunol*. 2010;126(2):187–197. doi:10.1016/j.jaci.2010.07.011
5. Paaso EMS, Jaakkola MS, Rantala AK, Hugg TT, Jaakkola JJK. Allergic diseases and asthma in the family predict the persistence and onset-age of asthma: a prospective cohort study. *Respir Res*. 2014;15:152. doi:10.1186/s12931-014-0152-8
6. Honkamäki J, Piirilä P, Hisinger-Mölkänen H, et al. Asthma remission by age at diagnosis and gender in a population-based study. *J Allerg Clin Immunol Pract*. 2021;9(5):1950–1959. doi:10.1016/j.jaip.2020.12.015
7. Amelink M, De Nijs SB, De Groot JC, et al. Three phenotypes of adult-onset asthma. *Allerg Eur J Allerg Clin Immunol*. 2013;68(5):674–680. doi:10.1111/all.12136
8. Ilmarinen P, Tuomisto LE, Kankaanranta H. Phenotypes, risk factors, and mechanisms of adult-onset asthma. *Mediators Inflamm*. 2015;2015:1–19. doi:10.1155/2015/514868
9. Tuomisto LE, Ilmarinen P, Niemelä O, Haanpää J, Kankaanranta T, Kankaanranta H. A 12-year prognosis of adult-onset asthma: Seinäjoki Adult Asthma Study. *Respir Med*. 2016;117:223–229. doi:10.1016/j.rmed.2016.06.017
10. Almqvist C, Worm M, Leynaert B. Impact of gender on asthma in childhood and adolescence: a GA 2LEN review. *Allerg Eur J Allerg Clin Immunol*. 2008;63(1):47–57.
11. Håland G, Carlsen KCL, Sandvik L, et al. Reduced lung function at birth and the risk of asthma at 10 years of age. *N Engl J Med*. 2006;355(16):1682–1689. doi:10.1056/NEJMoa052885
12. Khreis H, Cirach M, Mueller N, et al. Outdoor air pollution and the burden of childhood asthma across Europe. *Eur Respir J*. 2019;54(4):1802194. doi:10.1183/13993003.02194-2018
13. Silvestri M, Franchi S, Pistorio A, Petecchia L, Rusconi F. Smoke exposure, wheezing, and asthma development: a systematic review and meta-analysis in unselected birth cohorts. *Pediatr Pulmonol*. 2015;50(4):353–362. doi:10.1002/ppul.23037
14. Egan KB, Ettinger AS, Bracken MB. Childhood body mass index and subsequent physician-diagnosed asthma: a systematic review and meta-analysis of prospective cohort studies. *BMC Pediatr*. 2013;13(1):1–3. doi:10.1186/1471-2431-13-121
15. Pividori M, Schoettler N, Nicolae DL, Ober C, Im HK. Shared and distinct genetic risk factors for childhood-onset and adult-onset asthma: genome-wide and transcriptome-wide studies. *Lancet Respir Med*. 2019;7(6):509–522. doi:10.1016/S2213-2600(19)30055-4
16. Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol*. 2018;141(4):1169–1179. doi:10.1016/j.jaci.2018.02.004
17. Leynaert B, Neukirch C, Jarvis D, Chinn S, Burney P, Neukirch F. Does living on a farm during childhood protect against asthma, allergic rhinitis, and atopy in adulthood? *Am J Respir Crit Care Med*. 2001;164(10):1829–1834. doi:10.1164/ajrccm.164.10.2103137
18. Douwes J, Travier N, Huang K, et al. Lifelong farm exposure may strongly reduce the risk of asthma in adults. *Allergy*. 2007;62(10):1158–1165. doi:10.1111/j.1398-9995.2007.01490.x
19. Birzele LT, Depner M, Ege MJ, et al. Environmental and mucosal microbiota and their role in childhood asthma. *Allerg Eur J Allerg Clin Immunol*. 2017;72(1):109–119. doi:10.1111/all.13002
20. Von Ehrenstein OS, Von Mutius E, Illi S, Baumann L, Böhm O, Von Kries R. Reduced risk of hay fever and asthma among children of farmers. *Clin Exp Allergy*. 2000;30(2):187–193. doi:10.1046/j.1365-2222.2000.00801.x
21. Ege MJ, Frei R, Bieli C, et al. Not all farming environments protect against the development of asthma and wheeze in children. *J Allergy Clin Immunol*. 2007;119(5):1140–1147. doi:10.1016/j.jaci.2007.01.037
22. House JS, Wyss AB, Hoppin JA, et al. Early-life farm exposures and adult asthma and atopy in the Agricultural Lung Health Study. *J Allergy Clin Immunol*. 2017;140(1):249–256. doi:10.1016/j.jaci.2016.09.036
23. Kerminen S, Havulinna AS, Hellenthal G, et al. Fine-scale genetic structure in Finland. *G3 (Bethesda)*. 2017;7(10):3459–3468. doi:10.1534/g3.117.300217
24. Honkamäki J, Hisinger-Mölkänen H, Ilmarinen P, et al. Age- and gender-specific incidence of new asthma diagnosis from childhood to late adulthood. *Respir Med*. 2019;154:56–62. doi:10.1016/j.rmed.2019.06.003
25. Hisinger-Mölkänen H, Pallasaho P, Haahtela T, Lindqvist A, Sovijärvi A, Piirilä P. The increase of asthma prevalence has levelled off and symptoms decreased in adults during 20 years from 1996 to 2016 in Helsinki, Finland. *Respir Med*. 2019;155:121–126. doi:10.1016/j.rmed.2019.07.014
26. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol*. 2004;113(1):101–108. doi:10.1016/j.jaci.2003.10.041
27. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet*. 2010;376(9743):803–813. doi:10.1016/S0140-6736(10)61087-2
28. Pakkasela J, Ilmarinen P, Honkamäki J, et al. Age-specific incidence of allergic and non-allergic asthma. *BMC Pulm Med*. 2020;20(1):9. doi:10.1186/s12890-019-1040-2
29. Eduard W, Douwes J, Omenaas E, Heederik D. Do farming exposures cause or prevent asthma? Results from a study of adult Norwegian farmers. *Thorax*. 2004;59(5):381–386. doi:10.1136/thx.2004.013326
30. Douwes J, Gibson P, Pekkanen J, Pearce N. Non-eosinophilic asthma: importance and possible mechanisms. *Thorax*. 2002;57:643–648. doi:10.1136/thorax.57.7.643
31. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. *J Allergy Clin Immunol*. 2019;144(1):1–12. doi:10.1016/j.jaci.2019.05.031
32. Eduard W, Pearce N, Douwes J. Chronic bronchitis, COPD, and lung function in farmers: the role of biological agents. *Chest*. 2009;136(3):716–725. doi:10.1378/chest.08-2192
33. May S, Romberger DJ, Poole JA. Respiratory health effects of large animal farming environments. *J Toxicol Environ Health Part B Crit Rev*. 2012;15(8):524–541. doi:10.1080/10937404.2012.744288

