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## Cohort Profile: The West Sweden Asthma Study (WSAS): a multi-disciplinary population-based longitudinal study of asthma, allergy, and respiratory conditions in adults

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# ABSTRACT

**Purpose:** The West Sweden Asthma Study (WSAS) is a population-representative longitudinal study established to: (1) generate data on prevalence trends, incidence, and remission of asthma, allergy, and respiratory conditions; (2) elucidate on the risk and prognostic factors associated with these diseases; (3) characterise clinically relevant phenotypes of these diseases; and (4) catalyse relevant mechanistic, genomic, genetic, and translational investigations.

**Participants:** WSAS comprised of randomly selected individuals aged 16-75 years who are followed up longitudinally. The first stage involved a questionnaire survey (>42,000 participants) was undertaken in 2008 and 2016. A random sample (about 8000) of participants in the initial survey undergoes extensive clinical investigations every 8-10 years (first investigations in 2009-2012; second wave currently ongoing). Measurements undertaken at the clinical investigations involve structured interviews, self-completed questionnaire on personality traits, physical measurements, and extensive biological samples.

**Findings to date:** Some of our key findings have shown a 54% increase in the use of asthma medications between the 1990s and 2000s, primarily driven by a 5-fold increase in the use of inhaled corticosteroids. About 36% of asthmatics expressed at least one sign of severe asthma indicator, with differential lung performance, inflammation, and allergic sensitization among asthmatics with different signs of severe asthma. Multi-symptom asthmatics were at greater risk of having indicators of severe asthma. In all adults, being raised on a farm was associated with a decreased risk of allergic sensitization, rhinitis and eczema, but not asthma. However, among adolescents (i.e. those 16-20 years of age), being raised on a farm decreased the risk of asthma. Personality traits were associated with both beliefs of asthma medication and adherence to treatment.

**Future plans:** Follow-up of the cohort is being undertaken every 8-10 years. The repeated clinical examinations will take place in 2019-2022. The cohort data are currently being linked to routine Swedish healthcare registers for a continuous follow-up. Mechanistic, genomic, genetic, and translational investigations are ongoing.

# Strengths and limitations of this study:

- The West Sweden Asthma Study (WSAS) is a large-scale multi-disciplinary populationrepresentative longitudinal study on adult asthma and respiratory health, representing one of the largest of such cohorts in Europe.
- WSAS has several ongoing collaborations with investigators across the Nordic countries, with the OLIN studies, and the FinEsS studies in Finland, Estonia and Sweden and the survey instruments used have been adapted from these ongoing studies.
- With a large sample size, comprehensive measures, and long-term longitudinal design, WSAS provides an opportunity for a continuous generation of contemporary data on the trends in incidence and prevalence of adult asthma and successfully undertaking disease phenotyping.
- With the extensive clinical and molecular investigations being undertaken, WSAS represents one of unique platforms to undertake cutting-edge mechanistic, genomic, genetic, and translational investigations of the underlying pathogenesis of asthma.
- Although the participation rate in WSAS was overall average (with a decline between the surveys in 2008 and 2016), we anticipate, as reflected in current trends in population-based surveys, a continuous decline in response rate over time.

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## Introduction

According to the 2015 Global Burden of Disease study, nearly 400 million people live with asthma globally.<sup>1</sup> The report also ranked asthma among the ten causes of disability in 2015, with the disease burden affecting people of all ages, sexes, and races.<sup>1</sup> From the latter half of the last century, the prevalence of asthma was seen to be increasing across different parts of the world.<sup>2-5</sup> Whilst some recent data indicate a levelling off in some parts of the world, particularly in Australia<sup>2,6,7</sup> and some European countries,<sup>2,8-14</sup> other evidence suggests a continuing increase in urbanised settings of low-and middle-income countries<sup>15</sup> and some parts of Europe.<sup>16-18</sup> Much of the available data on asthma prevalence trends have however emanated from children and adolescent populations. There are paucity of data on the prevalence trends in adults, particularly data to help elucidate the trends after the 1990s.<sup>2</sup> Well-designed population-representative long-term longitudinal studies are required to obtain contemporary trends in the prevalence of asthma in adults.

Over the last decade, our understanding of the pathogenesis of asthma has been greatly advancing.<sup>19,20</sup> Contrary to previous understanding, it is now continuously appreciated that asthma is a complex and heterogeneous syndrome with different underlying distinct phenotypes.<sup>19-23</sup> These phenotypes tend to present with varying clinical pictures, prognosis, risk factors, and response to treatment.<sup>21-23</sup> Through analyses of several children cohorts, common asthma phenotypes have been characterized, including transient wheezing, non-atopic wheezing, and IgE-mediated wheezing.<sup>24,25</sup> In contrast, the lack of well-designed population-representative cohorts has meant that far less knowledge has been gained regarding asthma phenotypes in adults. There are today several partly similar suggested groupings of asthma phenotypes in adults; one of the common approaches has been to group them into three: (1) trigger-induced asthma (e.g. occupational asthma, cigarette smoke-induced asthma, exercise-induced asthma); (2) symptom-based asthma (e.g. asthma with persistent airflow limitation, adult-onset asthma, obesity-related asthma); and (3) biomarker-based asthma (e.g. eosinophilic associated asthma).<sup>22,24,26,27</sup> Adult-onset asthma is different from asthma in childhood<sup>28,29</sup> and it is less associated with allergy and atopy, but is often associated with obesity, represents more severe disease, has low remission rate, poor prognosis and faster decline in lung function.<sup>29,30</sup> Definitive phenotyping of adult asthma will engender better insights into the potential disease mechanisms and will help to identify potentially relevant biomarkers that can aid more targeted treatment.<sup>23,31,32</sup>

The West Sweden Asthma Study (WSAS)<sup>13</sup> is a large-scale multi-disciplinary populationrepresentative longitudinal study on asthma, which was established in 2008 with the overarching aim of contributing to better understanding of asthma in adults. WSAS has both short- and long-term goals (Figure 1). The short-term goal is to generate data on the trends in prevalence, incidence, and remission of asthma, respiratory conditions, chronic obstructive pulmonary disease (COPD), and allergic diseases in adults in the western Swedish population and to elucidate on the risk and

 prognostic factors associated with these diseases, as well as the patterns in asthma remission. The long-term goals are to: (1) characterise clinically relevant phenotypes of asthma, allergy and respiratory conditions and perform detailed clinical and molecular epidemiologic investigations of these conditions; and (2) catalyse relevant mechanistic, genomic, genetic, and translational investigations for better understanding of asthma.

## **Cohort description**

## Ethics approval

The study and its sub-studies have been approved by the local Ethics Committee at the University of Gothenburg.

## Study population

WSAS involves an initial cross-sectional survey of randomly selected individuals aged 16-75 years who are then subsequently followed up longitudinally (Figure 2).<sup>13,33</sup> The first survey (WSAS I) was undertaken in 2008 in which a random sample of 30 000 people (representative of the age and sex composition of the study area) were invited. Of these, excluding those who were not traceable (n=782), 18 087 (all 62%; women 67%; men 56%) participated in the study. From the participants, a random sample of 2000 people from all participants and additional 1524 subjects with asthma (altogether 3524 people) were invited to take part in extensive clinical investigations. Of those invited, 2006 participated in the clinical investigations, which took place between 2009 and 2012.33 A second survey (WSAS II) was carried out in 2016 in which a random sample of 50 000 people of the same age group as in WSAS I were invited to take part in the study. The sampling base (areas covered) in WSAS II did not fully overlap with WSAS I; moreover, each survey constitutes different participants. In total, 24 534 (all 50%; women 56%; men 46%) of the 50 000 invited participated in the study. About 2200 of those that participated in WSAS II have current asthma; in addition to these, 4000 random sample from all participants (altogether 6200 people) will be invited to take part in the extensive clinical phase of the study. The goal of WSAS II was to study prevalence change and also to expand the overall study base and to enhance the number of participants included in subsequent clinical phases of the study.

### Cohort follow-up

Those who participated in WSAS I in 2008 were invited for a follow-up survey in 2016. In addition, those who took part in the clinical investigations between 2009 and 2012 have been invited and are currently undergoing follow-up clinical investigations. Our goal is to capture incident cases of the outcomes, investigate the role of baseline risk factors in disease incidence, and to measure changes in clinical outcomes post-baseline. Continuous follow-up of the cohort will continue, and this is planned to take place at approximately 8-10 years, at which time measurable changes should have occurred in the study population. Those who participated in WSAS II will be similarly followed and

investigated as those in WSAS I. We also obtained consent from participants and ethical approval to link the study data to routine healthcare registers for a continuous follow-up. Linkable registers include the National Board of Health and Welfare (register of causes of deaths, hospitalizations, primary healthcare, and medication prescriptions), Statistics Sweden (containing information on demographics), and the Swedish Health Insurance Authority (register of working life, sickness leaves, and retirement).

#### Data collection

Box 1 contains a summary of the measurements undertaken at different phases of the study. At baseline, participants received a postal self-completed questionnaire that contained questions that have been previously used in the Obstructive Lung Diseases in Northern Sweden (OLIN),<sup>34,35</sup> the Global Allergy and Asthma European Network (GA<sup>2</sup>LEN) studies, the FinEsS studies in Finland, Estonia and Sweden,<sup>36,37</sup> and the European Community Respiratory Health Survey (ECRHS).<sup>38</sup> The questionnaire asked questions about asthma, rhinitis, eczema, chronic bronchitis, COPD, emphysema, respiratory symptoms, use of asthma medications, smoking habits, occupation, socioeconomic status, airborne occupational, and environmental exposures. At the clinical investigations, a detailed structured interview was conducted, asking questions about presence of asthma, asthma symptoms and exacerbations, use of medications, healthcare use, obstructive and non-obstructive diseases, smoking habits, asthma triggers, virus induced exacerbations, and food intolerance. A self-completed questionnaire was also carried out to assess issues of health psychology, asking questions related to self-efficacy, personality traits, depression and anxiety, and quality of life. The interview is followed by physical examinations including mainly lung function measurements with dynamic spirometry and in sub-samples lung volumes, furthermore bronchial provocation test with methacholine, fraction of exhaled NO, and measurement of various biological and blood samples including allergy testing with specific IgE, and skin prick tests. Other planned measurements will include proteomics, transcriptomics, genomics, genetics, and linkage to Swedish population registers.

