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Allergic rhinitis and allergic sensitisation are still increasing among Danish adults

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Abstract

Background: Only a limited number of studies have included objective measures of allergic sensitisation (such as skin-prick test [SPT] and serum specific IgE [sIgE]) when studying time trends in allergic respiratory disease in adults within the current millennium.

Methods: Five health examination studies of random samples of individuals aged 18–69 years resident in the Copenhagen region were conducted in 1990–1991, 2006–2008, 2010–2011, 2012–2015, and 2016–2017. Allergic sensitisation was defined by sIgE (in 1990–1991, 2006–2008, and, 2012–2015) or SPT (in 2006–2008, 2010–2011, and 2016–2017) to at least one of the allergens: birch, grass, house dust mite, or cat. Allergic rhinitis was defined as sensitisation and self-reported nasal symptoms.

Results: The age- and sex-standardised prevalence of sIgE-defined sensitisation increased from 16% in 1990–1991, to 26% in 2006–2008, and to 29% in 2012–2015. The age- and sex-standardised prevalence of SPT-defined sensitisation increased from 27% in 2006–2008, to 28% in 2010–2011, and to 32% in 2016–2017. Changes in sIgE-defined and SPT-defined allergic rhinitis showed similar increasing trends.

Conclusion: The prevalence of allergic sensitisation and allergic rhinitis increased in a general adult Danish population over the last three decades and has thus continued to increase in the current millennium.

KEYWORDS

allergic rhinitis, allergic sensitisation, prevalence, specific IgE, time trends

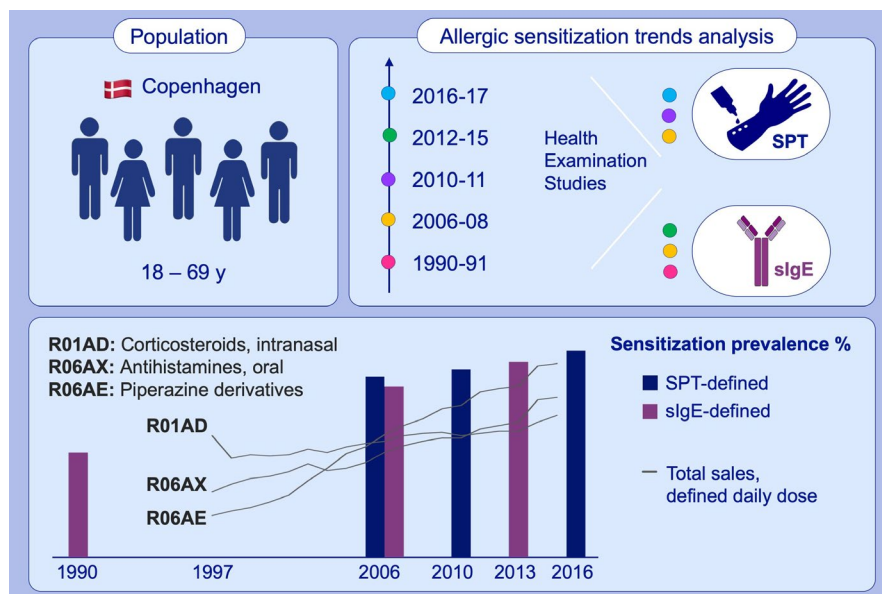
1 | INTRODUCTION

Several studies reported an increasing prevalence of allergic respiratory disease (ARD) in the last 40 years of the previous millennium.^{1–9} Evidence of current time trends in ARD is important to public health authorities and health care professionals to organise and prioritise within the health care system. However, it is not clear whether the increase in ARD has continued in the current millennium. Some studies among children and adolescents have reported a plateau or decrease in allergic sensitisation,^{10–13} hay fever,^{10,11,13,14} and asthma,^{10–13,15–19} whereas others have found an increase.^{14,17,19–21} Fewer time trend

studies have been conducted among adults,^{22–27} and only one of them assessed trends in the current millennium, albeit in a highly selected population of medical students.²⁷

Changes in awareness of ARD might affect self-reported symptoms of allergic rhinitis and bias studies of time trends in prevalence. Thus, it is important to include objective measures such as IgE sensitisation to inhalant allergens (eg skin-prick test and serum specific IgE).

We have previously reported an increase in allergic sensitisation among adults from 1990–1991 to 1998–1999^[1,28] and an increase from 1976–1977 to 1999–2001² using health examination studies (HESs) conducted in the same area in the Western part of



GRAPHICAL ABSTRACT

We assessed whether the prevalence of allergic respiratory disease has continued to increase in the current millennium among Danish adults. Both specific IgE (slgE) and skin-prick test (SPT) sensitization showed an increase from 2006 to 2013–2016. These trends were supported by a nationwide increase in annual sales (including over-the-counter drugs) of intranasal corticosteroids and oral antihistamines from 1997–2015.

Copenhagen. We aimed to investigate whether these trends continued in the current millennium. Thus, we assessed time trends in the prevalence of allergic sensitisation to common aeroallergens, allergic rhinitis, and self-reported physician-diagnosed hay fever in a general adult population, using five HESs from the Western part of the Copenhagen Region conducted at different points in time between 1990 and 2017. Additionally, to support a possible trend in the prevalence of ARD we examined nationwide time trends in total sales of pharmacotherapy for allergic rhinitis.