34. Wells AD, Poole JA, Romberger DJ. Influence of farming exposure on the development of asthma and asthma-like symptoms. *Int Immunopharmacol*. 2014;23(1):356–363. doi:10.1016/j.intimp.2014.07.014
35. Wlasiuk G, Vercelli D. The farm effect, or: when, what and how a farming environment protects from asthma and allergic disease. *Curr Opin Allergy Clin Immunol*. 2012;12(5):461–466. doi:10.1097/ACI.0b013e328357a3bc
36. Alfvén T, Braun-Fahrländer C, Brunekreef B, et al. Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle - the PARSIFAL study. *Allerg Eur J Allerg Clin Immunol*. 2006;61(4):414–421. doi:10.1111/j.1398-9995.2005.00939.x
37. Illi S, Depner M, Genuneit J, et al. Protection from childhood asthma and allergy in Alpine farm environments - the GABRIEL advanced studies. *J Allergy Clin Immunol*. 2012;129(6):1470–1477. doi:10.1016/j.jaci.2012.03.013
38. Riedler J, Braun-Fahrländer C, Eder W, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet*. 2001;358(9288):1129–1133. doi:10.1016/S0140-6736(01)06252-3
39. Kirjavainen PV, Karvonen AM, Adams RI, et al. Farm-like indoor microbiota in non-farm homes protects children from asthma development. *Nat Med*. 2019;25:1089–1095. doi:10.1038/s41591-019-0469-4
40. Pavilonis BT, Sanderson WT, Merchant JA. Relative exposure to swine animal feeding operations and childhood asthma prevalence in an agricultural cohort. *Environ Res*. 2013;122:74–80. doi:10.1016/j.envres.2012.12.008
41. Omland Ø, Hjort C, Pedersen OF, Miller MR, Sigsgaard T. New-onset asthma and the effect of environment and occupation among farming and nonfarming rural subjects. *J Allergy Clin Immunol*. 2011;128(4):761–765. doi:10.1016/j.jaci.2011.06.006
42. Eriksson J, Ekerljung L, Lötvall J, et al. Growing up on a farm leads to lifelong protection against allergic rhinitis. *Allerg Eur J Allerg Clin Immunol*. 2010;65(11):1397–1403. doi:10.1111/j.1398-9995.2010.02397.x
43. Gon Y, Hashimoto S. Role of airway epithelial barrier dysfunction in pathogenesis of asthma. *Allergol Int*. 2018;67(1):12–17. doi:10.1016/j.alit.2017.08.011
44. Walker JA, Barlow JL, McKenzie ANJ. Innate lymphoid cells-how did we miss them? *Nat Rev Immunol*. 2013;13(2):75–87. doi:10.1038/nri3349
45. Dhariwal J, Cameron A, Trujillo-Torralbo MB, et al. Mucosal type 2 innate lymphoid cells are a key component of the allergic response to aeroallergens. *Am J Respir Crit Care Med*. 2017;195(2):1586–1596. doi:10.1164/rccm.201609-1846OC
46. Schneider C, Lee J, Koga S, et al. Tissue-resident group 2 innate lymphoid cells differentiate by layered ontogeny and in situ perinatal priming. *Immunity*. 2019;50(6):1425–1438. doi:10.1016/j.immuni.2019.04.019
47. Meininger I, Carrasco A, Rao A, Soini T, Kokkinou E, Mjösberg J. Tissue-specific features of innate lymphoid cells. *Trends Immunol*. 2020;41(10):902–917. doi:10.1016/j.it.2020.08.009
48. Colonna M. Innate lymphoid cells: diversity, plasticity, and unique functions in immunity. *Immunity*. 2018;48(6):1104–1117. doi:10.1016/j.immuni.2018.05.013
49. Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. *J Allergy Clin Immunol*. 2015;135(3):626–635. doi:10.1016/j.jaci.2014.11.001
50. Melgert BN, Ray A, Hylkema MN, Timens W, Postma DS. Are there reasons why adult asthma is more common in females? *Curr Allergy Asthma Rep*. 2007;7(2):143–150. doi:10.1007/s11882-007-0012-4
51. Dykewicz MS. Occupational asthma: current concepts in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol*. 2009;123(3):519–528. doi:10.1016/j.jaci.2009.01.061
52. Smith AM. The epidemiology of work-related asthma. *Immunol Allergy Clin North Am*. 2011;31(4):663–675. doi:10.1016/j.iac.2011.07.009
53. Kankaanranta H, Tuomisto LE, Ilmarinen P. Age-specific incidence of new asthma diagnoses in Finland. *J Allergy Clin Immunol Pract*. 2017;5(1):189–191. doi:10.1016/j.jaip.2016.08.015
54. Torén K, Palmqvist M, Löwhagen O, Balder B, Tunsäter A. Self-reported asthma was biased in relation to disease severity while reported year of asthma onset was accurate. *J Clin Epidemiol*. 2006;59(1):90–93. doi:10.1016/j.jclinepi.2005.03.019
55. Räisänen P, Hedman L, Andersson M, et al. Non-response did not affect prevalence estimates of asthma and respiratory symptoms - results from a postal questionnaire survey of the general population. *Respir Med*. 2020;173:106017. doi:10.1016/j.rmed.2020.106017
56. Lau MYZ, Dharmage SC, Burgess JA, et al. The interaction between farming/rural environment and TLR2, TLR4, TLR6 and CD14 genetic polymorphisms in relation to early- and late-onset asthma. *Sci Rep*. 2017;7:43681. doi:10.1038/srep43681
57. Timm S, Frydenberg M, Abramson MJ, et al. Asthma and selective migration from farming environments in a three-generation cohort study. *Eur J Epidemiol*. 2019;34(6):601–609.
58. Warm K, Hedman L, Lindberg A, Lötvall J, Lundbäck B, Rönmark E. Allergic sensitization is age-dependently associated with rhinitis, but less so with asthma. *J Allergy Clin Immunol*. 2015;136(6):1559–1565. doi:10.1016/j.jaci.2015.06.015
59. Haarala AK, Sinikumpu S, Vaaramo E, et al. A childhood farm environment protects from allergic sensitization until middle age but not from new-onset sensitization in adulthood: a 15 year longitudinal study. *Int J Environ Res Public Health*. 2021;18(7078):7078.