Box 1 Main measurements at different phases of the West Sweden Asthma Study

Phase	Measurements
Baseline survey: 2008 (WSAS I); 2016 (WSAS I and WSAS II)	Self-completed questionnaire only: Self-reported asthma, allergy, respiratory symptoms, medication use Self-reported socio-economic status; smoking habits; and airborne, occupational, and environmental exposures
First clinical follow- up: 2009-12; 2018- ongoing	Structured clinical interview and self-administered questionnaire: Questions about asthma, allergy, respiratory symptoms, medication use Other questions about smoking habits, food intolerance; self-efficacy; personality traits; beliefs about asthma medications depression and anxiety; and quality of life
	Anthropometric measures: height and weight measurements
	<i>Clinical examinations:</i> Haemoglobin saturation; blood pressure; blood samples; nasal lavage; skin prick test; specific immunoglobulin E; differential cell counts in blood; component resolved diagnostics; body fat; muscle mass; metabolic age (impedance); hand strength with grip pit; forced impulse oscillometry; forced oscillometry technique (small airways); diffusion capacity; functional residual capacity and total lung capacity; dynamic spirometry (Jaeger's Masterscope); methacholine test); exhaled nitric oxide. Other clinical measurements** are: induced sputum, nasal biopsies, nasal swabs for virus determination and bronchoschopy including bronchial biopsies, bronchial lavage and bronchial brushings.
Ongoing/planned: 2019-	Proteomics (conventional proteomics and mass cytometry; CyTOF)** Genomics**
	Transcriptomics (i.e. RNA and microRNA analysis)** Linkage to national healthcare registers

\*\*Carried out in a sub-population of those that were clinically examined

# Findings to date

# Population characteristics

Table 1 shows the distribution of baseline background characteristics of the study population by age and sex. Up to the age of 60 years, more females than males had university education in both WSAS I (2008) and WSAS II (2016) surveys. Whilst the proportion of current smokers was higher in females than males in the youngest age group ( $\leq$ 30 years) in 2008, the proportion of current smokers was similar between males and females in 2016. Across all age groups, more males than females were exposed to gas and fumes at work place both in 2008 and 2016. The proportion of those raised on a farm was similar between males and females in both surveys and the proportion increased by age. More females than males in both surveys reported that they had a family history of allergy or asthma.

# Key findings

By comparing to a previous study performed in the study area in 1990, we determined that whilst the prevalence of most respiratory symptoms, including wheeze, sputum production, and longstanding

 cough, substantially decreased by 2008, the prevalence of physician diagnosed asthma (6% in 1990 versus 8% in 2008) remained relatively stable.<sup>13</sup> However, during the same period, there was a 54% increase in the use of asthma medications, which was primarily driven by a 5-fold (1.5% to 7.7%) increase in the use of inhaled corticosteroids.<sup>33</sup> We have also shown that individuals with multi-symptom asthma (i.e. report of concurrent presence of at least five asthma symptoms, present in 2% of the population) were at greater risk of having morbidity indicators of asthma severity, including lower FEV<sub>1</sub>, higher FeNO levels, elevated hyper-responsiveness, nasal blockage, and chronic rhinosinusitis compared to those with less asthma symptoms.<sup>39,40</sup> By constructing different degrees of asthma severity based on the number of signs of severe asthma indicators, our recent results showed that about 36% of asthmatics expressed at least one sign of severe asthma indicator and that clinical measures of lung performance, inflammation, and allergic sensitization differ among asthmatics with different signs of severe asthma.<sup>41</sup>

Based on our risk factor analyses (Table 2), we have shown that female gender (compared to males) was associated with an increased risk of current asthma and eczema, but not allergic rhinitis.<sup>41</sup> Having concomitant family history of asthma and allergic rhinitis (compared no family history of either conditions) was associated with an increased risk of current asthma and allergic rhinitis, but not current eczema.<sup>42</sup> A family history of allergic rhinitis only was also associated with an increased risk of allergic rhinitis, but not asthma and eczema; a family history of asthma only was not associated with asthma, rhinitis or eczema (Table 2).42 Being raised on a farm was associated with a decreased risk of allergic sensitization, allergic rhinitis and eczema;<sup>42,43,44</sup> whilst it was not associated with asthma among all adults.<sup>42</sup> However, there was a decreased risk of asthma among adolescents (i.e. those 16-20 years of age).<sup>45</sup> In that young age group, being raised on a farm significantly reduced the likelihood of using asthma medicine, OR 0.1 (0.02–0.95).<sup>45</sup> Obese individuals (compared to normal weight) was associated with the risk of asthma and allergic rhinitis, but not eczema.<sup>42</sup> Having at least one sibling was associated with an increased risk of asthma, but not allergic rhinitis, whereas, having two more siblings was associated with a decreased risk of eczema.<sup>42</sup> Sensitization to airborne allergens was associated with an increased risk of asthma, allergic rhinitis, and eczema. Finally, exposure to gas, dust or fumes at work place was associated with an increased risk of asthma and eczema, but not allergic rhinitis (Table 2).42 The risk factors observed for asthma were similarly seen for aspirin-intolerant and aspirin-tolerant asthma.<sup>46</sup> We also showed that personality traits were associated with both beliefs of asthma medication and adherence to treatment, which indicate that individual differences are important in efforts to improve adherence.<sup>47</sup> Ongoing mechanistic studies include analysis of airway and blood samples from well-defined asthma groups where we more specifically investigate the transcriptome profiles (i.e mRNA and microRNA expression). In addition, we are in collaboration the national mass cytometry facility SciLifeLab in Solna, Stockholm, Sweden, to develop a platform with approximately 40 cell surface or intracellular markers that will be analysed from asthmatics samples within WSAS.

## Strengths and limitations

Nordic countries have had a long tradition of implementing a systematic research approach in understanding chronic diseases and their underlying mechanisms: usually starting from population epidemiological studies to clinical investigations, and further to mechanistic investigations and translation. The establishment of population-wide disease and health registers and excellent and well-characterised longitudinal cohorts involving all age groups, with various social, economic, and biological measurements, has continuously allowed multidisciplinary investigations into different chronic diseases.<sup>48,49</sup> Some examples of these studies include the Nordic Medical Birth Registers,<sup>49,50</sup> the Copenhagen City Heart Study,<sup>51</sup> the Hordaland Health Study,<sup>52</sup> the Obstructive Lung Disease in Northern Sweden (OLIN) Studies,<sup>53</sup> and the European Community Respiratory Health Survey,<sup>54</sup> which are still ongoing, have provided longitudinal data, including on respiratory health, for the past 30-50 years. Now, WSAS, representing one example of these population cohort studies, represents one of the largest population-representative studies on asthma in Europe.

The multidisciplinary nature of WSAS – integrating aspects of population epidemiology, clinical and molecular epidemiology, mechanistic investigations, and various translational research approaches - establishes it as a major platform to significantly advance clearer understanding of adult asthma, respiratory conditions, and allergy and their consequent burden to the society. With the extensive clinical and molecular investigations being undertaken, WSAS represents one of unique platforms to undertake cutting-edge investigations of the underlying pathogenesis of asthma, involving detailed characterisation of the phenotypes, thereby potentially supporting more targeted therapy and personalized clinical decision-making. Both size of the study and comprehensiveness of measurements are of great significance in successful asthma phenotyping. Constituting a random sample of the population, findings from WSAS can be generalized to adult population of western Sweden. The survey instruments and procedures used in WSAS, having being largely adapted from other national and international population and clinical studies across Europe, ensures that the internal validity of the study is greatly enhanced, thus enabling direct comparison of our estimates to the findings from those studies both in time and space.<sup>19</sup> Although the participation rate in WSAS was overall average (with a decline between the survey in 2008 and 2016), current trends in population-based surveys also show a continuous decline in response rate over time.<sup>55</sup>

### Collaboration

We welcome discussions from researchers on collaborative projects that will involve the use of WSAS. Currently such collaborations have been established with investigators across the Nordic countries, with the OLIN study, and the FinEsS studies. We are also working towards developing a secure database for hosting data continuously generated from WSAS. The ultimate goal is that, in

due course, with the necessary permission processes in place, collaborators can gain access to the data for research.

## **Further details**

 We are working towards developing a full website that will be dedicated to the WSAS, but summarized descriptions are provided at the website of the Krefting Research Centre, University of Gothenburg, which hosts WSAS, at https://krefting.gu.se/KRC/research. For the meantime, interested researchers should send their enquiries to: linda.ekerljung@lungall.gu.se; bright.nwaru@gu.se; madeleine.radinger@lungall.gu.se.

