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NORDSTAR – Paving the way for a new era in asthma research

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Summary

NORDSTAR is a longitudinal dataset for the study of asthma comprising 3.3 million individuals and over 50 million person-years in four Nordic countries. The data include medication dispensing, use of resources and costs, socio-demographics, and mortality.

Introduction

Asthma is a heterogeneous, chronic airways disease with large variation in prevalence between geographies [1, 2]. In the Nordic countries, prevalence of asthma has been reported to be 10% in Denmark [1], 9–11% in Finland [1, 3], 11–12% in Norway [1], and 8–10% in Sweden [1, 4, 5]. Poor asthma control is associated with substantial reductions in patient quality of life [6-8], higher morbidity and mortality [9, 10], together with significantly increased direct and indirect costs [6, 11].

Comprehensive longitudinal follow-up of asthma patients in routine clinical care is essential to understand the nature of the disease, patient characteristics, and long-term trajectories to ultimately improve patient outcomes. Although many valuable asthma research datasets exist today [12-17], they typically include a limited number of follow-up visits involving clinical assessments for a modest number of patients, and only the Danish National Database for Asthma [18] comprises a nationwide population. In contrast, real-world assessments of entire asthma populations enable descriptions and assessments of patients, disease, and provision of healthcare in routine clinical care.

Each Nordic country maintains nationwide administrative and medical registries that are uniquely suited to studying patients at a population level. For decades, the Nordic countries have enforced mandatory reporting into each administrative registry, enabling complete, longitudinal coverage of each country's population in a real-world context [19] that is not possible in many other countries [20]. The automatic and standardised registration of all residents avoids the burden associated with study participant enrolment and administration [20], effectively minimising resource use and cost. A unique personal identification number (PIN) given to all Nordic residents can be used to link each dataset together at the patient level which aids in avoiding selection bias, which often limits epidemiological studies. Similarities in content and in reporting processes into these Nordic registries facilitates the use of comparable asthma-related definitions, such as severity and control, in addition to consistency in interpretation of results between countries [21].

To the best of our knowledge, there is no existing data containing long-term longitudinal follow-up of asthma populations in routine clinical care across multiple countries built on nation-wide data. A

multinational collaboration was initiated using the NORdic Dataset for aSThmA Research (NORDSTAR) to pursue a common goal of improving asthma patients' quality of life, by bringing together representatives active in clinical practice, academic research, and the pharmaceutical industry. To date, NORDSTAR includes patient-level information from four Nordic countries (Denmark, Finland, Norway, and Sweden). The purpose of this work is to describe NORDSTAR in terms of the patients included, research goals, data sources and contents, and administration of the data as a basis for future research and collaboration.

NORDSTAR data

The NORDSTAR data was retrieved across several years involving a variety of ethical boards, data holders, and research institutions. Ethical approvals were obtained according to the local and EU law and positive decisions regarding personal data protection assessments were received from the responsible authorities in each country Informed consent from individual patients is not required for registry studies on retrospective data in the Nordics and was therefore not obtained.

Each country included in NORDSTAR maintains administrative, population-based registries with complete nation-wide coverage. Healthcare is publicly financed and contacts with the public health care system must be reported by law [20, 21]. These data collection systems are independently and continuously maintained with longitudinal, individual-level information.

In each of the respective countries, the patient-level linkage between each administrative registry were conducted. The national organizations responsible for creating these statistics were: Statistics Denmark, the Swedish National Board of Health and Welfare, and Statistics Finland. No patient-level linkage between registries was performed for data from Norway as all data was extracted from a single registry, the Norwegian Prescribed Drug Registry. The unique PIN provided to each resident is assigned at birth or immigration and subsequently used throughout the patient's life. All data reported into the national registries include the PIN, enabling the extraction and amalgamation of patient-level data across all relevant data sources within each country. All data was pseudonymized before delivery to the research group.

A description of the NORDSTAR variables is presented in Table 1.