PUBLICATION IV

NSAID-Exacerbated Respiratory Disease (N-ERD): a Population Study

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NSAID-exacerbated respiratory disease: a population study

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Shareable abstract (@ERSpublications)
Population-based prevalence of N-ERD is 1.4%. N-ERD is symptomatic, with a rhinitis subgroup. The risk factors for N-ERD are older age, family history of asthma or allergic rhinitis, long-term smoking and exposure to environmental pollutants. https://bit.ly/3HxGftP

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Abstract

Background Nonsteroidal anti-inflammatory drugs (NSAIDs) may exacerbate respiratory symptoms. A recent European Academy of Allergy and Clinical Immunology position paper recommended the use of an acronym, N-ERD (NSAID-exacerbated respiratory disease), for this hypersensitivity associated with asthma or chronic rhinosinusitis with or without nasal polyposis. Our aim was to estimate the prevalence of N-ERD and identify factors associated with N-ERD.

Methods In 2016, a cross-sectional questionnaire survey of a random adult population of 16 000 subjects aged 20–69 years was performed in Helsinki and Western Finland. The response rate was 51.5%.

Results The prevalence was 1.4% for N-ERD, and 0.7% for aspirin-exacerbated respiratory disease (AERD). The prevalence of N-ERD was 6.9% among subjects with asthma and 2.7% among subjects with rhinitis. The risk factors for N-ERD were older age, family history of asthma or allergic rhinitis, long-term smoking and exposure to environmental pollutants. Asthmatic subjects with N-ERD had a higher risk of respiratory symptoms, severe hypersensitivity reactions and hospitalisations than asthmatic subjects without N-ERD. The subphenotype of N-ERD with asthma was most symptomatic. Subjects with rhinitis associated with N-ERD, which would not be included in AERD, had the fewest symptoms.

Conclusion We conclude that the prevalence of N-ERD was 1.4% in a representative Finnish adult population sample. Older age, family history of asthma or allergic rhinitis, cumulative exposure to tobacco smoke, secondhand smoke, and occupational exposures increased odds of N-ERD. N-ERD was associated with significant morbidity.

Introduction

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may exacerbate respiratory symptoms. Aspirin-exacerbated respiratory disease (AERD) and NSAID-exacerbated respiratory disease (N-ERD) are not interchangeable definitions, although the disease mechanisms are the same. Samter and Beers [1] described AERD in 1968, and the widely used AERD definition includes a triad of aspirin-induced dyspnoea, asthma and rhinosinusitis. Besides aspirin, other NSAIDs can induce dyspnoea. Recently, a new definition of N-ERD was introduced by the European Academy of Allergy and Clinical Immunology (EAACI) [2]. According to the definition, "N-ERD is a chronic eosinophilic inflammatory disorder of the respiratory tract occurring in patients with asthma and/or rhinosinusitis with nasal polyps (CRSwNP), whose symptoms are exacerbated by NSAIDs, including aspirin" [2]. The N-ERD definition is different to

the AERD definition, and further evidence on the clinical relevance of N-ERD compared to AERD is needed.

Patients with N-ERD react to aspirin or other NSAIDs with upper and/or lower airway symptoms usually within 30–180 min [2, 3]. These anaphylactoid reactions are cross-reactive hypersensitivity reactions to an NSAID due to the drug's pharmacological effect, *i.e.* inhibition of the cyclo-oxygenase (COX)-1 enzyme [4]. NSAIDs can cause true allergies or anaphylaxis *via* immunologically mediated single-NSAID-induced reactions [2, 4, 5].

The prevalence of respiratory hypersensitivity reactions to NSAIDs has been 1.9% in a European multicentre study, 1.2% in Finland and 1.3% in Sweden [6–8]. Although extensive AERD research has been carried out, only a limited number of studies have been population-based [7–10]. Most previous AERD prevalence studies have been conducted in asthma or rhinitis patients [11, 12]. These prior approaches did not address the whole N-ERD group, and difficulties might arise when assumptions on prevalence or risk factors are made using earlier, narrower definitions. Interrelationships between NSAID-induced dyspnoea, asthma and rhinitis in N-ERD and subphenotypes of N-ERD are incompletely described [2]. Furthermore, uncertainty still exists regarding the risk factors for N-ERD [8, 13–15].

To fill these gaps in knowledge, this study first aimed to ascertain the prevalence of N-ERD and its risk factors in a cross-sectional random adult population. Second, we explored and identified the relationship between asthma and N-ERD and its subgroups and compared the morbidity rate associated with each of them.

Methods

A cross-sectional survey was conducted in Helsinki and Western Finland as part of the FinEsS (Finland-Estonia-Sweden) study and in collaboration with the Nordic EpiLung study [16]. The population aged 20–69 years in the mainly urban Helsinki and the mostly rural Western Finland was included. In February 2016, the questionnaire was sent to a random sample of 16 000 participants from the Finnish Population Register. Two reminders were sent to those not responding.

Previous publications have detailed the study methods as well as nonresponder data [17, 18]. The response rate was 51.5%, and nonresponders were more often younger and male, which is in line with other studies of nonresponse [19]. Responders with incomplete smoking data (n=269) were excluded (supplementary figure S1). After exclusion, 7930 responders were included in the study. We combined the data from two similar surveys to minimise bias.

Definition of key parameters

NSAID-induced dyspnoea was defined as a positive response to the question "Have you ever experienced difficulties breathing within 3 h of taking a pain killer?" We asked participants to name the pain killer causing difficulties breathing, and 86% named NSAIDs with certainty.

Asthma was defined as a positive response to the question "Have you been diagnosed by a doctor as having asthma?"

Rhinitis was defined as a positive response to one of the following questions: "Have you been diagnosed by a doctor as having allergic rhinitis caused by pollen (from, *e.g.* birch, grass, mugwort)?"; "Have you been diagnosed by a doctor as having other allergic rhinitis (caused by, *e.g.* cat or dog, but not caused by pollen)?"; "Do you have now, or have you had previously, allergic rhinitis (*e.g.* hay fever)?"; "Have you had longstanding nasal congestion?"; and "Have you had longstanding rhinitis?" Nasal polyps were not asked about by name, but nasal congestion associates to nasal polyposis. N-ERD should be considered in patients with asthma and chronic rhinosinusitis whose symptoms are exacerbated after ingestion of aspirin and other COX-1 inhibitors [2].