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# **Competing interests**

None declared

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Table 1. Baseline back	ground charac	teristics of part	icipants in the	e West Swede	en Asthma St	udy (WSAS)	-2018-027888 and s	ex		
				WSAS I*	*		on 19 J Ig for u			
	Freq N = n	uency 18087 (%)	≤30 n = 2 n (	years 3948 (%)	31-45 n = 4 n (	years 4851 %)	Ises relate In the second sec	) years 4956 (%)	61-75 n = 4 n (	years 4312 (%)
	Males	Females	Males	Females	Males	Females		Females	Males	Females
Education level Less than high school High school Tertiary education Missing information Smoking status Non-smoker Ex-smoker Current smoker Occupational exposure to gas, dust and fumes No Yes Raised on a farm No Yes Family history of allergy No Yes	1817 (22.2)         3385 (41.3)         2842 (34.7)         146 (1.8)         5202 (63.5)         1837 (22.4)         1151 (14.0)         5587 (68.2)         2603 (31.8)         7004 (85.5)         1186 (14.5)         5746 (70.2)         2444 (29.8)	2226 (22.5) 3427 (34.6) 4063 (41.1) 181 (1.8) 6227 (62.9) 2139 (21.6) 1531 (15.5) 8551 (86.4) 1346 (13.6) 8526 (86.2) 1371 (13.8) 6010 (60.7) 3887 (39.3)	179 (10.6) 904 (53.3) 568 (33.5) 44 (2.6) 1369 (80.8) 97 (5.7) 229 (13.5) 1250 (73.7) 445 (26.2) 1544 (91.1) 151 (8.9) 952 (56.2) 743 (43.8)	234 (10.4) 1068 (47.4) 922 (40.9) 29 (1.3) 1650 (73.2) 203 (9.0) 400 (17.7) 1939 (86.1) 314 (13.9) 2091 (92.8) 162 (7.2) 1054 (46.8) 1199 (53.2)	151 (7.0) 1030 (47.5) 960 (44.3) 28 (1.3) 1552 (71.5) 330 (15.2) 287 (13.2) 1498 (69.1) 671 (30.9) 1964 (90.5) 205 (9.5) 1417 (65.3) 752 (34.7)	182 (6.8) 1019 (38.0) 1450 (54.1) 31 (1.2) 1801 (67.1) 497 (18.5) 384 (14.3) 2283 (85.1) 399 (14.9) 2443 (91.1) 239 (8.9) 1510 (56.3) 1172 (43.7)	Cupped 23.6)           Supped 29.1)           Supped 29.1)           Supped 29.1)           Supped 29.1)           Supped 29.1)           Supped 20.1)           Supped 20.10           Supped 20.10 </td <td>568 (21.4) 950 (35.7) 1107 (41.6) 34 (1.3) 1426 (53.6) 778 (29.3) 455 (17.1) 2279 (85.7) 380 (14.3) 2223 (83.6) 436 (16.4) 1731 (65.1) 928 (34.9)</td> <td>944 (46.6) 513 (25.3) 531 (26.2) 39 (1.9) 1021 (50.4) 741 (36.6) 265 (13.1) 1306 (64.4) 721 (35.6) 1568 (77.4) 459 (22.6) 1670 (82.4) 357 (17.6)</td> <td>1236 (54.1) 384 (16.8) 579 (25.3) 86 (3.8) 1343 (58.8) 655 (28.7) 287 (12.6) 2035 (89.1) 250 (10.9) 1757 (76.9) 528 (23.1) 1704 (74.6) 581 (25.4)</td>	568 (21.4) 950 (35.7) 1107 (41.6) 34 (1.3) 1426 (53.6) 778 (29.3) 455 (17.1) 2279 (85.7) 380 (14.3) 2223 (83.6) 436 (16.4) 1731 (65.1) 928 (34.9)	944 (46.6) 513 (25.3) 531 (26.2) 39 (1.9) 1021 (50.4) 741 (36.6) 265 (13.1) 1306 (64.4) 721 (35.6) 1568 (77.4) 459 (22.6) 1670 (82.4) 357 (17.6)	1236 (54.1) 384 (16.8) 579 (25.3) 86 (3.8) 1343 (58.8) 655 (28.7) 287 (12.6) 2035 (89.1) 250 (10.9) 1757 (76.9) 528 (23.1) 1704 (74.6) 581 (25.4)
				WSAS I	I		25 at , gies.			
	Freq N =	uency 24534 (%)	≤30 n = 4	years 4209 ′%)	31-45 n = t	years 5502 %)	Agen 46-60 ce n = B n 1	) years 6957 (%)	61-75 n = -	years 7866 %)
	Males <i>n</i> = 11204	Females <i>n</i> = 13330	Males <i>n</i> =1787	Females n = 2422	Males n = 2456	Females <i>n</i> = 3046	Majes n = 135	Females <i>n</i> = 3822	Males n = 3826	Females <i>n</i> = 4040
Education level	2006 (18 7)	2152 (16 1)	210 (11 7)	220 (0 1)	145 (5 0)	147 (4 8)		352 (0.2)	1203 (33.8)	1/133 (35 5)

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2	High school	4700 (41.9)	4591 (34.4)	969 (54.2)	1160 (47.9)	944 (38.4)	878 (28.8)	1467446.8)	1564 (40.9)	1320 (34.5)	989 (24.5)
3	Tertiary education	4294 (38.3)	6415 (48.1)	591 (33.1)	1020 (42.1)	1343 (54.7)	1995 (65.5)	101913(38.0)	1865 (48.8)	1169 (30.5)	1535 (38.0)
4	Missing information	114 (1.0)	172 (1.3)	17 (1.0)	22 (0.9)	24 (1.0)	26 (0.9)	<b>ຣົ</b> 29 <b>ຮ</b> ັບ.9)	41 (1.1)	44 (1.2)	83 (2.0)
5	Smoking status							or			
6	Non-smoker	7167 (64.0)	8585 (64.4)	1406 (78.7)	1865 (77.0)	1804 (73.5)	2226 (73.1)	2095 <u>4</u> 66.8)	2336 (61.1)	1862 (48.7)	2158 (53.4)
7	Ex-smoker	2725 (24.3)	3109 (23.3)	134 (7.5)	201 (8.3)	376 (15.3)	537 (17.6)	<u>6</u> 64 (21.2)	974 (25.5)	1551 (40.5)	1397 (34.6)
8	Current smoker	1312 (11.7)	1636 (12.3)	247 (13.8)	356 (14.7)	276 (11.2)	283 (9.3)	<b>875</b> 5€12.0)	512 (13.4)	413 (10.8)	485 (12.0)
9	Occupational exposure to gas,							sei			
10	dust and fumes							019 gne			
11	No	8147 (72.7)	11923 (89.4)	1385 (77.5)	2161 (89.2)	1865 (75.9)	2732 (89.7)	22258 (72.0)	3425 (89.6)	2639 (69.0)	3605 (89.2)
12	Yes	3057 (27.3)	1407 (10.6)	402 (22.5)	261 (10.8)	591 (24.1)	314 (10.3)	<b>879 (</b> 28.0)	397 (10.4)	1187 (31.0)	435 (10.8)
13	Raised on a farm							te Sch			
14	No	9892 (88.3)	11814 (88.6)	1651 (92.4)	2257 (93.2)	2272 (92.5)	2768 (90.9)	26	3424 (89.6)	3155 (82.5)	3365 (83.3)
15	Yes	1312 (11.7)	1516 (11.4)	136 (7.6)	165 (6.8)	184 (7.5)	278 (9.1)	<u></u>	398 (10.4)	671 (17.5)	675 (16.7)
16	Family history of allergy							da l fr			
17	No	7711 (68.8)	8041 (60.3)	928 (51.9)	1107 (45.7)	1514 (61.6)	1624 (53.3)	255 <b>3693</b> (69.5)	2334 (61.1)	3090 (80.8)	6066 (77.1)
18	Yes	3492 (31.2)	5289 (39.7)	859 (48.1)	1315 (54.3)	942 (38.4)	1422 (46.7)	<b>956</b> (30.5)	1488 (38.9)	736 (19.29	1800 (22.9)
19	**20 participants had mis	ssing informat	ion for age and	d were therefore	ore excluded	from age-stra	itified analyse	es n. St			
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Tables 2. Key results of risk factors for asthma,	allergic rhinitis, and atopic eczema reported from
the West Sweden Asthma Study (WSAS I)	

		Adjusted estimates <sup>1</sup>	
Risk factor	Current asthma <sup>2</sup>	Current allergic	Current eczema <sup>4</sup>
	OR (95% CI)	rhinitis <sup>3</sup>	OR (95% CI)
		OR (95% CI)	• • •
Female gender⁵	1.77 (1.15-2.70)	0.91 (0.69-1.21)	1.71 (1.17-2.51)
Family history of asthma and allergic rhinitis <sup>5</sup>			
None	1	1	1
Asthma only	1.29 (0.55-3.04)	0.61 (0.34-1.10)	1.45 (0.72-2.94)
Allergic rhinitis only	1.16 (0.66-2.03)	2.58 (1.79-3.72)	1.25 (0.77-2.04)
Both asthma and allergic rhinitis	4.33 (2.57-7.30)	2.76 (1.77-4.31)	1.61 (0.94-2.76)
Raised on a farm <sup>5,6</sup>	0.96 (0.52-1.77)	0.64 (0.42-0.96)	0.51 (0.27-0.99)
Body mass index			
Normal (20-25 kg/m <sup>2</sup> )	1	1	1
Underweight (<20 kg/m <sup>2</sup> )	0.95 (0.36-2.55)	1.42 (0.74-2.71)	1.00 (0.44-2.30)
Overweight (25-30 kg/m <sup>2</sup> )	1.04 (0.65-1.67)	1.04 (0.77-1.41)	1.02 (0.68-1.54)
Obese (>30 kg/m <sup>2</sup> )	1.95 (1.13-3.36)	2.30 (1.53-3.46)	1.34 (0.80-2.24)
Number of siblings			
0	1	1	1
1	3.09 (1.25-7.63)	1.16 (0.74-1.81)	0.72 (0.42-1.24)
2 or more	2.51 (1.02-6.15)	1.15 (0.74-1.79)	0.55 (0.32-0.94)
Allergic sensitization <sup>5,7</sup>	4.11 (2.71-6.25)	5.11 (3.77-6.93)	1.26 (0.85-1.85)
Exposure to gas, dust or fumes at work	1.85 (1.20-2.87)	1.03 (0.76-1.41)	2.08 (1.40-3.08)

<sup>1</sup>Respective to each outcome, the estimates adjusted for age, gender, family history of asthma and rhinitis, exposure to gas and gas fumes at work place, body mass index, number of siblings, daycare attendance during childhood, and being raised on a farm

<sup>2</sup>Current asthma was defined as follows: ever had asthma or ever diagnosed with asthma by a physician and at least one of: reported use of asthma medication, or recurrent wheeze, or attacks of shortness of breath during the last 12 months.

<sup>3</sup>Allergic rhinitis was defined as follows: having had sneezing, runny nose or nasal blocking apart from colds during the last 12 months and having these nasal symptoms occurred simultaneously with itching and running eyes"

<sup>4</sup>Defined as having ever had recurrent itchy rash for at least 6 months and having had itchy rash during the last 12 months

<sup>5</sup>Reported in Rönmark EP et al. Different risk factor patterns for adult asthma, rhinitis and eczema: results from West Sweden Asthma Study. *Clin Transl Allergy* 2016; 6:28.

<sup>6</sup>Reported in Eriksson J, et al. Growing up on a farm leads to lifelong protection against allergic rhinitis. *Allergy* 2010; 65: 1397-1403.

<sup>7</sup>Allergic sensitization defined as serum immunoglobulin E to ImmunoCAP® Phadiatop ≥0.35 KU/1 to at least one of the following 11 airborne allergens: timothy grass, birch, mugwort, olive, parietaria, cat, dog, horse, D. pteronyssinus, D. farinae, and C. herbarum.

# **BMJ Open**

## Cohort Profile: The West Sweden Asthma Study (WSAS): a multi-disciplinary population-based longitudinal study of asthma, allergy, and respiratory conditions in adults

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SCHOLARONE<sup>™</sup> Manuscripts

1 2	1	Cohort Profile: The West Sweden Asthma Study (WSAS): a multi-disciplinary population-								
3	2	based longitudinal study of asthma, allergy, and respiratory conditions in adults								
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41 42	26	Keywords: adults, allergy, asthma, cohort profile, longitudinal cohort, Sweden								
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#### ABSTRACT

Purpose: The West Sweden Asthma Study (WSAS) is a population-representative longitudinal study established to: (1) generate data on prevalence trends, incidence, and remission of asthma, allergy, and respiratory conditions; (2) elucidate on the risk and prognostic factors associated with these diseases; (3) characterise clinically relevant phenotypes of these diseases; and (4) catalyse relevant mechanistic, genomic, genetic, and translational investigations. 