2 | METHODS

We based this study on five HESs, all using similar population sampling: a random sample of individuals aged 18–69 years, born in Denmark and with Danish citizenship, resident in 11 municipalities in the Western part of the Copenhagen Region. All included HESs were conducted between 1990 and 2017 at the Research Centre for Prevention and Health, Glostrup, Denmark (now Center for Clinical Research and Prevention).

Allergy90 is a part of the Copenhagen Allergy Study, which began in 1990 where 6998 individuals responded to a mailed questionnaire (response rate 87%). A randomly selected group ($n = 793$) of the respondents were invited to participate in a health examination and 599 participated (participation rate 76%). The examinations were conducted between February 1990 and January 1991. We excluded individuals aged below 18 at the day of the health examination to make the sample compatible with later HESs.

In the Health2006 study 7770 randomly selected individuals were invited to a health examination and 3471 participated (participation rate 45%). Examinations were conducted between June 2006 and June 2008.²⁹

In the Health2010 study 3762 randomly selected individuals were invited to a health examination and 1522 participated (participation rate 40%). Examinations were conducted between February 2010 and October 2011.³⁰

In the DanFunD study (part two) 25 368 randomly selected individuals were invited to a health examination and 7493 participated (participation rate 30%). Examinations were conducted between November 2012 and June 2015.³¹

In the Health2016 study 4497 randomly selected individuals were invited to a health examination and 1251 participated (participation rate 28%). Examinations were carried out between May 2016 and December 2017.

2.1 | Allergic sensitisation

We assessed IgE sensitisation to the four most clinically relevant aeroallergens in Denmark—birch (*Betula verrucosa*), cat (*Felis domesticus*), grass (*Phleum pratense*), and house dust mite (HDM; *Dermatophagoides pteronyssinus*)—by either serum specific IgE (slgE) or skin-prick test (SPT).

Serum slgE was measured in Allergy90, Health2006, and DanFunD.

slgE-defined sensitisation was defined by a measurement ≥ 0.35 kU/L. In Allergy90 and Health2006, the ADVIA Centaur

IgE assay (Bayer Corporation) was used for measurements of sIgE against the four aeroallergens (birch, cat, grass and HDM). Serum samples from Allergy90 were stored at -20°C from 1990–1991 until analysed in 1999. Serum samples from DanFunD were analysed on a Phadia 250 system at Thermo Scientific ImmunoDiagnostics, Allerød. Samples were screened by using Phadiatop, and Phadiatop-positive (≥ 0.35 kU/L) samples were analysed for sIgE to birch, cat, grass and HDM. Studies have previously shown high correlation between the CAP system (a previous version of Phadia) and Centaur,^{32,33} however, there is an indication of CAP being more sensitive than Centaur. The discordant pairs are mainly found among lower values of sIgE.^{32,33} To minimise the potential bias introduced by the shift in assay from Health2006 to DanFunD, we conducted a sensitivity analysis, where sensitisation was defined as sIgE ≥ 0.70 kU/L to any of the included allergens.

SPT (Soluprick SQ, ALK-Abelló) was included in Health2006, Health2010, and Health2016. The first 1021 participants in Health2006 were not SP tested.

SPT-defined sensitisation was defined by a mean wheal diameter (MWD) ≥ 3 mm to one of the four aeroallergens (birch, cat, grass and HDM). Responders (MWD ≥ 3 mm) to the negative control and non-responders (MWD < 3 mm) to the positive control were excluded from the SPT sample. The SPTs were performed using lancets and a standard panel of ten aeroallergens including a negative control and a positive control (10 mg/mL histamine).

2.2 | Allergic rhinitis

To include a clinically relevant measure we studied time trends in allergic rhinitis; a combined measure requiring both allergic sensitisation and self-reported nasal symptoms. Information on nasal symptoms was collected in a questionnaire (Table S1) completed at home by the participants prior to the health examination.

Allergic rhinitis due to birch was defined as sensitisation to birch and nasal symptoms when near grass, trees, or flowers (Table S1; question a)

Allergic rhinitis due to cat was defined as sensitisation to cat and nasal symptoms when near furry animals (Table S1; question b)

Allergic rhinitis due to grass was defined as sensitisation to grass and nasal symptoms when near grass, trees, or flowers (Table S1; question a)

Allergic rhinitis due to HDM was defined as sensitisation to HDM and nasal symptoms when cleaning rooms or making beds, or when in bed (Table S1; question c)

Allergic rhinitis was defined as at least one of the four above.

2.3 | Self-reported physician-diagnosed hay fever

Self-reported data on physician-diagnosed hay fever from a questionnaire (Table S1; question d) were used to assess time trends in diagnosis of hay fever.

2.4 | Pharmacotherapy for allergic rhinitis

To support a possible time trend in prevalence of allergic rhinitis we examined total sales of pharmacotherapy for allergic rhinitis from 1997 to 2015. Total sales consist of all prescriptions, over-the-counter drugs, and drugs sold to hospitals and physicians in Denmark. However, only at an aggregated level. Total sales was assessed from The Register of Medical Product Statistics.³⁴ The register has existed since 1997 and contains information on ATC code and defined daily dose (DDD). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.³⁴ We assessed total sales in Denmark of oral antihistamines (ATC groups: R06AE and R06AX; primarily non-sedative) and intranasal corticosteroids (R01AD) in DDD per 1000 inhabitants per day from 1997 to 2015.

2.5 | Statistics

Age- and sex-standardised prevalence of sIgE- and SPT-defined sensitisation and allergic rhinitis for each HES were calculated using direct standardisation, where Allergy90 and Helbred2006 were used as the reference population, respectively. Age was categorised as “18–29”, “30–49”, and “50–69”. 95% confidence intervals (CIs) were calculated using the normal approximation to the binomial distribution.