Table 1: Variables included in NORDSTAR by country

Variable type	Denmark[1]	Finland[2]	Norway[3]	Sweden[4]
Demographics:				
Year of birth	X	X	X	X
Sex	X	X	X	X
Geography				
Availability	1986–2016	1992–2016	2004–2018	1987–2017
Migration date and type	X			X
Municipality of residence	X			X
County of residence	X	X	X	X
Death				
Availability	2004–2014	2006–2015	2007–2018	2006–2017
Date of death	X	X	X	X
Cause of death	X	X		X
Socioeconomics				
Availability	1990–2015	1987–2015	N/A	2004–2014
Individual disposable income*	X	X		X
Family disposable income*	X	X		X
Sickness benefit*		X		X
Welfare benefit*		X		X
Employment status	X	X		X
Number of days unemployed				X
Number of days with benefits				X
Education level	X	X		X
Primary healthcare				
Availability	N/A	2011–2016	N/A	N/A
Date registered for care contact		X		
Primary care diagnoses (ICD-10, ICPC2)		X		
Procedure codes		X		

[1]Danish Health Authority, Statistics Denmark

[2]National Institute for Health and Welfare, Social Insurance Institution of Finland

[3]Norwegian Institute of Public Health

[4]The National Board of Health and Welfare, Statistics Sweden.

*In local currency.

Secondary healthcare				
Availability	1995–2014	1992–2015	N/A	1987–2015
Date registered for care contact/hospitalisation	X	X		X
Date discharged	X	X		X
Secondary care diagnoses	X	X		X
Type of clinic discharged from (e.g. emergency)		X		X
Procedure codes	X	X		X
Planned or unplanned visit indicator	X			X
Inpatient or outpatient indicator	X	X		X
Date and procedure code for hospital-administered monoclonal antibody**	X			
Pharmacy dispensed medications***				
Availability	1995–2015	2011–2016	2004–2018	2005–2017
ATC code, product name, and substance	X	X	X	X
Date of dispensed prescription at pharmacy	X	X	X	X
Prescribing physician speciality	X			X
Number of dispensed packages	X	X	X	X
Inhaler type for asthma drugs	X	X	X	X
Package size and package daily defined doses (DDD)	X	X	X	X
Amount of dispensed medication (e.g. number of milligrams, millilitres, etc.)	X	X	X	X
Diagnosis code associated with prescription (primary and secondary)			X	

ATC: Anatomical Therapeutic Chemical, DDD: Daily defined dose; ICD: International classification of disease, ICPC: International classification of primary care, N/A: Not applicable

Patient population

Individuals were included in NORDSTAR if they fulfilled at least one of the two following criteria between 2006 and the latest available year of data:

**No information on the amount of drug administered nor other dosing information is available for hospital-administered monoclonal antibodies, only ATC or monoclonal antibody-specific procedure code and date of administration.

***Only available for pharmacy-dispensed medications, not for hospital-administered medications.

Inclusion criterion 1 (diagnosis): One or more asthma diagnosis (international classification of disease [ICD]-10: J45/J46) registered in secondary care[5]

Inclusion criterion 2 (medication): Dispensation with respiratory drugs (anatomical therapeutic chemical [ATC]: R03.xx.xx) on ≥2 occasions separated by at most 12 months.

A registered diagnosis of asthma in secondary care (inclusion criterion 1) is a reliable indicator of asthma, and similar medication-based proxy criteria for asthma (inclusion criterion 2) have previously been used [9, 22] and validated [23]. It is important to note that the diagnostic inclusion criterion applies only to patients treated in secondary care while the medication proxy criteria applies to patients receiving prescriptions in both primary and secondary care.