N-ERD was defined as NSAID-induced dyspnoea with asthma and/or rhinitis.

AERD was defined as a triad of NSAID-induced dyspnoea, asthma and rhinitis.

Definitions of other parameters are included in the supplementary material.

Compliance with ethical standards

General Data Protection Regulation (EU) 2016/679 was followed, and informed written consent was obtained from all individual participants. The ethics committee of the department of medicine of Helsinki

University Central Hospital approved this study (approval number 200/13/03/00/15). It was conducted according to the 1964 Helsinki declaration and its later amendments.

Statistical analysis

Statistical analyses were performed using SPSS Statistics software version 26 (IBM SPSS, Armonk, NY, USA). We used ANOVA to compare means, with Tukey *post hoc* analyses. Pearson's Chi-squared test was used to compare categorical variables with z-tests for multiple categories. A p-value <0.05 was considered significant. With indirect standardisation, the age-standardised symptom ratio (SR) was counted as actual symptoms divided by expected symptoms. The total cohort was the standard population. Symptom rates were calculated as the sum of symptoms per 1000 people in 10-year-interval age groups.

To study risk factors for N-ERD, we performed multivariable binary logistic regression analyses to calculate odds ratios with 95% confidence intervals using N-ERD as a dependent variable. The independent variables were age, sex, family history of asthma, family history of allergic rhinitis, cumulative exposure (smoking (current or ex-smoking), secondhand smoke (at home or work) or occupational exposure to vapours, gases, dusts and fumes (VGDF)), body mass index and living on a farm during the first 5 years of life.

Results

The prevalence of NSAID-induced dyspnoea was 1.7% (n=132) in the study population. A significant prevalence difference was observed between centres: the prevalence was 2.0% (n=79) in rural Western Finland *versus* 1.3% (n=53) in urban Helsinki (p=0.023).

The Venn diagram in figure 1 presents the interrelationship between NSAID-induced dyspnoea, asthma and rhinitis; how the N-ERD group was defined; and how the definition and prevalence differ from those of AERD. Of the responders, 11.1% (n=879) had asthma and 49.8% (n=3952) had rhinitis. A small subgroup of persons reported NSAID-induced dyspnoea, but did not have asthma or rhinitis (0.3%, n=22); thus, they were not included in the N-ERD group.

The prevalence of N-ERD was 1.4% (n=110), and that of AERD was 0.7% (n=56). The prevalence of N-ERD was 1.1% (n=89) with longstanding nasal congestion. The prevalence of N-ERD was 6.9% (n=61) among patients with asthma and 2.7% among patients with rhinitis (n=105).

Characteristics of N-ERD

The patient characteristics of the N-ERD, asthma without N-ERD, rhinitis without N-ERD and NSAID-induced dyspnoea without N-ERD groups are shown in table 1. The mean age of subjects with

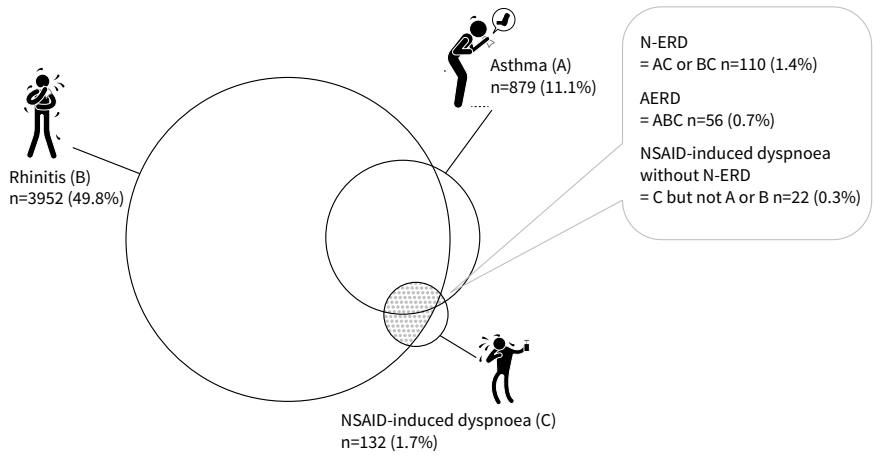

FIGURE 1 Proportional Venn diagram describing the overlap of asthma, rhinitis, nonsteroidal anti-inflammatory drug (NSAID)-induced dyspnoea, the definition of NSAID-exacerbated respiratory disease (N-ERD) and how it differs from aspirin-exacerbated respiratory disease (AERD) and NSAID-induced dyspnoea without N-ERD.

TABLE 1 Characteristics of nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD), asthma, rhinitis and NSAID-induced dyspnoea without N-ERD

	N-ERD	Asthma without N-ERD	Rhinitis without asthma or N-ERD	NSAID-induced dyspnoea without N-ERD	p-value
Patients	110	818	3168	22	
Age years	52±14	46±15*	46±14*	53±16	<0.001
Female	72 (65.5)	460 (56.2)	1767 (55.8)	16 (72.7)	0.090
BMI kg·m^{-2}	27.3±5.7	26.7±5.2	26.1±7.4	26.6±15.5	0.049
Age at asthma diagnosis years	32±17	25±18*	NA	NA	0.021
Asthma diagnosis					
<12 years	10 (16.4)	235 (30.1)	NA	NA	0.027
12–39 years	24 (39.3)	334 (42.8)			
⩾40 years	27 (44.3)	212 (27.1)			
Physician-diagnosed allergic rhinitis	48 (43.6)	471 (57.6)*	1264 (39.6)	0 (0.0)*	<0.001
Physician-diagnosed COPD	17 (15.5)	67 (8.2)	68 (2.1)*	0 (0.0)	<0.001
Family history of asthma	53 (48.2)	355 (43.4)	823 (26.0)*	5 (22.7)	<0.001
Never-smoker	49 (44.5)	383 (47.2)*	1689 (53.3)	6 (27.3)	<0.001
Current smoker	24 (21.8)	192 (23.5)	724 (22.9)	10 (45.5)	
Ex-smoker	37 (33.6)	240 (29.3)*	755 (23.8)	6 (27.3)	
Occupational exposure to VGDF	48 (45.7)	308 (38.8)	1064 (34.2)	5 (23.8)	0.007
Childhood exposure to farming environment	43 (39.8)	210 (26.2)*	702 (22.4)*	5 (29.4)	<0.001

Data are presented as n, mean±SD or n (%), unless otherwise stated. Missing data in the N-ERD group: body mass index (BMI) n=2, occupational exposure to vapours, gases, dusts and fumes (VGDF) n=3, childhood exposure to farming environment n=2. ANOVA was used for continuous variables with Tukey's *post hoc* test to determine statistically significant differences and multigroup comparisons. Pearson's Chi-squared test with the z-test was used for categorical variables. NA: not applicable. *: p<0.05 *versus* N-ERD group.