Changes in the prevalence were expressed by odds ratios (ORs) comparing Health2016 and Health2010 to Health2006 or comparing DanFunD and Allergy90 to Health2006 for SPT- and sIgE-defined sensitisation, respectively. Health2006 was chosen as reference due to our interest in exploring time trends after the millennium. ORs were adjusted for sex, age at health examination, and season of examination (winter, spring, summer, or autumn), and estimated using logistic regression.

For each analysis, only individuals with complete information in response and explanatory variables were included.

We used SAS, version 9.4 (SAS Institute Inc) to perform the analyses.

2.6 | Ethics

Included HESs were approved by the Ethics Committee of Copenhagen and the Danish Data Protection Agency. Recommendations of the Declaration of Helsinki were followed, and each participant gave informed written consent. The study was approved by the Danish Data Protection Agency (ref. 2012-58-0004). This manuscript was written according to reporting guidelines for observational studies (STROBE).

3 | RESULTS

We included 11 537 individuals from Allergy90, Health2006, and DanFunD for sIgE-defined sensitisation and 6244 individuals from

Health2006, Health2010, and Health2016 for SPT-defined sensitisation. Table 1 shows characteristics of the HESs according to age, sex, season of health examination and crude prevalence of allergic sensitisation and allergic rhinitis (slgE- and SPT-defined), as well as self-reported physician-diagnosed hay fever.

We had data on age, sex, and season of health examination for all individuals in our study population. Other variables had the following range of missing values for the five HESs: slgE 0.8%-1.1%; SPT 0.3%-2.3%; nasal symptoms 0.2%-5.0%, and self-reported physician diagnosis 0%-10.7%. The percent of missing values for questionnaire data from Health2016 was higher compared to the other

HESs. A complete list of missing values can be found in Table S2. We excluded 0.9%, 1.3%, and 1.2% from the SPT sample in Health2006, Health2010, and Health2016, respectively, due to skin response to the negative control or no skin response to the positive control.

3.1 | Crude prevalence

The crude prevalence was 26.0% and 32.4% of slgE-defined and SPT-defined sensitisation in 2012-2015 and 2016-2017, respectively (Table 1). Sensitisation to grass and birch were the most common: slgE (14.7% and 13.7%) and SPT (20.3% and 16.5%). In

TABLE 1 Characteristics of the included health examination studies and crude prevalence of sensitisation, allergic rhinitis, and physician-diagnosed hay fever

	Allergy90 (1990-1991)	Health2006 (2006-2008)	Health2010 (2010-2011)	DanFunD (2012-2015)	Health2016 (2016-2017)
N	573	3471 ^a	1522	7493	1251
Age, mean (SD)	42.97 (13.80)	49.37 (13.04)	50.39 (13.83)	51.98 (13.32)	50.83 (13.00)
Women (%)	286 (49.9)	1918 (55.3)	851 (55.9)	4037 (53.9)	676 (54.0)
Season (%)					
Autumn	177 (30.9)	1071 (30.9)	375 (24.6)	1742 (23.2)	406 (32.5)
Spring	164 (28.6)	830 (23.9)	477 (31.3)	2261 (30.2)	242 (19.3)
Summer	148 (25.8)	766 (22.1)	416 (27.3)	1682 (22.4)	317 (25.3)
Winter	84 (14.7)	804 (23.2)	254 (16.7)	1808 (24.1)	286 (22.9)
slgE-defined (%)					
Any allergen	91 (16.0)	797 (23.1)	NA	1927 (26.0)	NA
Birch	54 (9.5)	409 (11.9)	NA	1017 (13.7)	NA
Cat	20 (3.5)	231 (6.7)	NA	441 (6.0)	NA
Grass	48 (8.5)	450 (13.1)	NA	1087 (14.7)	NA
HDM	19 (3.4)	245 (7.1)	NA	870 (11.7)	NA
Allergic rhinitis	37 (6.5)	535 (15.8)	NA	1315 (17.9)	NA
Allergic rhinitis due to birch	25 (4.4)	269 (7.9)	NA	768 (10.4)	NA
Allergic rhinitis due to cat	≤ 5	146 (4.3)	NA	267 (3.6)	NA
Allergic rhinitis due to grass	25 (4.4)	341 (10.0)	NA	827 (11.2)	NA
Allergic rhinitis due to HDM	≤ 5	121 (3.6)	NA	341 (4.6)	NA
SPT-defined (%)					
Any allergen	NA	646 (27.3)	413 (27.6)	NA	397 (32.4)
Birch	NA	304 (12.8)	230 (15.4)	NA	202 (16.5)
Cat	NA	218 (9.2)	144 (9.6)	NA	113 (9.2)
Grass	NA	385 (16.2)	237 (15.8)	NA	249 (20.3)
HDM	NA	248 (10.5)	154 (10.3)	NA	158 (12.9)
Allergic rhinitis	NA	387 (16.7)	251 (17.0)	NA	254 (22.0)
Allergic rhinitis due to birch	NA	183 (7.8)	140 (9.5)	NA	135 (11.6)
Allergic rhinitis due to cat	NA	115 (4.9)	70 (4.7)	NA	53 (4.5)
Allergic rhinitis due to grass	NA	265 (11.3)	157 (10.6)	NA	161 (13.8)
Allergic rhinitis due to HDM	NA	97 (4.1)	64 (4.3)	NA	68 (5.8)
Self-reported physician-diagnosed					
Hay fever	46 (8.0)	611 (17.9)	281 (18.7)	1393 (18.9)	231 (20.7)

Note: Allergic rhinitis is defined by a combination of nasal symptoms and slgE- or SPT- defined sensitisation.

