










## ORIGINAL ARTICLE

# Trends in childhood asthma in Denmark, Finland, Norway and Sweden

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## 1 | INTRODUCTION

The burden of asthma has increased since around 1960 and is especially prevalent in high-income settings. However, a steady state may have occurred, as some studies report a plateau in prevalence in the 21st century.<sup>1</sup> Studies are often limited to a single country and do not involve entire populations, potentially introducing selection bias.<sup>2–4</sup> Moreover, studies vary significantly regarding design, study period and definition of asthma, hampering comparison across time and settings.

It is important to monitor the trends in asthma incidence and to compare incidences across different settings because this may elucidate differences in burden of disease and inspire future investigations into the diagnosis and treatment as well as the aetiology of disease. Population-based medical and pharmaceutical registers have previously been used to compare incidence rates of asthma across entire populations.<sup>5,6</sup> The Northern European countries Denmark, Finland, Norway and Sweden (the Nordic countries) provide a unique setting because they have comparable tax-financed health care, ensuring high and equal access to medical care and all have population-wide registers covering health information.<sup>7–9</sup> However, large population-based investigations assessing trends in the incidence of asthma across all the Nordic Countries have not been undertaken.

The aim of the present observational register study was to investigate the incidence of asthma among children aged 0–15 years, according to birth cohort, age and sex, in the Nordic countries, using an algorithm-based definition of asthma based on nationwide registers with information on hospital contacts and redeemed prescriptions.

## 2 | METHODS

### 2.1 | Setting and data sources

This study is based on data from the Nordic Network on Non-Specific Effects of vaccines and childhood morbidity (NONSENSE),<sup>9</sup> which utilises data from the extensive individual-level nationwide registers on health and sociodemographic information across the Nordic countries. Information from the registers is linkable using the personal identifier assigned to all individuals upon birth or immigration. Information on date of birth, death and migrations was obtained from population registers.<sup>8</sup> Information on hospital contacts is available from nationwide patient registers and includes information on dates of admission and discharge and diagnoses.<sup>10–13</sup> Since 1997, all the Nordic countries have coded diagnoses according to the International Classification of Diseases version 10 (ICD-10).<sup>14</sup> Information on redeemed prescriptions was obtained from the Danish National Prescription Registry,<sup>15</sup> the Norwegian Prescription Database,<sup>16</sup> and the Swedish Prescribed Drug Register<sup>17</sup> which contain information on all redeemed prescriptions in Danish, Norwegian and Swedish pharmacies, respectively. In Finland, we combined data from the Finnish Prescription Register and the Finnish Prescription Center, as described

### Key Notes

- Nationwide studies of the incidence of childhood asthma are limited.
- This study based on prescription of asthma medication and hospital diagnoses covering 2000–2017 indicates that preschool asthma may have plateaued in Denmark, Finland, Norway and Sweden, while school-age asthma declined in Denmark and Norway and increased in Sweden and Finland.
- Research into the impact of recording practices and early life exposures affecting the observed burden of childhood asthma is warranted.

elsewhere.<sup>9</sup> Medicines given to hospitalised or institutionalised patients are not captured by any of the registers.<sup>8</sup>

#### 2.1.1 | Register-based algorithm for school-age asthma and Preschool asthma

We developed an algorithm based on disease-specific prescription medicines including inhaled glucocorticoids, inhaled  $\beta_2$ -agonists, leukotriene receptor antagonists and hospital contacts with ICD-10-codes J45 (Asthma) and J46 (Status asthmaticus) (Box 1 and

#### BOX 1 Summary of the algorithm for asthma and preschool asthma in children 0–15 years.

Criterion 1:  $\geq 2$  treatments within 12 months with Inhaled glucocorticoids, fixed dose combination of inhaled  $\beta_2$ -agonists and glucocorticoids or leukotriene receptor antagonists

Criterion 2:  $\geq 3$  treatments within 12 months with inhaled  $\beta_2$ -agonists, inhaled glucocorticoids, fixed dose combination of inhaled  $\beta_2$ -agonists and glucocorticoids or leukotriene receptor antagonists\*

Criterion 3: Hospital contact with diagnosis ICD-10: J46 (Status Asthmaticus)

Criterion 4: Hospital contact with diagnosis ICD-10: J45 (Asthma), within 12 months followed by:

$\geq 1$  prescription with Inhaled glucocorticoids, fixed dose combination of inhaled  $\beta_2$ -agonists and glucocorticoids or leukotriene receptor antagonists

OR

$\geq 2$  prescriptions with Inhaled  $\beta_2$ -agonists

\* if single agent inhaled  $\beta_2$ -agonists is among the prescriptions, a total of 3 prescriptions must be redeemed.