Participants: WSAS comprised of randomly selected individuals aged 16-75 years who are followed up longitudinally. The first stage involved a questionnaire survey (>42,000 participants) was undertaken in 2008 and 2016. A random sample (about 8000) of participants in the initial survey undergoes extensive clinical investigations every 8-10 years (first investigations in 2009-2012; second wave currently ongoing). Measurements undertaken at the clinical investigations involve structured interviews, self-completed questionnaire on personality traits, physical measurements, and extensive biological samples.

Findings to date: Some of our key findings have shown a 54% increase in the use of asthma medications between the 1990s and 2000s, primarily driven by a 5-fold increase in the use of inhaled corticosteroids. About 36% of asthmatics expressed at least one sign of severe asthma indicator, with differential lung performance, inflammation, and allergic sensitization among asthmatics with different signs of severe asthma. Multi-symptom asthmatics were at greater risk of having indicators of severe asthma. In all adults, being raised on a farm was associated with a decreased risk of allergic sensitization, rhinitis and eczema, but not asthma. However, among adolescents (i.e. those 16-20 years of age), being raised on a farm decreased the risk of asthma. Personality traits were associated with both beliefs of asthma medication and adherence to treatment. 

Future plans: Follow-up of the cohort is being undertaken every 8-10 years. The repeated clinical examinations will take place in 2019-2022. The cohort data are currently being linked to routine Swedish healthcare registers for a continuous follow-up. Mechanistic, genomic, genetic, and translational investigations are ongoing.

2	77	Stren	gths and limitations of this study:
3 4 5 6 7	78 79 80 81	•	The West Sweden Asthma Study (WSAS) is a large-scale multi-disciplinary population- representative longitudinal study on adult asthma and respiratory health, representing one of the largest of such cohorts in Europe.
8 9 10 11 12	82 83 84 85	•	WSAS has several ongoing collaborations with investigators across the Nordic countries, with the OLIN studies, and the FinEsS studies in Finland, Estonia and Sweden and the survey instruments used have been adapted from these ongoing studies.
13 14 15 16 17	86 87 88 89 90	•	With a large sample size, comprehensive measures, and long-term longitudinal design, WSAS provides an opportunity for a continuous generation of contemporary data on the trends in incidence and prevalence of adult asthma and successfully undertaking disease phenotyping.
18 19 20 21 22	91 92 93 94	•	With the extensive clinical and molecular investigations being undertaken, WSAS represents one of unique platforms to undertake cutting-edge mechanistic, genomic, genetic, and translational investigations of the underlying pathogenesis of asthma.
23 24 25 26	95 96 97	•	Although the participation rate in WSAS was overall average (with a decline between the surveys in 2008 and 2016), we anticipate, as reflected in current trends in population-based surveys, a continuous decline in response rate over time.
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## 2 120 Introduction

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3 According to the 2015 Global Burden of Disease study, nearly 400 million people across all age 121 4 5 122 groups currently live with asthma globally.<sup>1</sup> The report also ranked asthma among the ten causes of 6 disability in 2015, affecting people of all ages, sexes, and races.<sup>1</sup> From the latter half of the last 123 7 8 124 century, the prevalence of asthma was seen to be increasing across different parts of the world.<sup>2-5</sup> 9 10 125 Whilst some recent data indicate a levelling off in some parts of the world, particularly in Australia<sup>2,6,7</sup> 11 and some European countries,<sup>2,8-14</sup> other evidence suggests a continuing increase in urbanised 126 12 settings of low- and middle-income countries<sup>15</sup> and some increase in some parts of Europe, e.g. 13 127 14 15 128 Finland, Italy, and Sweden.<sup>16-19</sup> Much of the available data on asthma prevalence trends have 16 129 however emanated from children and adolescent populations. There are paucity of data on the 17 18 130 prevalence trends in adults, particularly the trends after the 1990s.<sup>2</sup> Well-designed population-19 representative long-term longitudinal studies are required to obtain contemporary trends in the 131 20 prevalence of asthma in adults. 21 132

24 134 Over the last decade, our understanding of the pathogenesis of asthma has been greatly 25 <sub>26</sub> 135 advancing.<sup>19-21</sup> Contrary to previous understanding, it is now continuously appreciated that asthma <sup>27</sup> 136 is a complex and heterogeneous syndrome with different underlying distinct phenotypes.<sup>20-24</sup> These 28 29 137 phenotypes tend to present with varying clinical pictures, prognosis, risk factors, and response to 30 138 treatment.<sup>22-24</sup> Through analyses of several children cohorts, common asthma phenotypes have 31 32 139 been characterized, including transient wheezing, non-atopic wheezing, and IgE-mediated 33 140 wheezing.<sup>25,26</sup> In contrast, the lack of well-designed population-representative cohorts has meant 34 <sup>35</sup> 141 that far less knowledge has been gained regarding asthma phenotypes in adults. There are today 36 <sub>37</sub> 142 several partly similar suggested groupings of asthma phenotypes in adults; one of the common 38 143 approaches has been to group them into three: (1) trigger-induced asthma (e.g. occupational 39 asthma, cigarette smoke-induced asthma, exercise-induced asthma); (2) symptom-based asthma 40 144 41 (e.g. asthma with persistent airflow limitation, adult-onset asthma, obesity-related asthma); and (3) 145 42 43 146 biomarker-based asthma (e.g. eosinophilic associated asthma).<sup>23,25,27,28</sup> Adult-onset asthma is 44 45 147 different from asthma in childhood<sup>29,30</sup> and it is less associated with allergy and atopy, but is often <sup>46</sup> 148 associated with obesity, represents more severe disease, has low remission rate, poor prognosis 47 and faster decline in lung function.<sup>30,31</sup> Definitive phenotyping of adult asthma will engender better 48 149 49 150 insights into the potential disease mechanisms and will help to identify potentially relevant 50 biomarkers that can aid more targeted treatment.<sup>24,32,33</sup> 51 151

The West Sweden Asthma Study (WSAS)<sup>13</sup> is a large-scale multi-disciplinary populationrepresentative longitudinal study on asthma, which was established in 2008 with the overarching aim of contributing to better understanding of asthma in adults. WSAS has both short- and long-term goals (Figure 1). The short-term goal is to generate data on the trends in prevalence, incidence, and remission of asthma, respiratory conditions, chronic obstructive pulmonary disease (COPD), and

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<sup>19</sup> 169 20 **BMJ** Open

allergic diseases in adults in the western Swedish population and to elucidate on the risk and 2 158 3 prognostic factors associated with these diseases, as well as the patterns in asthma remission. The 159 4 5 160 long-term goals are to: (1) characterise clinically relevant phenotypes of asthma, allergy and 6 respiratory conditions and perform detailed clinical and molecular epidemiologic investigations of 161 7 8 162 these conditions; and (2) catalyse relevant mechanistic, genomic, genetic, and translational 9 investigations for better understanding of asthma. 10 163

#### 13 165 Cohort description

<sup>14</sup> 15 166 *Ethics approval* 

The study and its sub-studies have been approved by the local Ethics Committee at the University
 of Gothenburg.

#### 21 170 Study population

22 WSAS involves an initial cross-sectional survey of randomly selected individuals aged 16-75 years 171 23 24 172 who are then subsequently followed up longitudinally (Figure 2).<sup>13,34</sup> The first survey (WSAS I) was 25 <sub>26</sub> 173 undertaken in 2008 in which a random sample of 30 000 people (representative of the age and sex <sup>27</sup> 174 composition of the study area) were invited. Of the survey participants, excluding those who were 28 29 175 not traceable (n=782), 18 087 (all 62%; women 67%; men 56%) participated in the study. From the 30 176 participants, a random sample of 2000 people from all participants and additional 1524 subjects with 31 32 177 asthma (altogether 3524 people) were invited to take part in extensive clinical investigations. Of 33 178 those invited, 2006 participated in the clinical investigations, which took place between 2009 and 34 35 179 2012.33 A second survey (WSAS II) was carried out in 2016 in which a random sample of 50 000 36 <sub>37</sub> 180 people of the same age group as in WSAS I were invited to take part in the study. The sampling 38 181 base (areas covered) in WSAS II did not fully overlap with WSAS I; moreover, each survey 39 constitutes different participants. In total, 24 534 (all 50%; women 56%; men 46%) of the 50 000 40 182 41 183 invited participated in the study. About 2200 of those that participated in WSAS II have current 42 43 184 asthma; in addition to these, 4000 random sample from all participants (altogether 6200 people) will 44 45 <sup>185</sup> be invited to take part in the extensive clinical phase of the study. The goal of WSAS II was to study <sup>46</sup> 186 prevalence change and also to expand the overall study base and to enhance the number of 47 48 187 participants included in subsequent clinical phases of the study.

#### 51 189 Cohort follow-up

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52 Those who participated in WSAS I in 2008 were invited for a follow-up survey in 2016. In addition, 190 53 54 191 those who took part in the clinical investigations between 2009 and 2012 have been invited and are 55 <sub>56</sub> 192 currently undergoing follow-up clinical investigations. Our goal is to capture incident cases of the 57 193 outcomes, investigate the role of baseline risk factors in disease incidence, and to measure changes 58 59 194 in clinical outcomes post-baseline. Continuous follow-up of the cohort will continue, and this is 60 195 planned to take place at approximately 8-10 years, at which time measurable changes should have

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196 occurred in the study population. Those who participated in WSAS II will be similarly followed and 197 investigated as those in WSAS I. We also obtained consent from participants and ethical approval 198 to link the study data to routine healthcare registers for a continuous follow-up. Linkable registers 199 include the National Board of Health and Welfare (register of causes of deaths, hospitalizations, 200 primary healthcare, and medication prescriptions), Statistics Sweden (containing information on 10 201 demographics), and the Swedish Health Insurance Authority (register of working life, sickness 11 202 leaves, and retirement). 12