N-ERD was 52 years. The mean age of asthma diagnosis was 32 years, both being higher than in asthma without N-ERD, and the asthma diagnosis in N-ERD was made mainly after the 12th birthday (>83% of cases) and is often late-adult in onset (44% after age 40 years) (table 1). Childhood exposure to farming environment was more common in N-ERD than in asthma. Supplementary table S1 shows a comparison between N-ERD and healthy controls.

N-ERD compared to asthma

Dyspnoea modified Medical Research Council (mMRC) score ⩾2, tightness in the chest, sputum production and constant nasal blocking were more common in N-ERD than in asthma without N-ERD. No difference in wheezing or longstanding cough was evident between the groups (figure 2, supplementary table S2). Age-standardised symptom ratios were calculated, and in them, dyspnoea mMRC score ⩾2 had an SR of 4.0 in N-ERD and 2.9 in asthma without N-ERD compared to the total cohort (supplementary table S2).

The prevalence of severe allergic reactions or anaphylaxis was higher in N-ERD than in asthma without N-ERD (13.6% *versus* 5.3%, p<0.001). Drug reactions, mainly to NSAIDs, were the most common cause of anaphylaxis in N-ERD. Food reactions were the most common cause in asthma without N-ERD. The prevalence of asthma hospitalisations was two times higher in the N-ERD group than in the asthma without N-ERD group (4.5% *versus* 1.7%, p=0.049) (supplementary table S3).

Is the N-ERD definition valid?

To identify whether the rhinitis-only subgroup, not included in AERD, was clinically relevant, we decided to compare it to those with asthma (AERD) and those with only NSAID-induced dyspnoea. We decided to include eight patients with NSAID-induced dyspnoea with rhinitis and COPD, but without asthma in the asthma group due to their respiratory disease. Distinguishing between obstructive respiratory diseases can be challenging, both in clinical work and in surveys.

We compared the groups with NSAID-induced dyspnoea without N-ERD (n=22), rhinitis alone (n=46) and asthma (with or without rhinitis) (n=64). Figure 3 shows a clear trend of increasing respiratory symptoms, with the mildest symptoms in NSAID-induced dyspnoea without N-ERD and the most severe symptoms in the N-ERD subgroups (figure 3, supplementary table S4). The prevalence of severe allergic reactions/

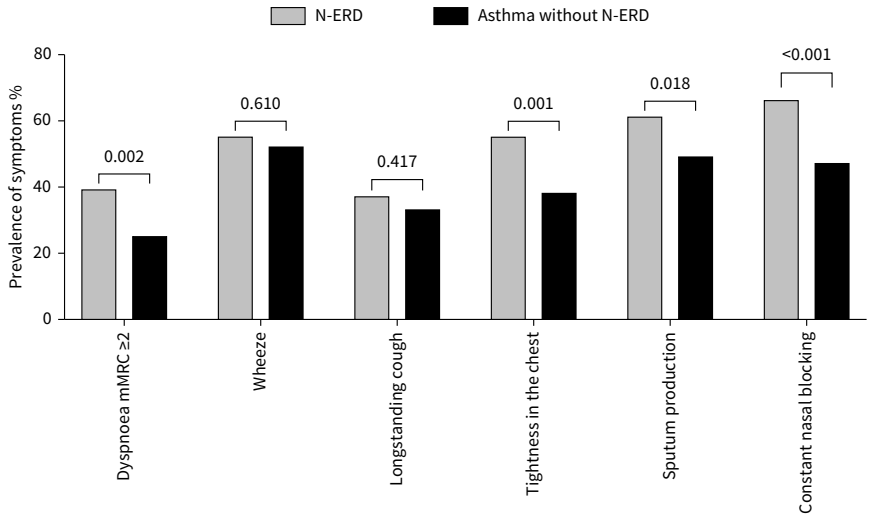

FIGURE 2 The prevalence of respiratory symptoms in nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) (n=110) and asthma without N-ERD (n=818). Comparison between groups was made using Pearson's Chi-squared test.

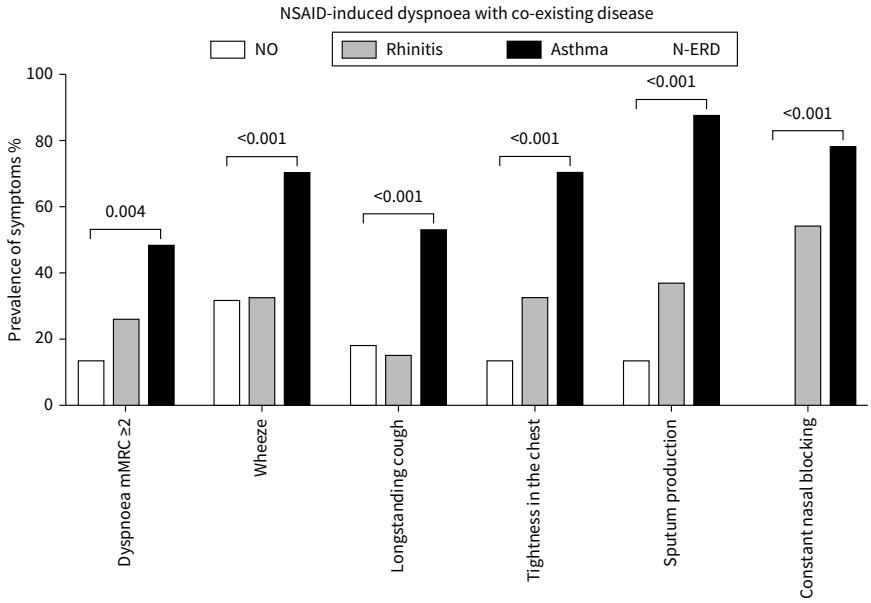

FIGURE 3 The prevalence of respiratory symptoms in nonsteroidal anti-inflammatory drug (NSAID)-induced dyspnoea without co-existing disease but with rhinitis or asthma; the latter two being NSAID-exacerbated respiratory disease (N-ERD) subgroups and the last one being part of aspirin-exacerbated respiratory disease. Comparison between groups was made using Pearson's Chi-squared test with the z-test.