Appendix S1). The algorithm was developed based on previous studies<sup>18–21</sup> and was adjusted in accordance with insights from paediatricians and register information specialists from each of the Nordic countries. For example, we specified that a hospital diagnosis of asthma should be followed by relevant prescription medication as it was not possible to distinguish between referral diagnoses and confirmed diagnoses in all countries.

As asthma symptoms in young children often resolve before school age,<sup>22</sup> we investigated children <6 years of age and ≥6 years of age separately. “Preschool asthma” was defined based on fulfilment of the algorithm in children <6 years of age. “School-age asthma” was defined as fulfilment of the algorithm from 6 years of age until turning 15 years. Children, who fulfilled the algorithm for preschool asthma, could also fulfil the algorithm for asthma from 6 years of age. Henceforward these algorithm-based definitions are referred to as “preschool asthma” and “school-age asthma” respectively.

## 2.2 | Population and study period

The study period started in 2000 in Denmark and Finland. In Norway, the study period started in 2008 when the personal identifier was included in the patient register.<sup>13</sup> In Sweden, the study period started in 2006 reflecting the availability of data from the Swedish Prescribed Drug Register.<sup>17</sup>

For preschool asthma, we included children born in Denmark and Finland from the year 2000, from 2008 in Norway and 2006 in Sweden. For school-age asthma, we followed children living in the respective country from their sixth year birthday. Thus, we included the birth cohorts from 1994 in Denmark and Finland, 2000 in Sweden and 2002 in Norway.

The algorithms rely on information on multiple redeemed prescriptions within 12 months, to avoid including children who had received just one prescription indicating transient asthma symptoms. To avoid overestimating the age of onset it was defined as the date of the first redeemed prescription, reflecting the age of onset of symptoms. Because 12 months of follow-up from the first prescription was required to fulfil the definition of preschool asthma or school-age asthma, children were censored 12 months before a possible death, migration, end of follow-up (December 31, 2017) or the date of turning 6 or 15 years of age for preschool asthma and school-age asthma, respectively, whichever came first. Thus, the latest birth cohort followed in any country was the 2015 birth cohort for preschool asthma and the 2009 birth cohort for school-age asthma.

## 2.3 | Statistical analysis

We estimated the cumulative incidence (CI) at the end of each one-year age interval by country and year of birth. Measuring CI of chronic conditions is not straightforward in routinely collected data, as validation of the condition relies on future registration, causing right

censoring.<sup>23</sup> In order to avoid underestimating the CI, we, therefore, estimated the CI for all children, who had been under observation for the entire age span the CI relates to. More specifically, we estimated the CI of preschool asthma as the proportion of children, who developed preschool asthma from birth to the day before they turned the specified age, among the children, who were under observation from birth until the day before they turned the specified age. For example, the CI when turning 5 years (CI-5) was estimated as number of children recorded with preschool asthma from birth until the day before turning 5 years divided by the number of children under observation from birth until the day before turning 5 years in the respective country. Similarly, we estimated CI of school-age asthma as the proportion of children, who were recorded with asthma from 6 years of age to the day before they turned the specified age among the children, who were under observation in the respective country from 6 years of age to the day before they turned the specified age.

The primary investigation visualised trends according to birth year and age for both sexes combined. In a secondary investigation, the CI according to age was visualised stratified by sex for the birth cohort 2008 for preschool asthma and for birth cohort 2002 for school-age asthma, reflecting the first birth cohort with data available in all countries. We only did this analysis for one birth cohort per outcome studied, to disentangle differences in CI across the Nordic countries from differences in incidence and follow-up time for the different birth cohorts.

We used Stata versions 17 and 18 (StataCorp, College Station, Texas, USA) to conduct the analyses and R version 3.3.3 to visualise data.