#### 15<sup>204</sup> Data collection

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16 205 Box 1 contains a summary of the measurements undertaken at different phases of the study. At 17 18 206 baseline, participants received a postal self-completed questionnaire that contained questions that 19 207 have been previously used in the Obstructive Lung Diseases in Northern Sweden (OLIN),<sup>35,36</sup> the 20 Global Allergy and Asthma European Network (GA<sup>2</sup>LEN) studies, the FinEsS studies in Finland, 21 208 22 209 Estonia and Sweden,<sup>37,38</sup> and the European Community Respiratory Health Survey (ECRHS).<sup>39</sup> The 23 24 210 questions adapted from OLIN and ECRHS focused on asthma, rhinitis. chronic 25 <sub>26</sub> 211 bronchitis/COPD/emphysema, respiratory symptoms, use of asthma medication and potential risk <sup>27</sup> 212 factors, including smoking habits, family history of respiratory diseases, type of occupation, 28 29 213 occupational and environmental exposures, co-morbidities, and socio-economic status. The 30 214 GA<sup>2</sup>LEN guestionnaire was used to add detailed guestions about rhinitis and eczema. The applicable 31 32 215 sections of the questionnaire were translated into Swedish before use in the study. A sample ECRHS 33 216 questionnaire is publicly available at http://www.ecrhs.org/Quests/ECRHSIImainquestionnaire.pdf. 34 <sup>35</sup> 217 At the clinical investigations, a detailed structured interview is conducted, asking questions about 36 <sub>37</sub> 218 presence of asthma, asthma symptoms and exacerbations, use of medications, healthcare use, 38 219 obstructive and non-obstructive diseases, smoking habits, asthma triggers, virus induced 39 exacerbations, and food intolerance. A self-completed questionnaire is also carried out to assess 40 220 41 221 issues of health psychology, asking questions related to self-efficacy, personality traits, depression 42 43 222 and anxiety, and quality of life. The interview is followed by physical examinations including mainly 44 45<sup>223</sup> lung function measurements with dynamic spirometry and in sub-samples lung volumes, furthermore <sup>46</sup> 224 bronchial provocation test with methacholine, fraction of exhaled NO, and measurement of various 47 48 225 biological and blood samples including allergy testing with specific IgE, and skin prick tests. Other 49 226 planned measurements will include proteomics, transcriptomics, genomics, genetics, and linkage to 50 51 227 Swedish population registers.

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54 229 Patient and Public Involvement 55

<sub>56</sub> 230 There was no patient or public involvement in this study.

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Box 1 Main measurements at different phases of the West Sweden Asthma Study

Phase	Measurements
Baseline survey: 2008 (WSAS I); 2016 (WSAS I and WSAS II)	Self-completed questionnaire only: Self-reported asthma, allergy, respiratory symptoms, medication use Self-reported socio-economic status; smoking habits; and airborne, occupational, and environmental exposures
First clinical follow- up: 2009-12; 2018- ongoing	Structured clinical interview and self-administered questionnaire: Questions about asthma, allergy, respiratory symptoms, medication use Other questions about smoking habits, food intolerance; self-efficacy; personality traits; beliefs about asthma medications depression and anxiety; and quality of life
	Anthropometric measures: height and weight measurements
	Clinical examinations: Haemoglobin saturation; blood pressure; blood samples; nasal lavage; skin prick test; specific immunoglobulin E; differential cell counts in blood; component resolved diagnostics; body fat; muscle mass; metabolic age (impedance); hand strength with grip pit; forced impulse oscillometry; forced oscillometry technique (small airways); diffusion capacity; functional residual capacity and total lung capacity; dynamic spirometry (Jaeger's Masterscope); methacholine test); exhaled nitric oxide. Other clinical measurements** are: induced sputum, nasal biopsies, nasal swabs for virus determination and bronchoschopy including bronchial biopsies, bronchial lavage and bronchial brushings.
Ongoing/planned:	Proteomics (conventional proteomics and mass cytometry; CyTOF)**
2019-	Transcriptomics (i.e. RNA and microRNA analysis)**

Carried out in a sub-population of those that were clinically examined

# Findings to date

## Population characteristics

Table 1 shows the distribution of baseline background characteristics of the study population by age and sex. Up to the age of 60 years, more females than males had university education in both WSAS 46 241 I (2008) and WSAS II (2016) surveys. Whilst the proportion of current smokers was higher in females 242 than males in the youngest age group (≤30 years) in 2008, the proportion of current smokers was similar between males and females in 2016. Across all age groups, more males than females were 49 243 exposed to gas and fumes at work place both in 2008 and 2016. The proportion of those raised on 244 52 245 a farm was similar between males and females in both surveys and the proportion increased by age. <sub>54</sub> 246 More females than males in both surveys reported that they had a family history of allergy or asthma. <sup>55</sup> 247

#### 56 57 248 Key findings

58 249 The following findings are based only in WSAS I as analyses of WSAS II are currently ongoing. The 59 following constitute the definitions used for the respective outcomes for which findings are reported 60 250

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1 251 below: Physician diagnosed asthma was defined based on a positive response to the question: 2 3 "Have you been diagnosed as having asthma by a doctor?" Current asthma was defined as ever had 252 4 5 253 asthma or diagnosed with asthma by a doctor and at least 1 of the following: reported use of asthma 6 254 medication, or recurrent wheeze, or attacks of shortness of breath during the last 12 months. Current 7 8 255 allergic rhinitis was defined as having had sneezing, runny nose, or nasal blocking apart from colds 9 10 256 during the last 12 months and having these nasal symptoms occurring simultaneously with itching 11 257 and running eyes. The definitions of eczema, which we have previously used,<sup>40</sup> were based on 12 answers to the following questions: Itchy rash: 'Have you ever had an itchy rash which was coming 13 258 14 259 and going for at least six months?' Hand eczema only: 'Does this (itchy rash) only affect your hands?' 15 16 260 Current atopic eczema: 'Have you had this itchy rash in the last 12 months?' Eczema ever: 'Have 17 18 261 you ever had eczema or any kind of skin allergy?' By comparing to a previous study performed in 19 262 the study area in 1990, we determined that whilst the prevalence of most respiratory symptoms, 20 including wheeze, sputum production, and longstanding cough, substantially decreased by 2008, 21 263 22 264 the prevalence of physician diagnosed asthma (6% in 1990 versus 8% in 2008) remained relatively 23 24 265 stable.<sup>13</sup> However, during the same period, there was a 54% increase in the use of asthma 25 <sub>26</sub> 266 medications, which was primarily driven by a 5-fold (1.5% to 7.7%) increase in the use of inhaled 27 267 corticosteroids.<sup>34</sup> We have also shown that individuals with multi-symptom asthma (i.e. report of 28 29 268 concurrent presence of at least five asthma symptoms, present in 2% of the population) were at 30 269 greater risk of having morbidity indicators of asthma severity, including lower FEV<sub>1</sub>, higher FeNO 31 32 270 levels, elevated hyper-responsiveness, nasal blockage, and chronic rhinosinusitis compared to 33 271 those with less asthma symptoms.<sup>41,42</sup> By constructing different degrees of asthma severity based 34 <sup>35</sup> 272 on the number of signs of severe asthma indicators, our recent results showed that about 36% of 36 <sub>37</sub> 273 asthmatics expressed at least one sign of severe asthma indicator and that clinical measures of lung 38 274 performance, inflammation, and allergic sensitization differ among asthmatics with different signs of 39 severe asthma.43 40 275 41

43 277 Based on our risk factor analyses (Table 2) of WSAS I only (analyses of WSAS II are ongoing and 44 45 278 not included in these results), we have shown that female gender (compared to males) was <sup>46</sup> 279 associated with an increased risk of current asthma and eczema, but not allergic rhinitis.43 Having 47 48 280 concomitant family history of asthma and allergic rhinitis (compared no family history of either 49 281 conditions) was associated with an increased risk of current asthma and allergic rhinitis, but not 50 51 282 current eczema.<sup>44</sup> A family history of allergic rhinitis only was also associated with an increased risk 52 283 of allergic rhinitis, but not asthma and eczema; a family history of asthma only was not associated 53 54 284 with asthma, rhinitis or eczema (Table 2).44 Being raised on a farm was associated with a decreased 55 <sub>56</sub> 285 risk of allergic sensitization, allergic rhinitis and eczema;<sup>44-46</sup> whilst it was not associated with asthma 57 286 among all adults.<sup>44</sup> However, there was a decreased risk of asthma among adolescents (i.e. those 58 59 287 16-20 years of age).<sup>47</sup> In that young age group, being raised on a farm significantly reduced the 60 288 likelihood of using asthma medicine, OR 0.1 (0.02–0.95).47 Obese individuals (compared to normal

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289 weight) was associated with the risk of asthma and allergic rhinitis, but not eczema.<sup>44</sup> Having at least one sibling was associated with an increased risk of asthma, but not allergic rhinitis, whereas, having 290 291 two more siblings was associated with a decreased risk of eczema.44 The strongest risk factor for 292 eczema was family history of both asthma and allergy.<sup>40</sup> Sensitization to airborne allergens was 293 associated with an increased risk of asthma, allergic rhinitis, and eczema. Finally, exposure to gas, 10 294 dust or fumes at work place was associated with an increased risk of asthma and eczema, but not 11 295 allergic rhinitis (Table 2).44 The risk factors observed for asthma were similarly seen for aspirin-12 intolerant and aspirin-tolerant asthma.<sup>48</sup> We also showed that personality traits were associated with 13 296 14 297 both beliefs of asthma medication and adherence to treatment, which indicate that individual 15 16 298 differences are important in efforts to improve adherence.<sup>49</sup> Ongoing mechanistic studies include 17 18 299 analysis of airway and blood samples from well-defined asthma groups where we more specifically 19 300 investigate the transcriptome profiles (i.e mRNA and microRNA expression). In addition, we are in 20 collaboration the national mass cytometry facility SciLifeLab in Solna, Stockholm, Sweden, to 21 301 22 302 develop a platform with approximately 40-cell surface or intracellular markers that will be analysed 23 24 303 from asthmatics samples within WSAS. 25

#### 305 Strengths and limitations

28 Nordic countries have had a long tradition of implementing a systematic research approach in 29 306 30 307 understanding chronic diseases and their underlying mechanisms: usually starting from population 31 32 308 epidemiological studies to clinical investigations, and further to mechanistic investigations and 33 309 translation. The establishment of population-wide disease and health registers and excellent and 34 <sup>35</sup> 310 well-characterised longitudinal cohorts involving all age groups, with various social, economic, and 36 <sub>37</sub> 311 biological measurements, has continuously allowed multidisciplinary investigations into different <sup>38</sup> 312 chronic diseases.<sup>50,51</sup> Some examples of these studies include the Nordic Medical Birth 39 40 313 Registers,<sup>51,52</sup> the Copenhagen City Heart Study,<sup>53</sup> the Hordaland Health Study,<sup>54</sup> the Obstructive 41 Lung Disease in Northern Sweden (OLIN) Studies,<sup>55</sup> and the European Community Respiratory 314 42 43 315 Health Survey,<sup>56</sup> which are still ongoing, have provided longitudinal data, including on respiratory 44 45 316 health, for the past 30-50 years. Now, WSAS, representing one example of these population cohort <sup>46</sup> 317 studies, represents one of the largest population-representative studies on asthma in Europe. 47