Despite the support from the literature for the inclusion criteria above, there are patient groups that may be misclassified and therefore the authors recommend the application of exclusion criteria to reduce the likelihood of including non-asthma patients in the population. In doing so, researchers must trade some degree of sensitivity for specificity with the balance varying by research project. Below are the key groups of patients at risk of inclusion, who are not true asthma patients, alongside the authors' recommendation for how to exclude those patients using definitions applicable to NORDSTAR:

1. Treatment for lower chronic respiratory conditions other than asthma managed in secondary care: Patients dispensing respiratory medication with no asthma diagnosis, but with a diagnosis of another chronic lower respiratory disease.
2. Possible chronic obstructive pulmonary disease (COPD) treated in primary care: Patients aged ≥ 45 years dispensing COPD medication (fixed combination long-acting muscarinic-antagonists [LAMA] / long-acting beta-antagonists [LABA], tiotropium Spiriva® HandiHaler® [not Spiriva® Respimat®], umeclidinium, aclidinium, glycopyrronium) with no chronic lower respiratory disease diagnosis (including asthma).
3. Suspected urticaria: Patients with a diagnosis of urticaria in secondary care, but no chronic lower respiratory disease diagnoses, in addition to treatment with omalizumab.

It is important to note that the suggested exclusion criteria do not aim to exclude asthma patients with comorbid conditions; the purpose is to exclude those who appear to be asthma patients according to the

[5]In Norway, ICD-10 diagnosis codes registered in association with prescriptions were used, as no data is available for patients visiting secondary care centers.

NORDSTAR inclusion criteria, but due to the features listed above are likely to primarily suffer from other non-asthma indications that use respiratory medicines.

The full NORDSTAR population includes a total of 3,301,773 patients where 799,347 were identified in Denmark (24%), 232,713 in Finland (7%), 853,450 in Norway (26%) and 1,416,263 in Sweden (43%). Female patients comprised 52%, 55%, 52%, and 54% of each country's population, respectively. The inclusion period differs according to the initiation of relevant registries in each country, but the overall NORDSTAR identification period occurred between 2004 and 2018. In all countries, over 65% of all patients included in NORDSTAR could be identified according to the medication inclusion criterion alone (2 dispensations with ATC code: R03+ within 12 months of each other).

Collaborative platform

NORDSTAR is supported by a multi-party, collaborative research platform comprising clinical expertise, pharmaceutical manufacturer perspectives, and data analytics competence: The Nordic Severe Asthma Network (NSAN) is a network of severe asthma specialists from the Nordic countries focusing on improving the diagnostics and treatment of severe and possible severe asthma. In the NORDSTAR project, the members of NSAN provide clinical insight to the interpretation of register data. The pharmaceutical industry partner provides insights into research and development and patient access. Quantify provides dedicated data access, management, and analytics services to expedite medical communications. The groups working with NORDSTAR welcome future collaboration with other stakeholders.

Remarks and context

NORDSTAR is a unique, multinational initiative in the Nordics enabling longitudinal follow-up of asthma patients in contemporary, routine clinical care. This population-based data provides a basis for comprehensive characterisation of all Nordic asthma patients and its longitudinal nature enables the study of temporal trends and identification of asthma-related events over patients' life-course. The data is well suited to research aiming to characterize and categorize asthma patients, study comparative effectiveness, analyse health economics and healthcare burden, describe patient and treatment pathways, and to provide a basis for comparisons between Nordic countries. NORDSTAR is unique in that it includes many patients from early stages of the disease through to potential severe asthma. The multinational aspect of the data also enables the study of certain structural differences between healthcare systems.

There are a variety of complexities and subtleties related to the secondary healthcare data included in NORDSTAR, which include patient composition, provision of treatment and care, patient registration, and data collection procedures, as well as interpretation of variables and results between countries. Each of these is nuanced and differ over time and geography. It is therefore essential that a collaborative multidisciplinary team is involved in the analysis of NORDSTAR data. The asthma healthcare professionals working alongside NORDSTAR, the NSAN, ensure that clinical perspectives and relevance are at the forefront of prioritizing, designing, and interpreting NORDSTAR-based research.