Abbreviations: HDM, house dust mite (*Dermatophagoides pteronyssinus*); SD, standard deviation; slgE, specific IgE; SPT, skin-prick test.

^aFor the SPT population n = 2450.

Health2006 where both sIgE and SPT were measured the prevalence of SPT-defined sensitisation was higher for all allergens compared to sIgE, 97% of those who were sIgE positive were also SPT positive and 79% of those who were SPT positive were also sIgE positive.

3.2 | Primary analyses

The age- and sex-standardised prevalence of sIgE-defined sensitisation to grass, birch, and HDM increased from 8.5%, 9.5%, and 3.4% in 1990-1991 to 15.1%, 12.4%, 8.8% in 2006-2008 and to 17.6%, 14.7%, and 14.9% in 2012-2015, whereas sensitisation to cat remained stable from 2006-2008 to 2012-2015 (Figure 1). The age- and sex-standardised prevalence of SPT-defined sensitisation showed the same pattern as the sIgE measures with an increase in sensitisation to grass, birch, and HDM from 2006-2008 to 2016-2017. For prevalence of allergic rhinitis (sex- and age-standardised) the time trends showed a similar pattern as sensitisation for both sIgE and SPT. Likewise, the results from logistic regression models (Table 2) showed an increasing odds of sIgE-defined and SPT-defined sensitisation; OR 0.53 (95% CI: 0.42-0.67) in 1990-1991, 1.24 (1.13-1.37)

in 2012-2015 and 1.03 (0.89-1.19) in 2010-11, 1.30 (1.11-1.52) in 2016-2017, compared to 2006-2008. Male sex and younger age were associated with sIgE- and SPT-defined allergic sensitisation and allergic rhinitis (data not shown).

3.3 | Sensitivity analysis

The results from logistic regressions using a higher threshold for sIgE-defined sensitisation (≥ 0.70 kU/L) showed similar results as the main logistic regressions with an OR of 0.48 (95% CI: 0.37-0.62) for any allergen in 1990-1991 and 1.21 (1.10-1.34) in 2012-2015 compared to Health2006 (Table S3). However, for sensitisation to HDM the OR was 1.65 (1.40-1.94) in 2012-2015, where the OR for 2012-15 was 1.88 (1.62-2.19) in the main analysis (Table 2). For SPT-defined sensitisation to HDM the OR was 1.28 (1.03-1.59) in 2016-2017 compared to 2006-2008.

3.4 | Self-reported physician-diagnosed hay fever

Compared to 2006-2008 there was an increase in self-reported physician-diagnosed hay fever from 1990-1991 (OR 0.38 [95% CI:

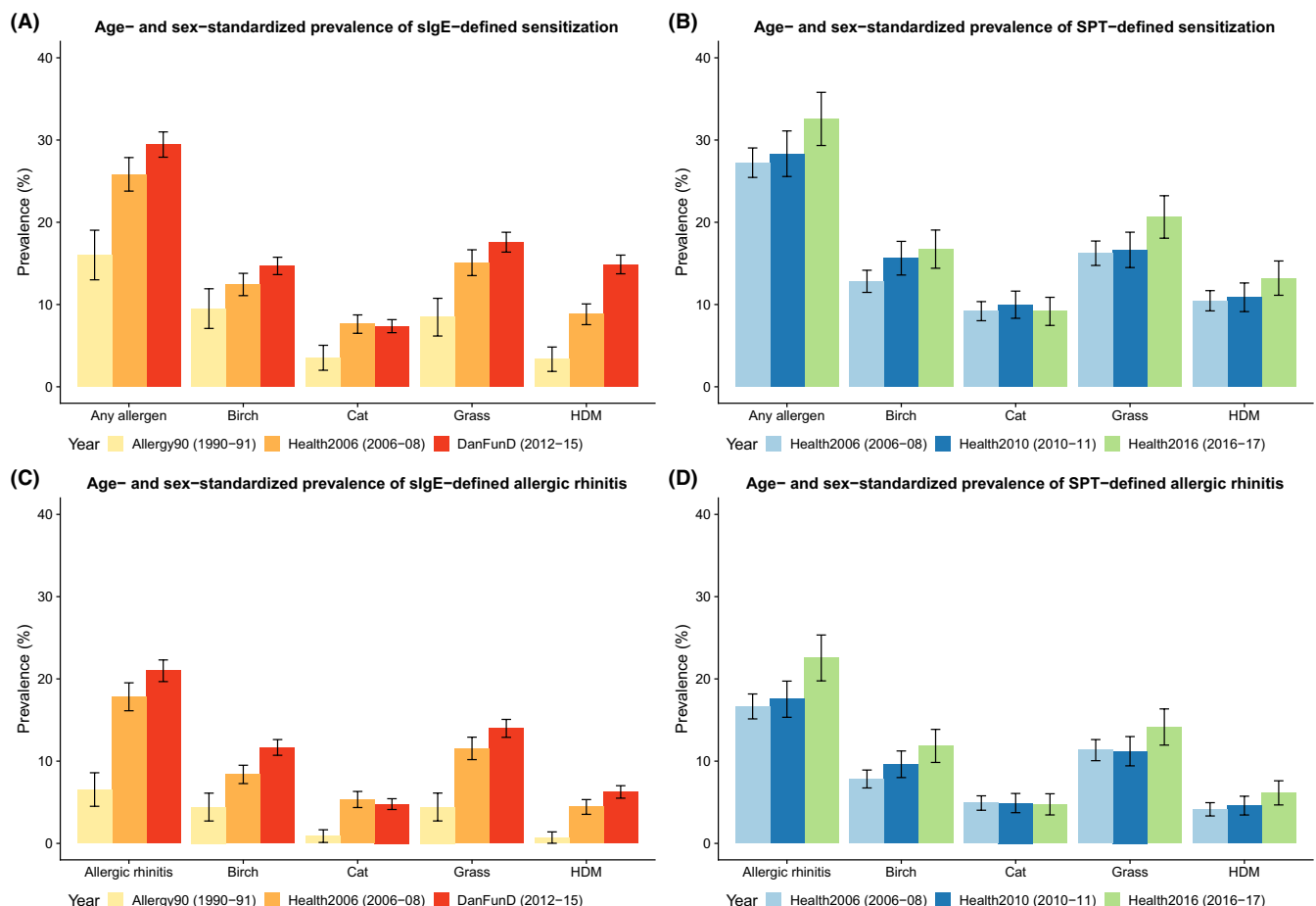


FIGURE 1 Age- and sex-standardised prevalence of specific IgE (sIgE) and skin-prick test (SPT)-defined sensitisation (A, B) and allergic rhinitis (C, D). HDM, house dust mite (*Dermatophagoides pteronyssinus*). Allergy90 is reference population in figure (A) and (C). Health2006 is reference population in figure (B) and (D). Allergic rhinitis is defined by a combination of nasal symptoms and sIgE- or SPT-defined sensitisation

TABLE 2 Changes in prevalence of specific IgE (sIgE) and skin-prick test (SPT) -defined sensitisation and allergic rhinitis, and self-reported physician-diagnosed hay fever

	Any allergen	Birch	Cat	Grass	HDM
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
sIgE-defined sensitisation					
Allergy90 (1990-1991)	0.53 (0.42-0.67)***	0.70 (0.52-0.95)*	0.42 (0.26-0.66)***	0.50 (0.36-0.68)***	0.35 (0.22-0.57)***
DanFunD (2012-2015)	1.24 (1.13-1.37)***	1.22 (1.08-1.38)**	0.93 (0.79-1.10)	1.23 (1.09-1.38)***	1.88 (1.62-2.19)***
SPT-defined sensitisation					
2010-2011	1.03 (0.89-1.19)	1.23 (1.02-1.48)*	1.06 (0.85-1.33)	0.98 (0.82-1.18)	1.00 (0.80-1.24)
2016-2017	1.30 (1.11-1.52)***	1.33 (1.10-1.62)**	1.04 (0.82-1.33)	1.35 (1.13-1.62)**	1.28 (1.03-1.59)*
sIgE-defined allergic rhinitis					
Allergy90 (1990-1991)	0.30 (0.21-0.43)***	0.46 (0.30-0.71)***	0.15 ^a (0.06-0.37)***	0.32 (0.21-0.49)***	0.15 ^a (0.05-0.40)***
DanFunD (2012-2015)	1.24 (1.11-1.39)***	1.41 (1.22-1.64)***	0.89 (0.73-1.10)	1.22 (1.06-1.40)**	1.45 (1.17-1.79)***
SPT-defined allergic rhinitis					
Health2010 (2010-2011)	1.04 (0.87-1.24)	1.24 (0.98-1.56)	0.99 (0.72-1.34)	0.94 (0.76-1.16)	1.04 (0.75-1.44)
Health2016 (2016-2017)	1.50 (1.25-1.80)***	1.59 (1.25-2.02)***	1.01 (0.72-1.42)	1.31 (1.05-1.62)*	1.46 (1.06-2.03)*
Self-reported physician-diagnosed hay fever					
	OR (95% CI)				
Allergy90 (1990-1991)	0.38 (0.27-0.52)***				
Health2010 (2010-2011)	1.06 (0.91-1.24)				
DanFunD (2012-2015)	1.09 (0.98-1.21)				
Health2016 (2016-2017)	1.20 (1.02-1.43)*				

Note: Health2006 is reference group in all analyses. Allergic rhinitis is defined by a combination of nasal symptoms and sIgE- or SPT -defined sensitisation. ORs are adjusted for sex, age at health examination, and season of health examination.

Abbreviations: OR, Odds ratio. HDM, house dust mite (*Dermatophagoides pteronyssinus*).

^a ≤ 5 events, thus the estimate must be interpreted with caution.

*>0.05.

**>0.01.

***>0.001.

0.27-0.52)) (Table 2). After 2006-08 there was an indication of an increase in self-reported physician-diagnosed hay fever, however only reaching statistical significant increase in 2016-2017 (1.20 [1.02-1.43]). Due to a high proportion of missing values in 2016-2017 (10.7%; Table S2), this result must be interpreted with caution.