49 319 The multidisciplinary nature of WSAS - integrating aspects of population epidemiology, clinical and 50 51 320 molecular epidemiology, mechanistic investigations, and various translational research approaches 52 321 – establishes it as a major platform to significantly advance clearer understanding of adult asthma, 53 54 322 respiratory conditions, and allergy and their consequent burden to the society. With the extensive 55 <sub>56</sub> 323 clinical and molecular investigations being undertaken, WSAS represents one of unique platforms <sup>57</sup> 324 to undertake cutting-edge investigations of the underlying pathogenesis of asthma, involving detailed 58 59 325 characterisation of the phenotypes, thereby potentially supporting more targeted therapy and 60 326 personalized clinical decision-making. Both size of the study and comprehensiveness of

measurements are of great significance in successful asthma phenotyping. Constituting a random 327 sample of the population, findings from WSAS can be generalized to adult population of western 328 329 Sweden. The survey instruments and procedures used in WSAS, having being largely adapted from other national and international population and clinical studies across Europe, ensures that the 330 331 internal validity of the study is greatly enhanced, thus enabling direct comparison of our estimates to 10 332 the findings from those studies both in time and space.<sup>20</sup> The main limitation of this study is the 11 anticipated decline in participation rate over time. Although the participation rate in WSAS was 333 12 13 334 overall average (with a decline between the survey in 2008 and 2016), current trends in population-14 based surveys also show a continuous decline in response rate over time.<sup>57</sup> Furthermore, as the 335 15 16 336 study primarily focused on asthma, clinical examination of the nose and skin was not performed. 17

#### Collaboration 338

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We welcome discussions from researchers on collaborative projects that will involve the use of 21 339 340 WSAS. Currently such collaborations have been established with investigators across the Nordic 24 341 countries, with the OLIN study, and the FinEsS studies. We are also working towards developing a 26 342 secure database for hosting data continuously generated from WSAS. The ultimate goal is that, in 343 due course, with the necessary permission processes in place, collaborators can gain access to the 29 344 data for research.

#### 32 346 **Contributorship statement**

347 Designed the study (BL, JL, LE). Responsible for the study database (LE, BN, MR). Participated in 348 data collection (BL, JL, LE, MR, RM, GW, CM, MA, AB). Planned and executed the statistical 37 349 analyses and drafted the manuscript (BN, BL, LE, RM, GW, AB). All authors participated in data 350 interpretation, writing of the manuscript and review the data presented. All authors approved the final manuscript. 40 351

#### 43 353 Data availability statement

45 354 Data collection is still ongoing and cannot be shared at the moment. Please contacts below for those <sup>46</sup> 355 would want to know more about the study and would like to collaborate.

#### 357 **Further details**

51 358 We are working towards developing a full website that will be dedicated to the WSAS, but 52 359 summarized descriptions are provided at the website of the Krefting Research Centre, University of 53 54 360 Gothenburg, which hosts WSAS, at https://krefting.gu.se/KRC/research. For the meantime, 55 <sub>56</sub> 361 interested researchers should send their enquiries to: linda.ekerljung@lungall.gu.se; 57 362 bright.nwaru@gu.se; madeleine.radinger@lungall.gu.se. 58

- 59 363
- 60 364 Funding

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The views expressed in this paper are those of the authors and not those of the funders. 368

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#### 377 **Competing interests**

21 378 None declared 22

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1 2 517	FIGURE LEGENDS
$\frac{3}{4}$ 518	Figure 1: Phases and components of investigations in the West Sweden Asthma Study
5 519	Figure 2: Participants flow in the West Sweden Asthma Study
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<b>Table 1</b> Baseline background characteristics of participants in the West Sweden Asthma Study (WSA)	S) byĽa	de and sex
Tuble II Bacane background characteristics of participants in the west Sweden Astrina Olday (WOA	⊂, Jy=u	Secure Sex