Diagnostic, phenotypic, and prognostic markers associated with the asthma disease course include forced expiratory volume in 1 second (FEV_1), tobacco usage, atopy, and airway inflammation. These risk factors are not currently available in NORDSTAR. This limitation implies that classifying patients into asthma severity and control categories must be done using proxy definitions tailored to administrative registry data instead of exact implementations using European Respiratory Society (ERS)/American Thoracic Society (ATS) [24] or Global Initiative for Asthma (GINA) [25] guidelines. This requires careful design and implementation of proxy measures, ideally those which have been validated. However, severe asthma definitions, based on medication use, i.e. high use of inhaled corticosteroids and leukotriene receptor antagonists and/or LABA, have been used efficiently in recent large epidemiological studies [9, 26-28], revealing opportunities to study severe asthma patient group as well.

NORDSTAR data exists alongside a variety of high-quality clinical cohorts in the Nordics containing many of the non-administrative variables discussed above, likely including many of the same patients within the same time frames as NORDSTAR. In this respect, NORDSTAR acts as a compliment to existing clinical data. In the future, some of these clinical cohorts may be added to NORDSTAR to extend the research possibilities. Study of additional research questions may require new ethical approvals and/or data extractions. At the time of writing, the existing NORDSTAR data was being updated to ensure it continues to be contemporary as treatment and patient landscapes change.

While many aspects of Nordic healthcare systems and administrative data are similar, Finland began a progressive transition to mandatory prescriber-registered electronic prescriptions during patient follow-up. Consequently, the coverage of patient prescriptions in NORDSTAR changes significantly over time for Finnish patients, reaching full coverage in approximately 2017. This is important for two reasons. First, since more patients are identified and included through the medication criterion instead of the diagnosis criterion, there is less opportunity, for administrative reasons, for Finnish patients to be identified overall resulting in relatively low patient numbers when compared with Denmark, Norway, and Sweden, even

after adjusting for each country's population size. Second, patients treated in primary care were identified in NORDSTAR via the prescription-based inclusion criteria only. Since this data is under-represented in Finland, it is expected that Finnish NORDSTAR patients are biased towards being more severe. The authors recommend the use of qualified statements, when making inter-country comparisons in general, and especially regarding Finland.

Currently, the Norwegian NORDSTAR data is limited to the prescription registry. However, Norway is unique in that the diagnosis codes in primary and secondary care are registered alongside prescriptions. Norway is the only country in NORDSTAR where the prescriptions can be directly linked to ICD diagnoses codes. While this is a useful attribute in many settings, reimbursement regulations may impact the way in which diagnoses are set for patients when reimbursement is linked to an asthma or COPD diagnoses, but not both. Norwegian asthma patients who did not fill a prescription for respiratory medication are not included in the NORDSTAR population, nor can patients' full comorbidity profile be assessed, since the diagnosis data is only available when linked to a prescription. Despite these shortcomings, it is expected that there is little selection bias in Norway, since few asthma patients receive only secondary care diagnoses, but no prescribed medication. Socioeconomic data is not available in Norway.

Monoclonal antibodies (MABs) indicated for severe asthma (benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab at the time of writing) are usually administered in the hospital setting as opposed to the secondary care clinics in the Nordic countries. Hospital-administered drugs are not directly dispensed to patients and are therefore not fully registered in the Finnish, Norwegian, or Swedish data. The data on hospital-administered medication is available in Denmark via ATC and procedures codes in the Danish patient registry but lacks information on dosing and amount of drug administered. In future updates of the NORDSTAR data, the coverage of MAB medication is expected to improve, as the hospital-based administration of MABs becomes less prevalent in favour of pharmacy-dispensed pre-filled syringes for home use.