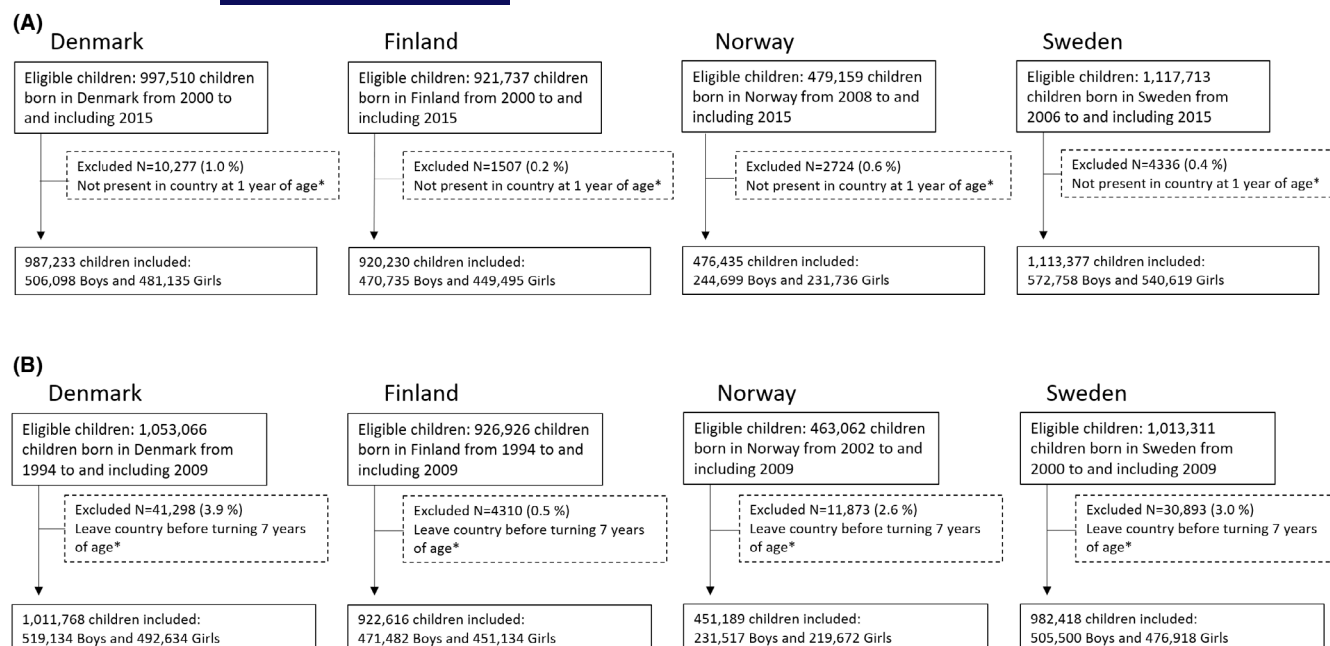
## 3 | RESULTS

We included 3497 275 children in the analyses of preschool asthma (Figure 1A) and 3367 991 children in the analyses of school-age asthma (Figure 1B).

### 3.1 | Preschool asthma (children <6 years)

Most children had redeemed asthma medication (criterion 1 or 2) as the first fulfilled criterion for preschool asthma (Table 1). In Sweden, 28.7% had a hospital diagnosis followed by a prescription for asthma medication (criterion 4) as the first fulfilled criteria for preschool asthma, compared with 9.0%–11.5% in the other countries (Table 1). In all countries, less than 1% fulfilled the criterion for status asthmaticus (J46, criterion 3).

For children born in 2000 in Denmark, the CI of preschool asthma when turning 1 year of age (CI-1) was 4.5%. (Figure 2, Table S1). The CI-1 peaked for the 2009 cohort at 6.2% and was lower again for later cohorts being 4.7% for the 2015 birth cohort. The CI of preschool asthma when turning 6 years of age (CI-6) was 12.2% for the birth cohort of 2000 and peaked for the birth cohort of 2008 (14.8%). The CI-6 was slightly lower for children born after 2008.



**FIGURE 1** Study population in Denmark, Finland, Norway and Sweden for preschool asthma (A) and school-age asthma (B) as measured by an algorithm including hospital diagnoses and prescription medication. \* The algorithms rely on information on multiple redeemed prescriptions within 12 months, thus children were censored 12 months before death, migration or end of follow-up (December 31, 2017), whichever came first. The algorithm for identifying preschool asthma and school-age asthma is described in [Box 1](#) and [Appendix S1](#).