1 2	Table 1. Baseline backg	ground charact	eristics of part	icipants in the	e West Swede	en Asthma St	udy (WSAS)	by <u>⊢</u> age	and s	ex		
3 4 5					WSAS I*	*		27808 on				
6 7 8		Freq N =	uency 18087 (%)	≤30 n = 5	years 3948 %)	31-45 n = 4	years 4851 %)	19 June Enst for uses	46-60 n = 4	years 4956 %)	61-75 n = 4	years 1312 %)
9 10 11		Males n = 8190	Females n = 9897	Males n = 1695	Females n = 2253	Males n = 2169	Females n = 2682	20789.22 relate8	es 297	Females n = 2659	Males n = 2027	Females n = 2285
12 13 14 15 16	Education level Less than high school High school Tertiary education Missing information	1817 (22.2) 3385 (41.3) 2842 (34.7) 146 (1.8)	2226 (22.5) 3427 (34.6) 4063 (41.1) 181 (1.8)	179 (10.6) 904 (53.3) 568 (33.5) 44 (2.6)	234 (10.4) 1068 (47.4) 922 (40.9) 29 (1.3)	151 (7.0) 1030 (47.5) 960 (44.3) 28 (1.3)	182 (6.8) 1019 (38.0) 1450 (54.1) 31 (1.2)	ow Noad Sa Tro ent 옃ubeffett? to textrained dat	3.6) 0.8) 4.1) .5)	568 (21.4) 950 (35.7) 1107 (41.6) 34 (1.3)	944 (46.6) 513 (25.3) 531 (26.2) 39 (1.9)	1236 (54.1) 384 (16.8) 579 (25.3) 86 (3.8)
17 18 19 20	Smoking status Non-smoker Ex-smoker Current smoker	5202 (63.5) 1837 (22.4) 1151 (14.0)	6227 (62.9) 2139 (21.6) 1531 (15.5)	1369 (80.8) 97 (5.7) 229 (13.5)	1650 (73.2) 203 (9.0) 400 (17.7)	1552 (71.5) 330 (15.2) 287 (13.2)	1801 (67.1) 497 (18.5) 384 (14.3)		54.8) 9.1) 6.1)	1426 (53.6) 778 (29.3) 455 (17.1)	1021 (50.4) 741 (36.6) 265 (13.1)	1343 (58.8) 655 (28.7) 287 (12.6)
21 22 23 24	dust and fumes No Yes	5587 (68.2) 2603 (31.8)	8551 (86.4) 1346 (13.6)	1250 (73.7) 445 (26.2)	1939 (86.1) 314 (13.9)	1498 (69.1) 671 (30.9)	2283 (85.1) 399 (14.9)	1 traib3176	6.6) 3.3)	2279 (85.7) 380 (14.3)	1306 (64.4) 721 (35.6)	2035 (89.1) 250 (10.9)
25 26 27	No Yes	7004 (85.5) 1186 (14.5)	8526 (86.2) 1371 (13.8)	1544 (91.1) 151 (8.9)	2091 (92.8) 162 (7.2)	1964 (90.5) 205 (9.5)	2443 (91.1) 239 (8.9)	1992638 1992638 1971610	83.8) 6.1)	2223 (83.6) 436 (16.4)	1568 (77.4) 459 (22.6)	1757 (76.9) 528 (23.1)
27 28 29	Family history of allergy No Yes	5746 (70.2) 2444 (29.8)	6010 (60.7) 3887 (39.3)	952 (56.2) 743 (43.8)	1054 (46.8) 1199 (53.2)	1417 (65.3) 752 (34.7)	1510 (56.3) 1172 (43.7)	ila 1705 (7	74.2) 5.8)	1731 (65.1) 928 (34.9)	1670 (82.4) 357 (17.6)	1704 (74.6) 581 (25.4)
30 31 32					WSAS I	I		2, 2025 Inologie				
33 34 35		Frequency N = 24534		≤30 years n = 4209 n (%)		31-45 years n = 5502 n (%)		46-60 years		years 6957 %)	61-75 years n = 7866 n (%)	
36 37		Males <i>n</i> = 11204	Females <i>n</i> = 13330	Males <i>n</i> =1787	Females <i>n</i> = 2422	Males <i>n</i> = 2456	Females <i>n</i> = 3046	Maje n = #1	es  35	Females <i>n</i> = 3822	Males <i>n</i> = 3826	Females <i>n</i> = 4040
38 39 40	Education level Less than high school High school	2096 (18.7) 4700 (41.9)	2152 (16.1) 4591 (34.4)	210 (11.7) 969 (54.2)	220 (9.1) 1160 (47.9)	145 (5.9) 944 (38.4)	147 (4.8) 878 (28.8)	448 314 14679(4	4.3) 6.8)	352 (9.2) 1564 (40.9)	1293 (33.8) 1320 (34.5)	1433 (35.5) 989 (24.5)
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Tertiary education       4294 (38.3)       6415 (48.1)       591 (33.1)       1020 (42.1)       1343 (64.7)       1995 (65.5)       190       41 (1.1)       44 (1.2)       83 (2.0)         Smoking statulus       7167 (44.4)       3106 (23.3)       1106 (75.1)       1986 (77.0)       1996 (65.5)       557 (77.8)       1985 (46.8)       1415 (48.7)       1995 (45.5)       1853 (40.7)       1585 (53.4)         Current smoker       2177 (44.4)       3106 (23.3)       247 (13.8)       356 (14.7)       276 (11.2)       2338 (61.1)       1585 (47.6)       1853 (40.7)       1585 (40.7)       158 (47.7)       1987 (40.4)       1385 (77.5)       2161 (80.5)       1866 (75.5)       1782 (40.7)       1873 (10.8)       424 (80.6)       158 (40.7)       158 (40.7)       158 (40.7)       158 (40.7)       158 (40.7)       158 (40.7)       158 (40.7)       158 (40.7)       158 (40.7)       158 (40.7)       158 (40.7)       158 (40.7)       158 (40.7)       1	Pag	je 17 of 20				BMJ Oper	n		bmjopen-20 d by copyrig			
3       Missing information       114 (1.0)       172 (1.3)       17 (1.0)       22 (0.9)       24 (1.0)       28 (0.9)       20 (0.9)       24 (1.1)       44 (1.1)       44 (1.2)       83 (2.0)         5       Monosmoker       7167 (64.0)       8685 (64.4)       1406 (78.7)       1986 (77.0)       1940 (73.6)       53 (75.1)       65 (64.1)       1882 (47.7)       2158 (53.4)         7       Current smoker       1121 (1.1)       1636 (12.3)       247 (13.8)       366 (14.7)       276 (15.2)       537 (17.6)       65 (2.2)       512 (13.4)       413 (10.8)       446 (12.0)         6       Occupation algoposite to gas.       0       0       1182 (12.7)       11923 (80.4)       1385 (77.5)       2161 (89.2)       1386 (75.9)       2732 (89.7)       3425 (89.6)       2639 (60.0)       3605 (89.2)         11       Yes       0.057 (27.3)       1407 (10.6)       402 (22.5)       2261 (10.8)       591 (24.1)       314 (10.8)       65 (88.1)       1314 (10.3)       65 (88.1)       1314 (10.3)       65 (88.1)       1314 (10.3)       65 (88.1)       1314 (10.3)       65 (88.1)       1314 (10.3)       65 (88.1)       1314 (10.3)       65 (88.1)       1314 (10.3)       65 (88.1)       1314 (10.3)       65 (88.1)       1342 (10.1)       13000 (80.8)	1 2	Tertiary education	4294 (38.3)	6415 (48.1)	591 (33.1)	1020 (42.1)	1343 (54.7)	1995 (65.5)		1865 (48.8)	1169 (30.5)	1535 (38.0)
5       Mon-Smoker       7157 (64.0)       8585 (64.4)       1406 (78.7)       1964 (73.5)       2226 (73.1)       959 (74.2)       951 (42.5)       151 (42.5)       1337 (34.6)         6       Current smoker       2725 (24.3)       3109 (23.3)       134 (7.5)       2216 (14.7)       238 (9.3)       134 (10.6)       452 (12.0)       1337 (34.6)         7       Output smoker       8141 (72.7)       11923 (69.4)       1385 (77.5)       216 (18.2)       1965 (75.0)       238 (9.3)       137 (42.5)       151 (40.5)       1337 (34.6)         7       No       8141 (72.7)       11923 (69.4)       1385 (77.5)       216 (18.9.2)       1965 (75.0)       2732 (69.7)       1342 (10.6)       452 (12.0)         7       No       8147 (72.7)       11923 (69.4)       1385 (77.5)       216 (18.9.2)       1965 (75.0)       2732 (69.7)       342 (69.6)       183 (28.2)       365 (68.2)         17       No       9057 (27.3)       1407 (10.6)       402 (22.5)       221 (10.6)       134 (10.2)       425 (69.6)       384 (10.2)       396 (10.4)       157 (17.5)       675 (16.7)         18       711 (17.7)       1192 (11.7)       1161 (14.6)       136 (74.5)       154 (16.1)       1624 (153.3)       334 (10.1)       306 (10.2)       1322 (11.7)	3	Missing information	114 (1.0)	172 (1.3)	17 (1.0)	22 (0.9)	24 (1.0)	26 (0.9)	<u>ត</u> 29 <b>2</b> 0.9)	41 (1.1)	44 (1.2)	83 (2.0)
5       Non-smoker       7167 (64.0)       8685 (64.4)       1406 (78.7)       1806 (77.0)       1804 (73.5)       327 (71.5)       323 (61.1)       1802 (48.7)       215 (53.4)         7       Current smoker       1312 (11.7)       158 (12.3)       134 (72.7)       1192 (18.7)       326 (14.7)       276 (12.2)       283 (9.3)       76 (12.2)       974 (25.4)       515 (14.6)       445 (12.0)         9       Occupational exposure to gas, 0       8147 (72.7)       1192 (18.9)       1385 (77.5)       2161 (89.2)       1865 (75.9)       2732 (89.7)       3997 (10.4)       1187 (31.0)       445 (12.0)         10       No       3057 (27.3)       1407 (10.6)       402 (22.5)       281 (10.8)       591 (24.1)       314 (10.3)       397 (10.4)       1187 (31.0)       445 (12.0)         11       Yes       3057 (27.3)       1407 (10.6)       402 (22.5)       281 (10.8)       591 (24.1)       314 (10.3)       397 (10.4)       1187 (31.0)       445 (10.8)         12       No       9892 (88.3)       1181 (88.6)       1651 (92.4)       2257 (93.2)       2272 (93.2)       278 (9.3)       278 (89.3)       342 (89.6)       3155 (62.5)       3365 (63.3)         13       No       989 (48.1)       1305 (15.3)       942 (38.4)       1422 (46.7) <td>4</td> <td>Smoking status</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>i08 udi</td> <td></td> <td></td> <td></td>	4	Smoking status							i08 udi			
6         Exampler         2725 (24.3)         3109 (23.3)         134 (7.5)         201 (8.3)         376 (15.2)         537 (17.6)         194 (25.2)         194 (25.5)         1551 (40.5)         1397 (13.6)           7         Current smoker         1312 (11.7)         11923 (19.4)         1386 (14.7)         276 (11.2)         283 (9.3)         376 (15.2)         517 (21.3)         413 (10.8)         445 (12.0)           10         No         8147 (72.7)         11923 (19.4)         1386 (77.5)         2161 (18.9.2)         1966 (75.9)         2758 (19.7)         3425 (19.6)         283 (19.2)         3425 (19.6)         3606 (19.2)         435 (10.8)         360 (42.7)         435 (10.8)         342 (10.6)         435 (10.8)         360 (14.7)         275 (12.2)         248 (10.3)         216 (18.9.2)         134 (10.3)         435 (10.8)         366 (14.7)         275 (12.2)         342 (10.4)         138 (13.1)         435 (10.8)         366 (14.7)         757 (17.6)         636 (18.0)         369 (10.4)         1187 (13.1)         435 (10.8)         366 (14.7)         757 (18.7)         342 (10.4)         342 (10.3)         342 (10.3)         342 (10.3)         342 (10.4)         342 (10.3)         342 (10.4)         342 (10.3)         342 (10.4)         342 (10.4)         342 (10.4)         342 (10.3)         342 (10.4	5	Non-smoker	7167 (64.0)	8585 (64.4)	1406 (78.7)	1865 (77.0)	1804 (73.5)	2226 (73.1)	<b>20</b> 959(66.8)	2336 (61.1)	1862 (48.7)	2158 (53.4)
7       Current smoker       1312 (11.7)       1636 (12.3)       247 (13.8)       336 (14.7)       276 (11.2)       283 (9.3)       376 (12.2)       512 (13.4)       413 (10.8)       485 (12.0)         9       dust and fumes       8147 (72.7)       11923 (89.4)       1385 (77.5)       2161 (89.2)       1865 (77.5)       2732 (89.7)       3476 (22.0)       3425 (89.6)       2639 (69.0)       3605 (89.2)         11       Raised on a farm       9992 (88.3)       11814 (88.6)       1661 (92.4)       2257 (93.2)       276 (90.1)       314 (10.3)       432 (10.8)       3424 (89.6)       3165 (82.5)       3366 (83.3)         12       Yes       1312 (11.7)       1658 (11.9)       1107 (45.7)       1514 (16.6)       1624 (53.3)       3424 (89.6)       3165 (82.5)       3366 (87.1)         13       Yes       3442 (31.2)       529 (39.7)       459 (48.1)       1315 (54.3)       942 (38.4)       1422 (46.7)       1488 (38.9)       736 (19.29       1800 (22.9)         14       Yes       3442 (31.2)       529 (39.7)       459 (48.1)       1315 (54.3)       942 (38.4)       1422 (46.7)       1488 (38.9)       736 (19.29       1800 (22.9)         17       *20 participants had missing information for age and were therefore excluded from age-stattlifed analyses       Yes	6	Ex-smoker	2725 (24.3)	3109 (23.3)	134 (7.5)	201 (8.3)	376 (15.3)	537 (17.6)	<b>6</b> 64 (21.2)	974 (25.5)	1551 (40.5)	1397 (34.6)
a couparional excount to gas, dust and fumes No 9 Spec (28.3) 1447 (72.7) 11923 (89.4) 1385 (77.5) 2161 (89.2) 1865 (75.9) 2732 (89.7) 2425 (89.6) 2639 (69.0) 3605 (89.2) 17 Yes 1312 (11.7) 1516 (11.4) 136 (7.6) 165 (62.8) 184 (7.5) 276 (9.0.9) Yes 1312 (11.7) 1516 (11.4) 136 (7.6) 165 (62.8) 184 (7.5) 276 (9.0.9) Yes 1312 (11.7) 1516 (11.4) 136 (7.6) 165 (62.8) 184 (7.5) 278 (9.1) 197 (95.7) 1514 (14.1) 1315 (7.6) 165 (62.8) 184 (7.5) 278 (9.1) 197 (95.7) 1384 (9.8) 1355 (62.5) 3385 (63.3) 184 (7.5) 278 (9.1) 197 (95.7) 1384 (9.8) 1355 (92.5) 1338 (10.4) 671 (17.5) 675 (16.7) Yes 1312 (11.7) 1516 (11.4) 135 (7.6) 1107 (45.7) 1514 (16.6) 1624 (53.3) 922 (80.9) 1007 (45.7) 1514 (41.6) 1624 (53.3) 923 (61.9) 1007 (45.7) 1514 (41.6) 1624 (53.3) 930 (50.5) 1233 (61.1) 3090 (80.8) 6066 (7.7) 1 197 Yes 1488 (38.9) 736 (19.29 1800 (22.9) 1488 (38.9) 736 (19.29 1800 (22.9) 1800 (22.9) 1800 (22.9) 1800 (22.9) 1800 (22.9)	7	Current smoker	1312 (11.7)	1636 (12.3)	247 (13.8)	356 (14.7)	276 (11.2)	283 (9.3)	<u>3</u> 76 (12.0)	512 (13.4)	413 (10.8)	485 (12.0)
10       No       8147 (72.7)       11923 (89.4)       1385 (77.5)       2732 (89.7)       2734 (81.7)       2736 (91.2)       2734 (61.7)       2736 (91.2)       2734 (61.7)       2736 (91.2)       2734 (61.7)       2736 (91.2)       2734 (61.7)       2736 (91.2)       2734 (61.7)       2736 (91.2)       2734 (91.7)       2734 (9	8 9	Occupational exposure to gas, dust and fumes							une 2 Ensei ses re			
1       Yes       3057 (27.3)       1407 (10.6)       402 (22.5)       281 (10.8)       591 (24.1)       314 (10.3)       17 (10.4)       1187 (31.0)       435 (10.8)         Raised on a farm       9892 (88.3)       11814 (88.6)       1651 (92.4)       2257 (93.2)       278 (90.6)       3424 (89.6)       3155 (82.5)       3385 (83.3)         Yes       1312 (11.7)       1516 (11.4)       136 (7.6)       165 (8.8)       184 (7.5)       278 (9.1)       366 (10.4)       671 (17.5)       675 (16.7)         Yes       711 (88.8)       8041 (80.3)       928 (51.9)       11315 (54.3)       942 (36.4)       1422 (46.7)       3090 (80.8)       6066 (77.1)         Yes       734 (10.8)       5289 (39.7)       859 (48.1)       11315 (54.3)       942 (36.4)       1422 (46.7)       3090 (80.8)       6066 (77.1)         Yes       734 (10.8)       5289 (39.7)       859 (48.1)       11315 (54.3)       942 (36.4)       1422 (46.7)       3090 (80.8)       6066 (77.1)         Yes       736 (19.24)       1800 (22.9)       1380 (7.6)       135 (54.8)       136 (7.6)       162 (45.7)       1488 (38.8)       736 (19.24)       1800 (22.9)         Yes       942 (36.7)       859 (48.1)       137 (10.8)       1422 (46.7)       1488 (38.8)       736	10	No	8147 (72.7)	11923 (89.4)	1385 (77.5)	2161 (89.2)	1865 (75.9)	2732 (89.7)	2 58 72.0)	3425 (89.6)	2639 (69.0)	3605 (89.2)
12       Related on a farm       9692 (86.3)       11814 (86.6)       1651 (92.4)       2257 (93.2)       2276 (95.6)       2768 (90.9)       3382 (10.4)       6751 (17.5)       3675 (16.7)         13       1312 (11.7)       1516 (11.4)       136 (7.6)       165 (68.2)       184 (7.5)       2778 (9.1)       398 (10.4)       6771 (17.5)       675 (16.7)         14       1312 (11.7)       1516 (11.4)       136 (7.6)       165 (68.2)       184 (7.5)       2778 (9.1)       398 (10.4)       6771 (17.5)       675 (16.7)         14       1422 (17.2)       5228 (39.7)       889 (48.1)       1315 (54.3)       942 (38.4)       1422 (46.7)       1428 (38.3)       736 (19.2)       1800 (22.9)         14       1422 (46.7)       1428 (38.3)       736 (19.2)       1800 (22.9)       1800 (23.9)       1800 (23.9)       1800 (23.9)       1800 (23.9)       1800 (23.9)       1800 (23.9) <td< td=""><td>11</td><td>Yes</td><td>3057 (27.3)</td><td>1407 (10.6)</td><td>402 (22.5)</td><td>261 (10.8)</td><td>591 (24.1)</td><td>314 (10.3)</td><td><b>8</b>73 (28.0)</td><td>397 (10.4)</td><td>1187 (31.0)</td><td>435 (10.8)</td></td<>	11	Yes	3057 (27.3)	1407 (10.6)	402 (22.5)	261 (10.8)	591 (24.1)	314 (10.3)	<b>8</b> 73 (28.0)	397 (10.4)	1187 (31.0)	435 (10.8)
No       9882 (88.)       11814 (88.6)       1651 (92.4)       2257 (93.2)       2768 (90.9)       ####################################	12	Raised on a farm							ton			
13       Yes       1312 (11.7)       1516 (11.4)       136 (7.6)'       165 (6.8)'       184 (7.5)'       278 (9.1)'       388 (10.4)'       671 (17.5)'       675 (16.7)'         14       Yes       3492 (31.2)'       5289 (39.7)'       859 (48.1)       1315 (54.3)       942 (33.4)       1422 (46.7)'       1488 (38.9)       736 (19.2)'       1800 (22.9)         **20 participants had missing information for age and were therefore excluded from age-stratified analyse       Attack (38.9)       736 (19.2)'       1800 (22.9)         1312       141       151 <td< td=""><td>12</td><td>No</td><td>9892 (88.3)</td><td>11814 (88.6)</td><td>1651 (92.4)</td><td>2257 (93.2)</td><td>2272 (92.5)</td><td>2768 (90.9)</td><td>278 <b>1</b>,43 (89.8)</td><td>3424 (89.6)</td><td>3155 (82.5)</td><td>3365 (83.3)</td></td<>	12	No	9892 (88.3)	11814 (88.6)	1651 (92.4)	2257 (93.2)	2272 (92.5)	2768 (90.9)	278 <b>1</b> ,43 (89.8)	3424 (89.6)	3155 (82.5)	3365 (83.3)
Termily history of allergy       7711 (88.8)       8041 (60.3)       928 (51.9)       1107 (45.7)       1514 (61.6)       1624 (53.3)       3496 (50.5)       2334 (61.1)       3090 (60.8)       6066 (77.1)         **20 participants had missing information for age and were therefore excluded from age-stratified analyses       3492 (31.2)       5289 (39.7)       859 (43.1)       1315 (54.3)       942 (38.4)       1422 (46.7)       3690 (60.8)       6066 (77.1)         **20 participants had missing information for age and were therefore excluded from age-stratified analyses       3490 (70.8)       6000 (22.9)       1800 (22.9)         **20 participants had missing information for age and were therefore excluded from age-stratified analyses       3490 (70.8)       6006 (77.1)       1800 (22.9)         **21 participants had missing information for age and were therefore excluded from age-stratified analyses       3490 (70.8)       6006 (77.1)       1800 (22.9)         **22 participants had missing information for age and were therefore excluded from age-stratified analyses       3490 (70.8)       6006 (77.1)       1800 (72.9)         **33       **34 (70.8)       **34 (70.8)       **34 (70.8)       **34 (70.8)       **36 (70.8)       6006 (77.1)         **34       **35 (70.8)       **36 (70.8)       **36 (70.8)       **36 (70.8)       **36 (70.8)       **36 (70.8)       **36 (70.8)       **36 (70.8)       **36	14	Yes	1312 (11.7)	1516 (11.4)	136 (7.6)	165 (6.8)	184 (7.5)	278 (9.1)	<b>§25 §</b> 10.2)	398 (10.4)	671 (17.5)	675 (16.7)
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10       Yes       3492 (31.2)       5269 (39.7)       859 (48.1)       1315 (54.3)       942 (38.4)       1422 (46.7)       1488 (38.9)       736 (19.22)       1800 (22.9)         **20 participants had missing information for age and were therefore excluded from age-stratified analyses       1428 (38.9)       736 (19.22)       1800 (22.9)         12       4       4       1429 (46.7)       1498 (38.9)       736 (19.22)       1800 (22.9)         13	15	No	7711 (68.8)	8041 (60.3)	928 (51.9)	1107 (45.7)	1514 (61.6)	1624 (53.3)	24 £9-(69.5)	2334 (61.1)	3090 (80.8)	6066 (77.1)
*20 participants had missing information for age and were therefore excluded from age-stratified analyses and the second of the	16	Yes	3492 (31.2)	5289 (39.7)	859 (48.1)	1315 (54.3)	942 (38.4)	1422 (46.7)	856 (30.5)	1488 (38.9)	736 (19.29	1800 (22.9)
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Tables 2. Key results of risk factors for asthma,	allergic rhinitis, and atopic eczema reported from
the West Sweden Asthma Study (WSAS I)	· · · ·