The data included in NORDSTAR are clearly relevant to the Nordic context, but many aspects of NORDSTAR-based research are generalizable to other settings. Epidemiological study of patient characteristics, patient trajectories, and treatment effectiveness are likely to be highly applicable to other Western patient groups. Research related to provision of healthcare including treatment patterns, costs, and resource use may be combined with expert advisory boards, such as Delphi panels to promote cross-national applications. This approach may be best suited to non-Nordic candidate populations that also operate within single-payer healthcare systems. Finally, NORDSTAR is an inspiring example of a successful

collaboration in the era of big data between different stakeholders including academia, the pharmaceutical industry, and government authorities that could drive large amounts of innovation and research for the benefit of patients.

NORDSTAR is a population-based multinational Nordic dataset developed alongside active research collaboration with Nordic asthma specialists through the NSAN, for conducting contemporary, real-world research on asthma patients to improve clinical practice and patients' quality of life.

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References

1. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, Boulet L-P. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012: 12(1): 204.

2. Braman SS. The global burden of asthma. *Chest* 2006: 130(1 Suppl): 4s-12s.

3. Honkamaki J, Hisinger-Molkanen H, Ilmarinen P, Piirila P, Tuomisto LE, Andersen H, Huhtala H, Sovijarvi A, Backman H, Lundback B, Ronmark E, Lehtimaki L, Kankaanranta H. Age- and gender-specific incidence of new asthma diagnosis from childhood to late adulthood. *Respir Med* 2019: 154: 56-62.

4. Backman H, Räisänen P, Hedman L, Stridsman C, Andersson M, Lindberg A, Lundbäck B, Rönmark EJC, Allergy E. Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016—results from three population surveys. *Clin Exp Allergy* 2017: 47(11): 1426-1435.

5. Bjerg A, Ekerljung L, Middelveld R, Dahlen SE, Forsberg B, Franklin K, Larsson K, Lotvall J, Olafsdottir IS, Toren K, Lundback B, Janson C. Increased prevalence of symptoms of rhinitis but not of asthma between 1990 and 2008 in Swedish adults: comparisons of the ECRHS and GA(2)LEN surveys. *PloS one* 2011: 6(2): e16082.

6. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, FitzGerald JM. Economic burden of asthma: a systematic review. *BMC pulmonary medicine* 2009: 9: 24.

7. Chen S, Golam S, Myers J, Bly C, Smolen H, Xu X. Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA Steps 4 or 5 treatment. *Curr Med Res Opin* 2018: 1-14.

8. Jansson S-A, Axelsson M, Hedman L, Leander M, Stridsman C, Rönmark E. Subjects with well-controlled asthma have similar health-related quality of life as subjects without asthma. *Respiratory Medicine* 2016: 120: 64-69.

9. von Bulow A, Kriegbaum M, Backer V, Porsbjerg C. The prevalence of severe asthma and low asthma control among Danish adults. *J Allergy Clin Immunol Pract* 2014: 2(6): 759-767.

10. Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. *J Allergy Clin Immunol* 2001: 107(6): 937-944.

11. Janson C, Lisspers K, Stallberg B, Johansson G, Telg G, Thuresson M, Nordahl Christensen H, Larsson K. Health care resource utilization and cost for asthma patients regularly treated with oral corticosteroids - a Swedish observational cohort study (PACEHR). *Respir Res* 2018: 19(1): 168.

12. Fleming L, Murray C, Bansal AT, Hashimoto S, Bisgaard H, Bush A, Frey U, Hedlin G, Singer F, van Aalderen WM, Vissing NH, Zolkipli Z, Selby A, Fowler S, Shaw D, Chung KF, Sousa AR, Wagers S, Corfield J, Pandis I, Rowe A, Formaggio E, Sterk PJ, Roberts G, Group UBS. The burden of severe asthma in childhood and adolescence: results from the paediatric U-BIOPRED cohorts. *The European respiratory journal* 2015: 46(5): 1322-1333.

13. Hyrkas H, Ikaheimo TM, Jaakkola JJ, Jaakkola MS. Asthma control and cold weather-related respiratory symptoms. *Respir Med* 2016: 113: 1-7.