TABLE 2 Factors associated with nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) determined by multivariable binary logistic regression

	Crude OR (95% CI)	Adjusted[#] OR (95% CI)
Age		
20–39 years (ref.)		
40–59 years	2.15 (1.25–3.68)	2.11 (1.19–3.76)
60–69 years	2.90 (1.68–4.99)	3.08 (1.68–5.64)
Female sex	1.57 (1.06–2.33)	1.46 (0.94–2.28)
Family history of asthma	2.98 (2.04–4.34)	2.34 (1.53–3.57)
Family history of allergic rhinitis	2.46 (1.68–3.59)	2.47 (1.60–3.83)
Cumulative exposure[¶]		
0 exposures (ref.)		
1 exposure	1.63 (0.97–2.75)	1.49 (0.86–2.59)
2 exposures	2.65 (1.53–4.57)	2.41 (1.34–4.34)
3 exposures	3.83 (1.98–7.39)	3.68 (1.82–7.46)
BMI		
<25 kg·m^{-2} (ref.)		
25–29.99 kg·m^{-2}	1.27 (0.82–1.98)	1.02 (0.64–1.64)
⩾30 kg·m^{-2}	1.72 (1.05–2.81)	1.14 (0.67–1.95)
Childhood exposure to farming environment	1.75 (1.18–2.57)	1.38 (0.90–2.12)

Ref.: reference category (without N-ERD); BMI: body mass index. [#]: adjusted to all variables in the model; [¶]: cumulative exposure was classified from zero to three exposures calculating smoking (current or ex-smoking), secondhand smoke (smoke exposure at home or at work) and occupational exposure to vapours, gases, dusts and fumes.

anaphylaxis during the past year was similar between the N-ERD subgroups and those with NSAID-induced dyspnoea without N-ERD (supplementary table S5).

Factors associated with N-ERD

We performed univariable and multivariable binary logistic regression analyses to evaluate factors associated with N-ERD. In these analyses, N-ERD was compared to a reference category of those without N-ERD. Older age, family history of asthma, allergic rhinitis and a cumulative total of two or three exposures to particulate matter had higher odds for N-ERD in adjusted analyses, whereas childhood exposure to farming environment increased odds only in unadjusted analyses (table 2). Cumulative exposure was classified as zero to three exposures to smoking (current or ex-smoking), secondhand smoke (smoke exposure at home or work) and/or occupational exposure to VGDF. Unadjusted and adjusted analyses for these components of exposure are shown in supplementary table S6.

Discussion

The recent EAACI position paper recommended that N-ERD is a more proper term to describe the syndrome of respiratory hypersensitivity to NSAIDs associated with asthma and/or chronic rhinosinusitis with nasal polyposis. N-ERD has a broader definition than the previous AERD. This study showed that the prevalence of N-ERD in a random population sample was 1.4%. The risk factors were older age, family histories of asthma and allergic rhinitis and the dose-response to cumulative exposure to tobacco smoke, secondhand smoke and occupational particulate matter. Asthma in N-ERD mainly had an adult onset. Compared to asthma without N-ERD, participants with N-ERD were more symptomatic.

Comparison to previous prevalence studies

We found a population-based prevalence of 1.4% for N-ERD. The prevalence of AERD was 0.7%, similar to that reported by other population-based studies, 0.5% in Sweden and 0.6% in Poland, externally validating our results [8, 9]. In contrast to the previous AERD definition, the N-ERD definition includes those patients with only one disease combined with respiratory hypersensitivity reactions to NSAIDs, such as chronic rhinosinusitis with polyposis. Therefore, the prevalence of AERD is only half that of N-ERD. In patients with asthma, the N-ERD definition is similar to the previous AERD definition. To illustrate, the prevalence of N-ERD was 6.9% among participants with asthma in our study, similar to a recent meta-analysis reporting a 7.2% prevalence of AERD [11]. However, the prevalence of N-ERD among participants with asthma in our study was somewhat lower than the 9.0% reported based on the oral provocation challenge test and 9.9% noted in a questionnaire-based survey among adults with asthma [12].

The prevalence of respiratory hypersensitivity reactions to NSAIDs found in our study, 1.7%, was similar to that previously reported [6–8]. The prevalence of NSAID-induced dyspnoea showed variation between rural and urban centres in our research. These results corroborate the findings of a study comparing the prevalence of NSAID-induced dyspnoea between 15 countries, where it was reported to be lowest, at 0.9%, in the city of Skopje and highest, at 4.9%, in the city of Katowice [6]. These and our results support a possible role for environmental factors in N-ERD pathogenesis.

The natural history of N-ERD

N-ERD is a new disease definition, so much of our knowledge on the risk factors and pathogenesis comes from studies on AERD. Pathological changes in N-ERD and/or AERD have been proposed to involve chronic immune dysregulation, T2 immunity with eosinophils, mast cells, group 2 innate lymphoid cell infiltration and genetic variation in diverse molecular pathways of arachidonic acid metabolism [2, 3, 20]. In a previous study, a family history of AERD was a risk factor for AERD [13], and a family history of asthma and allergic rhinitis were risk factors for N-ERD in our study, confirming that hereditary and/or genetic factors play a role in the pathogenesis of N-ERD.

Our study strengthens previous evidence derived from studies on AERD on the role of occupational exposure to VGDF and smoke exposure as risk factors [8, 15]. We found an increased risk of N-ERD with cumulative exposure, in concordance with a previous study where the risk of AERD was higher for those with smoking exposure both as a child and as an adult [15]. One possible pathway mediating this is that tobacco smoke and other environmental exposures are drivers of microbial dysbiosis in the airways [21]. For example, IgE antibodies to *Staphylococcus aureus* enterotoxin were significantly increased in patients with CRSwNP and AERD compared with controls and CRSwNP without AERD [22]. Much uncertainty still exists about the accumulation of factors sufficient for the disease process to begin. Still, our study supports the idea that the risk is higher and possibly dose-dependent with cumulative exposure to particulate matter. Childhood exposure to farming environment was significantly more common in N-ERD than asthma without N-ERD, whereas a nonsignificant trend was seen compared to healthy controls. In our recent study, childhood exposure to farming environment had lower odds of early-diagnosed asthma and higher odds of late-diagnosed asthma [23].