**TABLE 1** The first fulfilled criteria for preschool asthma and school-age asthma, respectively, in Denmark, Finland, Norway and Sweden.

	Denmark		Finland		Norway		Sweden	
	N	%	N	%	N	%	N	%
Fulfilment of criteria for preschool asthma								
Criterion 1	62 461	49.5%	35 721	45.3%	36 522	65.2%	66 754	50.7%
Criterion 2	52 024	41.2%	34 901	44.2%	12 983	23.2%	27 026	20.5%
Criterion 3	374	0.3%	223	0.3%	87	0.2%	95	0.1%
Criterion 4	11 292	9.0%	8105	10.3%	6464	11.5%	37 712	28.7%
Fulfilment of criteria for school-age asthma								
Criterion 1	46 985	68.5%	46 904	56.2%	22 615	71.2%	44 406	54.1%
Criterion 2	18 287	26.7%	22 541	27.0%	6401	20.2%	17 316	21.1%
Criterion 3	356	0.5%	176	0.2%	44	0.1%	35	<0.1%
Criterion 4	2965	4.3%	13 828	16.6%	2694	8.5%	20 344	24.8%

Note: See [Box 1](#) and [Appendix S1](#) for description of the criteria.

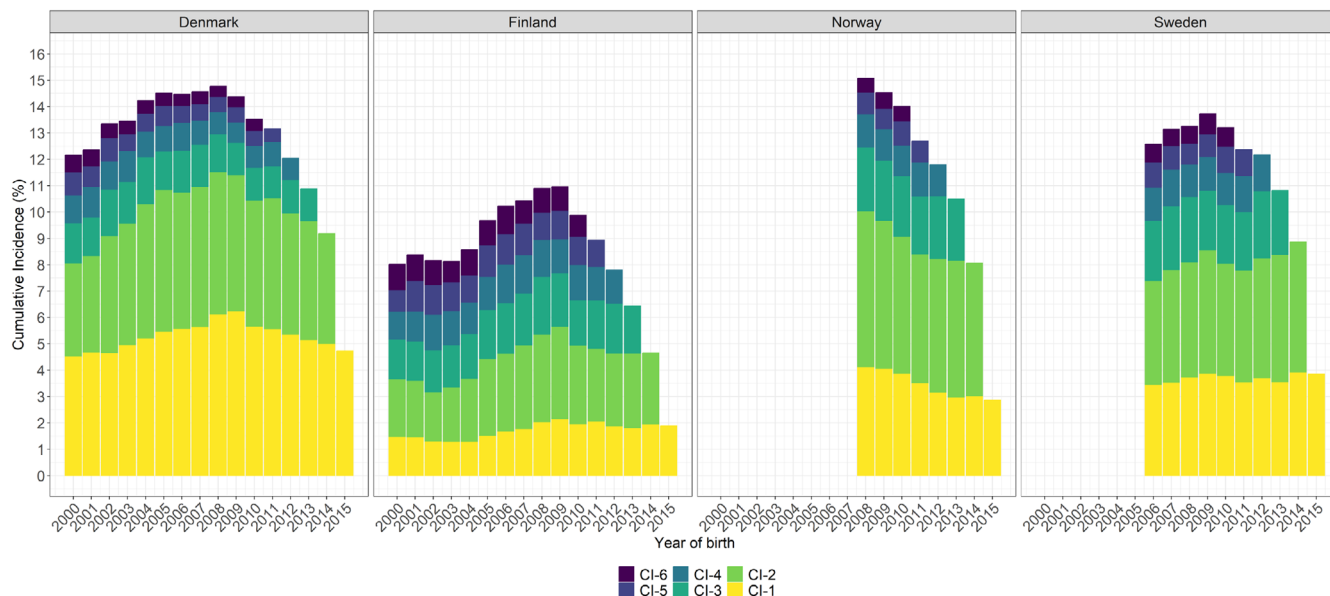
In Finland, children born in 2000 had a CI-1 of 1.5%, peaking for the 2009 cohort at 2.2% while the CI-1 was 1.9% for birth cohort 2015 ([Figure 2](#), [Table S1](#)). The CI-6 was 8.0% for children born in 2000 and gradually increased with each birth cohort from 2003 until 2009, where it peaked at 11.0%.

In Norway, the CI-1 decreased from 4.1% for children born in 2008 to 2.9% for children born in 2015. The highest CI-6 was 15.1% in the 2008 birth cohort ([Figure 2](#), [Table S1](#)).