3.5 | Pharmacotherapy for allergic rhinitis

From 1997 to 2015 annual sales of intranasal corticosteroids (ATC group R01AD) and oral antihistamines (ATC-groups R06AX and R06AE) increased from 11.1; 6.1; 4.0 to 12.9; 14.5; 17.5 DDD per 1000 inhabitants per day, respectively (Figure 2). For the two groups of oral antihistamines sales increased continually. The increase was driven mainly by increasing sales of Cetirizine (ATC: R06AE07; Table S4). Sales of intranasal corticosteroids decreased from 1997 to 1998 and from 2002 to 2003, but increased continuously afterwards. From 2013 the intranasal corticosteroids group contains a combination drug (ATC code R01AD58). However, the combination drug only accounts for maximum 0.5 DDD per 1000 inhabitants per day, and

thus, it does not affect the overall time trends in sales of intranasal corticosteroids.

4 | DISCUSSION

We aimed to investigate whether ARD have continued to increase in the current millennium among Danish adults and found an increase in the prevalence of allergic sensitisation and allergic rhinitis due to birch, grass, and HDM. Additionally, these trends were paralleled by a nationwide increase in annual sales of intranasal corticosteroids and oral antihistamines from 1997 to 2015.

4.1 | Comparison with previous studies

Sensitisation to birch and grass were most common which have also been observed in Germany (2008-2011) and the south-western part of Sweden (2008).^{23,26} Whereas sensitisation to cat was considerably higher in Finland (2001-2003) and Sweden (2008 and 2009)^{23,25,35} than in our study, in Germany (2008-2011) and

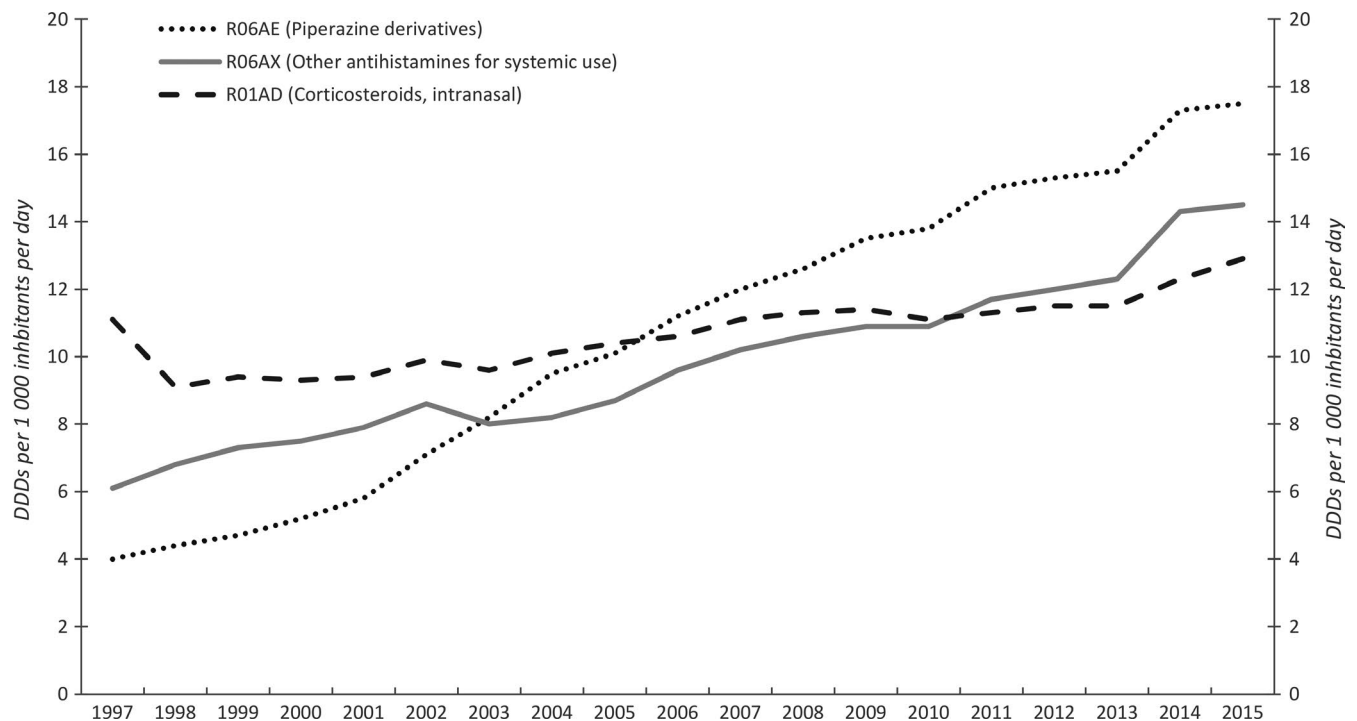


FIGURE 2 Annual sales (DDD per 1000 inhabitants) of intranasal corticosteroids (ATC group R01AD) and oral antihistamines (ATC groups R06AE and R06AX) in Denmark from 1997–2015. DDD, defined daily dose. Source: Register of Medical Product Statistics, www.Medstats.dk June 24, 2019. Prescription drugs, drugs sold to hospitals, and over-the-counter drugs are included. ATC groups R06AE and R06AX includes primarily non-sedative oral antihistamines. ATC group R01AD contains a combination drug from 2013, however this only accounts for maximum 0.5 DDD/1000 inhabitants/day [Color figure can be viewed at wileyonlinelibrary.com]

Switzerland (2007–2015) the prevalence was at the same level as our results.^{26,27}

Only a few Danish studies investigating time trends in allergic sensitisation have been conducted. While Linneberg et al^{1,2,28} have reported an increase in allergic rhinitis and allergic sensitisation among adults, Thomsen et al showed no increase in sensitisation among children and adolescents living in Copenhagen from 1986 to 2001.¹² In line with our findings, two Swedish studies from different geographic areas have shown an increase in sensitisation to pollen among adults from mid-90s to 2009–2010.^{23,25} However, they found no increase in sensitisation to HDM. Haftenberger and colleagues reported an increase in the prevalence of sensitisation to aeroallergens among women from 1998 to 2008–2011.²⁶ To our knowledge only one study has assessed time trends in allergic sensitisation within this millennium; Steinegger et al²⁷ showed an increase from 2007–2015 in prevalence of sensitisation to grass, birch and HDM among Swiss 3rd year medical students. This finding in a highly selected population is similar to our results in a Danish general adult population.