14. Kupczyk M, Haque S, Sterk PJ, Nizankowska-Mogilnicka E, Papi A, Bel EH, Chanez P, Dahlen B, Gaga M, Gjomarkaj M, Howarth PH, Johnston SL, Joos GF, Kanniess F, Tzortzaki E, James A, Middelveld RJ, Dahlen SE, investigators B. Detection of exacerbations in asthma based on electronic diary data: results from the 1-year prospective BIOAIR study. *Thorax* 2013: 68(7): 611-618.

15. Lötvall J, Ekerljung L, Rönmark EP, Wennergren G, Lindén A, Rönmark E, Torén K, Lundbäck B. West Sweden Asthma Study: Prevalence trends over the last 18 years argues no recent increase in asthma. *Respiratory Research* 2009: 10(1): 94-94.

16. Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, Hastie AT, Bleecker ER, Meyers DA, Peters SP, Castro M, Coverstone AM, Bacharier LB, Ly NP, Peters MC, Denlinger LC, Ramratnam S, Sorkness RL, Gaston BM, Erzurum SC, Comhair SAA, Myers RE, Zein J, DeBoer MD, Irani AM, Israel E, Levy B, Cardet JC, Phipatanakul W, Gaffin JM, Holguin F, Fajt ML, Aujla SJ, Mauger DT, Jarjour NN. Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age. *J Allergy Clin Immunol Pract* 2018: 6(2): 545-554 e544.

17. Tuomisto E, L., Kankaanranta H, Ilmarinen P, Kankaanranta T. Seinäjoki Adult Asthma Study (SAAS): a protocol for a 12-year real-life follow-up study of new-onset asthma diagnosed at adult age and treated in primary and specialised care. *NPJ Prim Care Respir Med* 2015: 25: 1-4.

18. Backer V, Lykkegaard J, Bodtger U, Agertoft L, Korshoej L, Brauner EV. The Danish National Database for Asthma. *Clinical epidemiology* 2016: 8: 601-606.

19. Gavrielov-Yusim N, Friger M. Use of administrative medical databases in population-based research. *Journal of Epidemiology and Community Health* 2014: 68(3): 283.

20. Ludvigsson JF, Haberg SE, Knudsen GP, Lafolie P, Zoega H, Sarkkola C, von Kraemer S, Weiderpass E, Norgaard M. Ethical aspects of registry-based research in the Nordic countries. *Clinical epidemiology* 2015: 7: 491-508.

21. Maret-Ouda J, Tao W, Wahlin K, Lagergren J. Nordic registry-based cohort studies: Possibilities and pitfalls when combining Nordic registry data. *Scandinavian journal of public health* 2017: 45(17_suppl): 14-19.

22. Schatz M, Cook EF, Joshua A, Petitti D. Risk factors for asthma hospitalizations in a managed care organization: development of a clinical prediction rule. *Am J Manag Care* 2003: 9(8): 538-547.

23. Ortqvist AK, Lundholm C, Wettermark B, Ludvigsson JF, Ye W, Almqvist C. Validation of asthma and eczema in population-based Swedish drug and patient registers. *Pharmacoepidemiology and drug safety* 2013: 22(8): 850-860.

24. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet LP, Brightling C, Chanez P, Dahlen SE, Djukanovic R, Frey U, Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness RL, Teague WG. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *The European respiratory journal* 2014: 43(2): 343-373.

25. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention; 2018.

26. Larsson K, Stallberg B, Lisspers K, Telg G, Johansson G, Thuresson M, Janson C. Prevalence and management of severe asthma in primary care: an observational cohort study in Sweden (PACEHR). *Respir Res* 2018: 19(1): 12.

27. Backman H, Jansson SA, Stridsman C, Eriksson B, Hedman L, Eklund BM, Sandstrom T, Lindberg A, Lundback B, Ronmark E. Severe asthma-A population study perspective. *Clin Exp Allergy* 2019: 49(6): 819-828.

28. Hekking PP, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015: 135(4): 896-902.