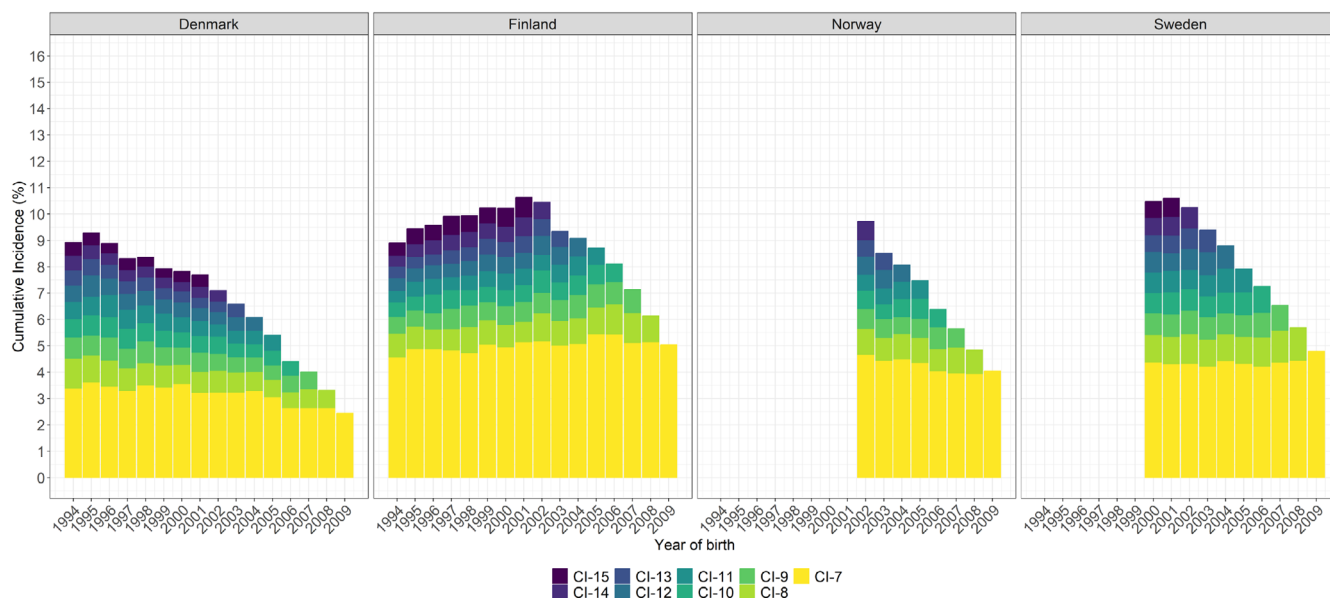
In Sweden, the CI-1 was relatively stable during the study period, ranging from 3.5% to 3.9% from 2006 to 2015 ([Figure 2](#), [Table S1](#)).

The CI-6 was 12.6% for the 2006 birth cohort, peaked at 13.7% for the 2009 birth cohort, whereafter it decreased slightly in the 2010 birth cohort (13.2%) ([Figure 2](#), [Table S1](#)).

In all countries, the CI of preschool asthma for the cohort of 2008 was higher among boys compared with girls at all ages. The absolute difference in CI between girls and boys increased with age: the absolute difference at CI-1 ranged from 1.8 to 3.6 percentage points across the countries whereas the absolute difference at CI-6 ranged from 4.7 to 5.3 percentage points ([Table S1](#), [Figure S1](#)).



**FIGURE 2** Cumulative incidence of algorithm-based preschool asthma from birth up to 6 years of age, according to year of birth in Denmark, Finland, Norway and Sweden. The algorithm for identifying asthma is described in [Box 1](#) and [Appendix S1](#). The CI at age  $t$  was calculated as the proportion of children, who developed preschool asthma before  $t$  among the children not censored at  $t$ . The colours indicate the age  $t$ .



**FIGURE 3** Cumulative incidence of algorithm-based school-age asthma from 6 up to 15 years of age, according to year of birth in Denmark, Finland, Norway and Sweden. The algorithm for identifying asthma is described in [Box 1](#) and [Appendix S1](#). The CI at age  $t$  was calculated as the proportion of children, who developed school-age asthma before  $t$  among the children not censored at  $t$ . The colours indicate the age  $t$ .