ine west Sweden Astrina Study (WSAS I)						
	Adjusted estimates <sup>1</sup>					
Risk factor	Current asthma <sup>2</sup>	Current allergic	Current eczema4			
	OR (95% CI)	rhinitis <sup>3</sup>	OR (95% CI)			
		OR (95% CI)				
Female gender <sup>5</sup>	1.77 (1.15-2.70)	0.91 (0.69-1.21)	1.71 (1.17-2.51)			
Family history of asthma and allergic rhinitis <sup>5</sup>						
None	1	1	1			
Asthma only	1.29 (0.55-3.04)	0.61 (0.34-1.10)	1.45 (0.72-2.94)			
Allergic rhinitis only	1.16 (0.66-2.03)	2.58 (1.79-3.72)	1.25 (0.77-2.04)			
Both asthma and allergic rhinitis	4.33 (2.57-7.30)	2.76 (1.77-4.31)	1.61 (0.94-2.76)			
Raised on a farm <sup>5,6</sup>	0.96 (0.52-1.77)	0.64 (0.42-0.96)	0.51 (0.27-0.99)			
Body mass index						
Normal (20-25 kg/m <sup>2</sup> )	1	1	1 5			
Underweight (<20 kg/m <sup>2</sup> )	0.95 (0.36-2.55)	1.42 (0.74-2.71)	1.00 (0.44-2.30)			
Overweight (25-30 kg/m <sup>2</sup> )	1.04 (0.65-1.67)	1.04 (0.77-1.41)	1.02 (0.68-1.54)			
Obese (>30 kg/m <sup>2</sup> )	1.95 (1.13-3.36)	2.30 (1.53-3.46)	1.34 (0.80-2.24)			
Number of siblings						
0	1	1	1			
1	3.09 (1.25-7.63)	1.16 (0.74-1.81)	0.72 (0.42-1.24)			
2 or more	2.51 (1.02-6.15)	1.15 (0.74-1.79)	0.55 (0.32-0.94)			
Allergic sensitization <sup>5,7</sup>	4.11 (2.71-6.25)	5.11 (3.77-6.93)	1.26 (0.85-1.85)			
Exposure to gas, dust or fumes at work	1.85 (1.20-2.87)	1.03 (0.76-1.41)	2.08 (1.40-3.08)			

<sup>1</sup>Respective to each outcome, the estimates adjusted for age, gender, family history of asthma and rhinitis, exposure to gas and gas fumes at work place, body mass index, number of siblings, daycare attendance during childhood, and being raised on a farm

<sup>2</sup>Current asthma was defined as follows: ever had asthma or ever diagnosed with asthma by a physician and at least one of: reported use of asthma medication, or recurrent wheeze, or attacks of shortness of breath during the last 12 months.

<sup>3</sup>Allergic rhinitis was defined as follows: having had sneezing, runny nose or nasal blocking apart from colds during the last 12 months and having these nasal symptoms occurred simultaneously with itching and running eyes"

<sup>4</sup>Defined as having ever had recurrent itchy rash for at least 6 months and having had itchy rash during the last 12 months

<sup>5</sup>Reported in Rönmark EP et al. Different risk factor patterns for adult asthma, rhinitis and eczema: results from West Sweden Asthma Study. *Clin Transl Allergy* 2016; 6:28.

<sup>6</sup>Reported in Eriksson J, et al. Growing up on a farm leads to lifelong protection against allergic rhinitis. *Allergy* 2010; 65: 1397-1403.

<sup>7</sup>Allergic sensitization defined as serum immunoglobulin E to ImmunoCAP® Phadiatop ≥0.35 KU/1 to at least one of the following 11 airborne allergens: timothy grass, birch, mugwort, olive, parietaria, cat, dog, horse, D. pteronyssinus, D. farinae, and C. herbarum.