The latency period of N-ERD might be decades. According to a previous study, NSAID hypersensitivity may occur before the onset of apparent respiratory disease, usually marking the beginning of asthma/CRSwNP [2]. The group with NSAID-induced dyspnoea without N-ERD in our survey conceivably represents subclinical disease. This group had a similar age to the N-ERD group, but less family history of asthma. Upper airway symptoms might precede asthma by 1–5 years in N-ERD [24], upper airway disease in N-ERD is usually CRSwNP and upper respiratory symptoms are on average worse than in NSAID-tolerant patients [25]. In line with previous reports, the onset of symptoms and the usual time of diagnosis are in the third or fourth decades of life in subjects with AERD [26]. In our study, the mean age of the asthma diagnosis was higher in N-ERD than in asthma without N-ERD. The prevalence of N-ERD increased with age, similar to previous findings on AERD [8].

The majority of N-ERD participants were female and overweight, parallel to previous findings [8, 14]. Our results reflect other studies showing that upper airway disease in N-ERD patients was dominated by nasal blockage and/or nasal congestion [27]. In contrast to results from another cohort [27], most of the rhinitis was nonallergic in the current study. In our study, dyspnoea mMRC score $\geqslant$2, tightness in the chest, sputum production and constant nasal blockage were more common in N-ERD than in asthma without N-ERD. In agreement with previous data on AERD, asthma morbidity was increased considerably in N-ERD [8, 12].

N-ERD was associated with morbidity in our study. The rate of hospitalisation due to asthma exacerbation during the past year was twice as high in N-ERD as in asthma without N-ERD. No statistically significant trend was observed in emergency department visits. These results are consistent with results from a multicentre population study in which the risk of uncontrolled asthma in N-ERD patients was increased twofold and asthma-related hospitalisations increased by 40% [12]. Self-reported severe allergic reactions during the past year were more common in N-ERD than in asthma without N-ERD.

In a recent study, the clinical phenotypes of AERD were characterised by genetic variation within multiple pathways for arachidonic acid metabolism, inflammation and immune responses [20]. Asthma in AERD is heterogeneous, as it might be mild, severe or uncontrolled [28]. To evaluate if the N-ERD rhinitis subgroup had undiagnosed asthma, we compared this subgroup to those with asthma and they had milder symptoms but were symptomatic compared to those with only NSAID-induced dyspnoea. Our grouping

might be helpful for clinicians planning treatment together with endotyping different IgE levels, eosinophil counts, plasma tryptase, urinary leukotriene E4 and mast cell-derived prostaglandin D2 [28–31].

Strengths and limitations

This study's strengths were its large general population-based random sample and its validated questionnaire to evaluate the prevalence and risk factors of N-ERD [17, 18, 32]. Although the sample was large, participants with N-ERD were limited in number (n=110). N-ERD subgroups were slightly small for making comparisons, and we could not examine factors associated with different N-ERD phenotypes.

The present study is based on a self-reported diagnosis; thus, the absence of clinical data can be considered a limitation. We consider self-reported physician asthma diagnosis reliable due to reimbursement policies ensuring objective diagnosis. Rhinitis also included allergic rhinitis and was assessed with four questions. Questions regarding nasal polyposis, hyposmia or anosmia were not asked, but longstanding nasal congestion is a symptom of nasal polyposis. With that criterion, the N-ERD prevalence estimate would be slightly lower, at 1.1%. In addition, self-reported reactions probably include milder allergic reactions and might include other mechanisms causing dyspnoea. Compared to the reported frequency of severe allergic reactions, 0.001% annually in Finland [33], the prevalence of severe allergic reactions in our study was high and was most prevalent in the NSAID-induced dyspnoea without N-ERD group. As a possible explanation to the high prevalence of allergic reactions, anaphylaxis has been linked to mast cell activation [33, 34], and recently, mast cell-derived prostaglandin D2 was considered a central pathogenic mediator in N-ERD [29].

Like other recent surveys, this one found that younger individuals and males may be under-represented due to lower participation rates in these subgroups [19, 35]. We combined data from two study centres to minimise bias and increase the sample size due to the moderate response rate. The effect of nonresponder bias may be limited, since the N-ERD patients' mean age and age of asthma onset were higher. Therefore, we consider the results reliable. Despite limitations, this study offers new, clinically important insight into the prevalence and clinical significance of N-ERD.

Clinical implications

A better understanding of pathogenesis may lead to new treatments, and secondary preventive therapies for those with N-ERD rhinitis might stop progression of the disease to asthma in the future. The most common cause of severe allergic reaction in N-ERD was drug reactions, mainly to NSAIDs, so further efforts in patient education about anaphylaxis and public awareness about the avoidance of COX-1 inhibitors might be required.

Conclusions

The prevalence of N-ERD was 1.4% in the Finnish adult population. Risk factors for N-ERD were older age, family histories of asthma and allergic rhinitis and cumulative exposure to tobacco smoke, secondhand smoke and occupational exposures. N-ERD was associated with significant morbidity compared to asthma without N-ERD, although it includes patients with rhinitis. The prevalence of anaphylaxis was higher in N-ERD than in asthma without N-ERD, raising concerns that need further research.

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Data statement: All data generated or analysed during this study are included in this published article (and its supplementary material). According to the ethical permission and data-protection laws of Finland, single-person data cannot be made available.

Author contributions: H. Andersén, P. Ilmarinen, L. Lehtimäki and H. Kankaanranta conceived the design of the study and drafted the manuscript. All authors designed the study, assisted in the acquisition of data, wrote the manuscript, and contributed to the analysis and interpretation of the data. All authors revised the work critically and approved the final version of the manuscript. All authors take responsibility for the accuracy and integrity of the work.

Conflict of interest: H. Andersén, J. Honkamäki, E. Rönmark, A. Sovijärvi, L. Lehtimäki and P. Piirilä have nothing to disclose. P. Ilmarinen is an employee of GlaxoSmithKline, and reports personal fees from AstraZeneca, Mundipharma and Novartis outside the submitted work. L.E. Tuomisto reports personal fees and nonfinancial support from Boehringer Ingelheim, and personal fees from Astra Zeneca, outside the submitted work. H. Hisinger-Mölkänen is an employee of GlaxoSmithKline. H. Backman reports personal fees from AstraZeneca and Boehringer Ingelheim outside the submitted work. B. Lundbäck reports grants from AstraZeneca and ThermoFisher, and personal fees from Sanofi, outside the submitted work. T. Haahtela reports lecturing fees from GSK, Mundipharma, Orion Pharma and Sanofi, outside the submitted work. H. Kankaanranta reports personal fees and nonfinancial support from AstraZeneca, Boehringer Ingelheim and Orion Pharma, and personal fees from Chiesi, Novartis, Mundipharma, SanofiGenzyme and GlaxoSmithKline, outside the submitted work.