### 3.2 | School-age asthma (children 6 years and older)

Most children fulfilled the algorithm for school-age asthma through criterion 1 or 2 (i.e. redeemed asthma medication) ([Table 1](#)).

In Denmark, the CI when turning 7 years (CI-7) was 3.4% for the 1994 birth cohort ([Figure 3](#), [Table S2](#)). The CI-7 was stable across birth cohorts 1994–2000, with a tendency towards a slight decrease

after 2000: The CI-7 was lowest at 2.4% for children born in 2009. The CI when turning 15 years (CI-15) changed across the period from 8.9% for the 1994 birth cohort to 7.7% for the 2001 birth cohort (last birth cohort with follow-up until the day before turning 15 years of age).

In Finland, The CI-7 was 4.6% for children born in 1994 and 5.0% for children born in 2009 ([Figure 3](#), [Table S2](#)). CI-15 was 8.9% for the

1994 birth cohort and increased with later birth cohorts, reaching 10.6% for the birth cohort of 2001.

In Norway, CI-7 was 4.7% for the 2002 birth cohort and 4.0% for children born in 2009 (Figure 3, Table S2). No data was available regarding CI-15, because data was only available for birth cohort 2002 onwards, thus follow-up stopped the day before turning 14 years of age.

In Sweden, the CI-7 was 4.4% for the 2000 birth cohort and 4.8% for the 2009 birth cohort (Figure 3, Table S2). The CI-15 was 10.5% and 10.6% for the 2000 and 2001 cohort, respectively.

The youngest cohort for which we had data from their 6th birthday in all countries was the 2002 cohort, thus allowing a maximum follow-up until the day before turning 14 years of age. For this birth cohort, the CI of school-age asthma before turning 14 years of age (CI-14) was lowest in Denmark with 7.1% compared with 10.5% in Finland, 9.7% in Norway and 10.2% in Sweden (Figure S2, Table S2). In all countries, boys had a higher CI of school-age asthma across all ages compared with girls (Figure S2, Table S2). The absolute female-male rate difference was stable across age in all countries.

## 4 | DISCUSSION

Based on the algorithm, preschool asthma was common, with a peak CI of around 15% when turning 6 years of age in Denmark, Norway and Sweden, and 10% in Finland. After the birth cohorts of 2008/2009, slightly lower CIs of preschool asthma were observed in Denmark, Norway and Finland whereas stable CIs were observed in Sweden. School-age asthma CIs were around 10% when turning 14 years among the 2002 birth cohorts in Finland, Norway and Sweden, compared with 7% in Denmark. Remarkably, Finland had a very high CI of school-age asthma, while the CI of preschool asthma was lower compared with the other Nordic countries. Focusing on CI-7, for which the CI could be assessed for most consecutive birth cohorts, a tendency of a decline was observed across time in Denmark and Norway, whereas a slight increase was observed in Sweden and Finland.

Boys consistently had a higher CI of both preschool and school-age asthma compared with girls. The absolute rate difference between boys and girls increased with age for preschool asthma, whereas it was stable for school-age asthma, indicating that sex differences are driven by higher incidence among preschool boys.

### 4.1 | Strengths and limitations

Our study benefits from whole birth cohorts, followed for up to 16 consecutive years. A limitation pertains to the varying years with available data across countries, which prevented comparison of trends across multiple years across all countries. Our register-based algorithm avoided bias associated with recall of previous asthma diagnoses and treatment. The algorithm relied on cases

having multiple redeemed prescriptions to fulfil the criteria, thus preventing over-reporting due to transient symptoms. The date of symptom onset was defined according to the first redeemed prescription or hospital contact, reflecting the age of onset. Using the date the algorithm was fulfilled would have overestimated age at onset.

Most cases were identified through prescription medicines only. In Norway and Sweden, it was not possible to separate referral diagnoses from final diagnoses in the patient registers. We, therefore, required children with hospital diagnosed asthma (ICD10: J45) to have received 1–2 redeemed prescriptions of asthma medication following their hospital contact to validate the diagnosis (Box 1).

Our algorithm was based on insights from previous studies to define asthma outcomes using register data.<sup>18–21</sup> These found positive predictive values of 75%–94% and sensitivities and specificities of 84% and 81% respectively, of medical register-based data using a doctor's diagnosis of asthma as the gold standard.