4.2 | Strengths and limitations

Our study benefits from a large sample size and inclusion of five general HESs conducted in the same geographical area using similar methodology for selection of participants, but at different points in time. We used two different objective measures of allergic

sensitisation (sIgE and SPT), which might be less affected by changes in awareness of ARD compared to self-reported symptoms and diagnoses. Additionally, to ensure clinical relevance we also studied time trends in allergic rhinitis, a combined measure requiring both sensitisation and self-reported nasal symptoms. This yielded a lower prevalence, but similar time trends as for allergic sensitisation. Finally, we included nationwide annual sales of intranasal corticosteroids and oral antihistamines, which also showed an increasing trend. Ideally, we would have shown the number of individuals buying pharmacotherapy for allergic rhinitis instead of annual sales. But, due to increasing sales of oral antihistamines over-the-counter, this would not yield a reliable picture of time trends. Compared to total sales of antihistamines, the increase in sales of intranasal corticosteroids is minor. This could be due to limited access to this drug class over-the-counter. A limitation of pharmacotherapy for allergic rhinitis to assess time trends is that it can reflect a change in prescription-patterns or availability of drugs. Secondly, included drugs can be used for other indications than allergic rhinitis.

One limitation of this study is the decreasing participation rate (from 75% in Allergy90 to 28% in 2016). An analysis of Health2006 responders showed that responders were older, more likely to be female and had higher educational level and personal income compared to non-responders.²⁹ High social class has been shown to be associated with allergic sensitisation,³⁶ but its role might have changed over time.³⁷ If there is a higher probability of participating in a HES among those with ARD in the later HESs then it can

bias our results by overestimating the prevalence in the later HESs. Except for Allergy90, all included HESs have had multiple aims thus not targeting ARD specially, arguing against a selection of individuals with ARD. Additionally, nationwide annual sales of intranasal corticosteroids and oral antihistamines increased over the studied period, indicating a general trend. Finally, as described above we see a similar pattern as Steinegger et al in a study not suffering from the same challenge with decreasing response rate. Another limitation is the change in immunoassay from Health2006 (AVIDA Centaur) to DanFunD (Phadia 250). Correlation among the two assays is generally high, but among lower sIgE values Phadia tend to be more sensitive. The sensitivity analysis (using a cut-off at 0.70 kU/L) showed overall no difference in the general time trend. However, the change in assay seemed to explain some of the increase for HDM. Time trends were also examined for SPT-defined sensitisation in 2006–2008, 2010–2011, and 2016–2017, which showed the same pattern as time trends for sIgE-defined sensitisation. Thus, we do not find it plausible that the change in assay explains the increase. Only four aeroallergens (birch, cat, grass and HDM) were included in our study, however >90% of individuals with a positive response to one of the ten allergens included in the SPT standard panel are sensitised to at least one of birch, cat, grass and HDM (data not shown). A final limitation of our study is the higher percent of missing values from the questionnaire in Health2016. This is likely due to introducing a novel internet-based electronic questionnaire in Health2016. There is, however, few missing (1%) for the SPT measures, and thus the data on SPT-defined sensitisation are not affected.

To conclude, the prevalence of allergic sensitisation and allergic rhinitis (defined by allergic sensitisation and self-reported nasal symptoms) due to pollen and HDM is still increasing in a Danish general adult population. This holds true for allergic sensitisation assessed by both sIgE and SPT. These trends are supported by a nationwide increase in annual sales of intranasal corticosteroids and oral antihistamines from 1997–2015.

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CONFLICTS OF INTEREST

Katja Biering Leth-Møller is an industrial PhD student at ALK-Abelló A/S and University of Copenhagen. Allan Linneberg has received lecture fees from ALK-Abelló A/S. Tea Skaaby declares no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the design of the study. Allan Linneberg initiated the study and was involved in the data collection process. Katja Biering Leth-Møller (KLM) analysed the data and all authors

contributed to interpretation of the study results. KLM drafted the article, while all authors critically revised the article. All authors approved the final version.

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SUPPORTING INFORMATION

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

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Table S1: Questions related to allergic rhinitis symptoms and physician-diagnosed hay fever

Allergic rhinitis, symptoms	
a)	Itchy or stuffy nose or sneezing when near grass, trees, or flowers within the last 12 months
b)	Itchy or stuffy nose or sneezing when near furry animals within the last 12 months
c)	Itchy or stuffy nose or sneezing when cleaning rooms or making beds, or when in bed within the last 12 months
Physician-diagnosed hay fever	
d)	Has a physician ever told you that you have hay fever?