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References

1 Samter M, Beers RF. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Ann Intern Med* 1968; 68: 975–983.
2 Kowalski ML, Agache I, Bavbek S, *et al.* Diagnosis and management of NSAID-exacerbated respiratory disease (N-ERD) – a EAACI position paper. *Allergy* 2019; 74: 28–39.
3 Eastman JJ, Cavagnero KJ, Deconde AS, *et al.* Group 2 innate lymphoid cells are recruited to the nasal mucosa in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2017; 140: 101–108.
4 Wöhrl S. NSAID hypersensitivity – recommendations for diagnostic work up and patient management. *Allergo J Int* 2018; 27: 114–121.
5 Doña I, Barrionuevo E, Salas M, *et al.* NSAIDs-hypersensitivity often induces a blended reaction pattern involving multiple organs. *Sci Rep* 2018; 8: 16710.
6 Makowska JS, Burney P, Jarvis D, *et al.* Respiratory hypersensitivity reactions to NSAIDs in Europe: the global allergy and asthma network (GA^2LEN) survey. *Allergy* 2016; 71: 1603–1611.
7 Hedman J, Kaprio J, Poussa T, *et al.* Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 1999; 28: 717–722.
8 Eriksson J, Ekerljung L, Bossios A, *et al.* Aspirin-intolerant asthma in the population: prevalence and important determinants. *Clin Exp Allergy* 2015; 45: 211–219.
9 Kasper L, Sladek K, Duplaga M, *et al.* Prevalence of asthma with aspirin hypersensitivity in the adult population of Poland. *Allergy* 2003; 58: 1064–1066.
10 Vally H, Taylor ML, Thompson PJ. The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients. *Thorax* 2002; 57: 569–574.
11 Rajan JP, Wineinger NE, Stevenson DD, *et al.* Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. *J Allergy Clin Immunol* 2015; 135: 676–681.
12 Morales DR, Guthrie B, Lipworth BJ, *et al.* NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. *Allergy* 2015; 70: 828–835.
13 Bavbek S, Yilmaz I, Çelik G, *et al.* Prevalence of aspirin-exacerbated respiratory disease in patients with asthma in Turkey: a cross-sectional survey. *Allergol Immunopathol* 2012; 40: 225–230.
14 Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2002; 89: 474–478.
15 Chang JE, Ding D, Martin-Lazaro J, *et al.* Smoking, environmental tobacco smoke, and aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2012; 108: 14–19.
16 Axelsson M, Lindberg A, Kainu A, *et al.* Respiratory symptoms increase health care consumption and affect everyday life – a cross-sectional population-based study from Finland, Estonia, and Sweden. *Eur Clin Respir J* 2016; 3: 31024.
17 Hisinger-Mölkänen H, Pallasaho P, Haahtela T, *et al.* The increase of asthma prevalence has levelled off and symptoms decreased in adults during 20 years from 1996 to 2016 in Helsinki, Finland. *Respir Med* 2019; 155: 121–126.
18 Honkamäki J, Hisinger-Mölkänen H, Ilmarinen P, *et al.* Age- and gender-specific incidence of new asthma diagnosis from childhood to late adulthood. *Respir Med* 2019; 154: 56–62.
19 Räisänen P, Hedman L, Andersson M, *et al.* Non-response did not affect prevalence estimates of asthma and respiratory symptoms – results from a postal questionnaire survey of the general population. *Respir Med* 2020; 173: 106017.

20 Dahlin A, Weiss ST. Genetic and epigenetic components of aspirin-exacerbated respiratory disease. *Immunol Allergy Clin North Am* 2016; 36: 765–789.

21 Eguiluz-Gracia I, Mathioudakis AG, Bartel S, *et al.* The need for clean air: the way air pollution and climate change affect allergic rhinitis and asthma. *Allergy* 2020; 75: 2170–2184.

22 Derycke L, Pérez-Novo C, Van Crombruggen K, *et al. Staphylococcus aureus* and chronic airway disease. *World Allergy Organ J* 2010; 3: 223–228.

23 Andersén H, Ilmarinen P, Honkamäki J, *et al.* Influence of childhood exposure to a farming environment on age at asthma diagnosis in a population-based study. *J Asthma Allergy* 2021; 14: 1081–1091.

24 Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. *J Allergy Clin Immunol* 2006; 118: 773–786.

25 Fokkens WJ, Lund VJ, Hopkins C, *et al.* European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology* 2020; 58: Suppl. S29, 1–464.

26 Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J* 2000; 16: 432–436.

27 Stevens WW, Peters AT, Hirsch AG, *et al.* Clinical characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract* 2017; 5: 1061–1070.

28 Bochenek G, Kuschill-Dziurda J, Szafraniec K, *et al.* Certain subphenotypes of aspirin-exacerbated respiratory disease distinguished by latent class analysis. *J Allergy Clin Immunol* 2014; 133: 98–103.

29 Borish L. Aspirin-exacerbated respiratory disease: a syndrome of mast cell-mediated PgD2 overproduction. *Am J Respir Crit Care Med* 2019; 200: 651–652.

30 Lee HY, Ye YM, Kim SH, *et al.* Identification of phenotypic clusters of nonsteroidal anti-inflammatory drugs exacerbated respiratory disease. *Allergy* 2017; 72: 616–626.

31 Cahill KN, Murphy K, Singer J, *et al.* Plasma tryptase elevation during aspirin-induced reactions in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2019; 143: 799–803.

32 Pakkasela J, Ilmarinen P, Honkamäki J, *et al.* Age-specific incidence of allergic and non-allergic asthma. *BMC Pulm Med* 2020; 20: 9.

33 LoVerde D, Iweala OI, Eginli A, *et al.* Anaphylaxis. *Chest* 2018; 153: 528–543.

34 Metcalfe DD, Peavy RD, Gilfillan AM. Mechanisms of mast cell signaling in anaphylaxis. *J Allergy Clin Immunol* 2009; 124: 639–646.

35 Tolonen H, Koponen P, Borodulin K, *et al.* Language as a determinant of participation rates in Finnish health examination surveys. *Scand J Public Health* 2018; 46: 240–243.