### 4.2 | Interpretation of findings

There are several factors that may have contributed to the observed variation both between countries and within countries over time.

#### 4.2.1 | Differences in diagnostic and treatment practices

Diagnosing asthma is challenging, especially in young children. Historically asthma has been diagnosed based on symptoms,<sup>24,25</sup> but in recent years the importance of lung function tests and demonstrated air flow variation for correctly diagnosing asthma has been emphasised.<sup>26–28</sup> This may result in both diagnosing more children with asthma, but also to rule out asthma in more children.

It is not possible to estimate exactly how much of the variation that is caused by differences in diagnostic and prescription habits and how much is due to true differences in incidence between countries. However, there are some indications that varying treatment practices may be of significance. A study of asthma medication use in the Netherlands, UK and Italy showed that use of short acting  $\beta_2$  agonists was more pronounced in the UK whereas use of inhaled corticosteroids (ICS) was highest in Italy.<sup>29</sup> A Norwegian study found pronounced variation in prescribed asthma medication between Norwegian counties.<sup>30</sup> These differences are so large that it seems unlikely that they are due to clinical variation. In the present study Finland had a markedly lower CI of preschool asthma than the other Nordic countries. This difference might reflect a more restrictive diagnostic and prescription pattern in young children in Finland. The Finnish guidelines, in use during the study period, recommended use of Impulse ocillometry to diagnose asthma in children from 3 years of age.<sup>31</sup> This was not the case in, for example, the Danish guidelines,<sup>32</sup> which may explain



some of the observed difference, even though the difference was greatest in the first 2 years of life. Notably, the CI for school-age asthma in Finland was among the highest. The current study does not have data to examine why this is the case.

In all the Nordic countries, access to general practitioners is free of charge for children, ensuring equal access to assessment of asthma symptoms. During the study period, a small patient fee was charged for inpatient care in Finland. All asthma medication needs a prescription, but asthma medication is free of charge for children in Norway and Sweden.

The similar CI of school-age asthma across Finland, Norway and Sweden indicate similar diagnostics and care despite different health-care structures. However, in Sweden, paediatric specialist clinics are more common than in the other countries and serves more children with atopic conditions.<sup>9</sup> These out-patient clinics report to the patient registers, which likely explains the higher proportion of children that fulfilled the algorithm by a hospital diagnosis (criterion 4) in Sweden.

#### 4.3 | Environment

The high CI of preschool asthma was mainly driven by high incidences in the two first years of life. Daycare attendance is associated with higher risk of viral respiratory tract infections,<sup>33</sup> which is the predominant driver of wheezing symptoms in this age group.<sup>34</sup> The CIs of preschool asthma in the present investigation correlate with daycare attendance in the respective countries: During the study period from 2000 to 2015, only 25%–30% of children aged 0–2 years of age attended daycare in Finland<sup>35</sup> where the lowest CI of preschool asthma by 2 years of age was observed. The corresponding daycare rate was 56%–66% in Denmark, which had the highest CI by 2 years of age.<sup>35</sup> Norway and Sweden with a daycare attendance of 26%–55% and 40%–48% respectively, had intermediate CIs.<sup>35</sup> Earlier studies found wheezing symptoms in a young age to be linked to day-care attendance.<sup>36,37</sup> Interestingly, one of those<sup>37</sup> found daycare attendance to have different effect of wheeze according to age, as it was a risk factor for wheezing in children <2 years of age and protective of late onset wheezing (onset after 2 years of age). Even though age intervals were different from ours, this observation may explain the Finnish results of a low incidence of preschool asthma and high incidence of school-age asthma.

We have earlier reported a higher use of antibiotics in young children in Finland compared with the other Nordic countries. Use of antibiotics could potentially protect against prolonged wheezing, but interestingly, antibiotics in young children have also been linked to asthma later in life.<sup>38</sup>

Passive smoking and indoor and outdoor air quality are other well-known risk factors for wheezing?<sup>36,39,40</sup> During the study period both the proportion of daily smokers<sup>41–44</sup> and outdoor pollution declined in all the countries.<sup>45</sup> These environmental factors may account for some of the variation both across countries and across birth cohorts.