Table S2: Percent missing values in the five health examinations studies

	Allergy90 (1990–91)	Health2006 (2006–08)	Health2010 (2010–11)	DanFunD (2012–15)	Health2016 (2016–17)
Specific IgE	0.9	0.8	NA	1.1	NA
Skin prick test	NA	2.3	0.3	NA	1.0
Nasal symptom (a)	0.3	1.3	1.2	0.4	5.0
Nasal symptom (b)	0.2	1.1	1.2	0.4	5.0
Nasal symptom (c)	0.2	1.2	1.2	0.5	4.3
Question (d)	0.0	1.9	1.1	1.6	10.7

Table S3: Sensitivity analysis of changes in prevalence of IgE-defined sensitisation (sIgE ≥ 0.70)

	Any allergen	Birch	Cat	Grass	HDM
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Allergy90 (1990–91)	0.48 (0.37–0.62)***	0.67 (0.49–0.93)*	0.44 (0.26–0.73)**	0.44 (0.31–0.63)***	0.29 (0.17–0.50)***
DanFunD (2013–15)	1.21 (1.10–1.34)***	1.18 (1.03–1.34)*	0.86 (0.71–1.03)	1.21 (1.06–1.38)**	1.65 (1.40–1.94)***

Table note: Health2006 is reference group in all analyses. OR = Odds ratio. ORs are adjusted for age, sex at health examination, and season of health examination. HDM=house dust mite (*Dermatophagoides pteronyssinus*).

* >0.05 ; ** >0.01 ; *** >0.001

Table S4: Annual sales (DDD per 1,000 inhabitants) of drugs included in ATC groups R01AD, R06AE, and R06AX in Denmark from 1997–2015

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
R01AD01 (Beclometasone)	0.8	0.8	0.7	0.7	0.7	0.6	0.6	0.7	0.6	0.5	0.5	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.3
R01AD04 (Flunisolide)	0.1	0.1	0.1	0.1	0	0	0	-	-	-	-	-	-	-	-	-	-	-	-
R01AD05 (Budesonide)	8.2	5.9	5.8	5.5	5.3	5.3	4.9	4.9	4.7	4.6	4.5	4.3	3.9	3.4	3.1	3	2.7	2.6	2.5
R01AD08 (Fluticasone)	2	2.1	2.1	2	2	2.1	2	2	2.4	2.4	2.5	2.6	2.6	2.4	2.3	2.3	2.3	2.4	2.4
R01AD09 (Mometasone)	0	0.2	0.5	0.7	1	1.5	1.7	2.2	2.4	2.8	3.3	3.4	3.6	3.8	3.9	3.9	4	4.3	4.7
R01AD11 (Triamcinolone)	-	0	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.1	0.1	0.1
R01AD12 (Fluticasone furoate)	-	-	-	-	-	-	-	-	-	-	-	0.3	0.7	1	1.4	1.7	1.9	2.1	2.3
R01AD58 (Fluticasone, combinations)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.1	0.4	0.5
R06AE03 (Cyclizine)	0.5	0.5	0.5	0.6	0.6	0.7	0.7	0.7	0.7	0.7	0.7	0.3	0.5	0.5	0.6	0.5	0.5	0.5	0.6
R06AE04 (Chlorcyclizine)	0.1	0.1	0.1	0.1	0.1	0.1	0	-	-	-	-	-	-	-	-	-	-	-	-
R06AE05 (Meclozine)	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.2	0.4	0.2	0.2	0.1	0.1	0.1	0.1	0.2
R06AE07 (Cetirizine)	3.2	3.6	3.9	4.4	4.9	6.1	7	8	8.5	9.6	10.2	10.9	11.8	12.3	13.5	13.8	14.1	15.9	16
R06AE09 (Levocetirizine)	-	-	-	-	-	0.1	0.4	0.7	0.8	0.8	0.9	1	0.9	0.9	0.8	0.8	0.7	0.8	0.7
R06AX02 (Cyproheptadine)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0	-	0	-	-	-	-	-	-	-	-	-
R06AX09 (Azatadine)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R06AX11 (Astemizole)	0.4	0.3	0.1	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R06AX12 (Terfenadine)	1.2	0.8	0.4	0.4	0.3	0.3	0.2	0	-	-	-	-	-	-	-	-	-	-	-
R06AX13 (Loratadine)	3.1	3.6	4	4.3	4.4	4.3	3.8	3.9	3.8	4.1	4	3.8	3.7	3.4	3.4	3.3	3.1	3.3	3.1
R06AX18 (Acrivastine)	1.1	1.2	1.1	1.1	1.1	1.2	1.1	1.2	1.2	1.4	1.4	1.4	1.3	1.2	1.3	1.3	1.3	1.5	1.4
R06AX22 (Ebastine)	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.5	0.6	0.7	0.8	0.8	0.7	0.7	0.7	0.6	0.7	0.7
R06AX25 (Mizolastine)	-	0	0.1	0.1	0.1	0	0	0	0	0	-	-	-	-	-	-	-	-	-
R06AX26 (Fexofenadine)	-	0.4	1.1	1.3	1.5	1.7	1.5	1.8	2	2.2	2.6	2.9	3.3	3.5	3.9	4.3	4.5	5.4	5.8
R06AX27 (Desloratadine)	-	-	-	-	0.2	0.6	0.9	1	1.2	1.3	1.5	1.6	1.9	2	2.3	2.5	2.7	3.3	3.5
R06AX28 (Rupatadine)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
R06AX29 (Bilastine)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.1	0.2

Table note: DDD = defined daily dose. Source: Register of Medical Product Statistics, www.Medstats.dk, June 24, 2019. Prescription drugs, drugs sold to hospitals, and over-the-counter drugs are included.

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