#### 4.4 | Sex differences

We consistently observed higher CI of both preschool asthma and school-age asthma among boys compared with girls, which is consistent with earlier findings<sup>4,46</sup> and thus points towards a biological difference.<sup>47</sup>

#### 4.5 | Comparison with other studies

Time trends in asthma was vividly debated during the last decades. The International Study of Asthma and Allergies in Childhood (ISAAC) estimated trends in asthma prevalence based on standardised questionnaires from almost 500 000 children and adolescents in countries all over the world.<sup>1</sup> From 1994–1995 to 2000–2003, a slight decrease in prevalence was observed for adolescents in western European countries, whereas an increase of 0.2% per year was observed in the 6–7-year-old children. Few studies have examined the incidence of asthma diagnosis including entire populations in high-income settings. A Canadian study found that the CI of asthma at 8 years of age increased in children born between 1993 and 2000, driven by diagnoses before 3 years of age.<sup>48</sup> A Dutch study found increasing incidence rates in 5–18-year-old children from 2000 to 2008, after which the rates declined.<sup>6</sup> A study of Danish and Swedish children found increasing incidence in Denmark up to 2006, after which it declined for children aged 0–15 years, while an increase from 2006 to 2010 was observed in Swedish children aged 0–4 years.<sup>5</sup> Similarly, higher incidence of school-age asthma in Finland and Sweden, compared with Denmark, is also supported by findings in other studies.<sup>49</sup>

### 5 | CONCLUSION

Based on our algorithm for identifying cases of asthma by information on hospital diagnoses and prescription in national health registers, preschool asthma was common in all four countries, but least common in Finland. The CIs of preschool asthma peaked for birth cohorts of 2008 and 2009 in all countries after which a slight decrease was observed. School-age asthma was less common in Denmark compared with the other Nordic countries. During the study period, a slight decline in school-age asthma CI was observed across birth cohorts in Denmark and Norway and a slight increase in Sweden and Finland. Differences in diagnostic, coding and prescription practices may explain part of the differences found, but multiple factors, including infectious disease burden, daycare attendance and environmental exposures such as air pollution and passive smoking may also contribute to the variation. Our study calls for research to identify and investigate the impact of diagnostic, coding and prescription practices and early life exposures as possible explanations for the different burdens of algorithm-identified preschool asthma and school-age asthma across the Nordic countries. Further research could elucidate if the differences found are likely due to diagnostic, coding or prescription practices and/or early life exposures.

## AUTHOR CONTRIBUTIONS

**Signe Vahlkvist:** Methodology; writing – original draft; conceptualization; project administration; visualization; writing – review and editing. **Lise Gehrt:** Conceptualization; methodology; data curation; project administration; visualization; writing – original draft; formal analysis; funding acquisition; investigation; writing – review and editing. **Thomas Houmann Petersen:** Writing – review and editing; conceptualization; methodology. **Hélène Englund:** Conceptualization; writing – review and editing; data curation; funding acquisition; methodology; project administration. **Heta Nieminen:** Conceptualization; writing – review and editing; data curation; funding acquisition; investigation; methodology; project administration. **Ida Laake:** Conceptualization; writing – review and editing; data curation; funding acquisition; investigation; methodology; project administration. **Poul-Erik Kofoed:** Methodology; writing – review and editing; conceptualization; data curation; funding acquisition; investigation; project administration. **Berit Feiring:** Conceptualization; writing – review and editing; methodology; project administration; supervision. **Christine Stabell Benn:** Conceptualization; writing – review and editing; data curation; funding acquisition; investigation; methodology; project administration; supervision. **Lill Trogstad:** Writing – review and editing; conceptualization; data curation; funding acquisition; investigation; methodology; project administration. **Signe Sørup:** Conceptualization; methodology; supervision; writing – review and editing; data curation; formal analysis; funding acquisition; investigation; project administration.

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## CONFLICT OF INTEREST STATEMENT

LG is currently employed at Novo Nordisk A/S, the current employment has no implications for the work presented in this publication as this was undertaken as part of LGs previous employment with SDU. HN is an investigator in vaccine-related studies for which THL has received funding from GSK, Pfizer and Sanofi Pasteur. These fundings are not relevant to the current study. Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, the employer of SS, receives institutional research funding from public and private entities for studies of medicines and vaccines, to and administered by Aarhus University. None of these are relevant to the current study. The remaining authors report no relation that could be construed as a conflict of interest.

## ETHICS STATEMENT

Informed consent from participants is not mandated for register-based studies in any of the Nordic countries.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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