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Impact of socioeconomic status on the use of inhaled corticosteroids in young adult asthmatics

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Summary
Objective: The aim of this population-based longitudinal study was to examine the associations between socioeconomic status (SES) and anti-asthmatic treatment with inhaled corticosteroids (ICS) among young Danish adult asthmatics, and to investigate whether these associations were consistent over time.
Methods: We extracted data on prescription drug use, education, and income in 97 665 users of anti-asthmatic drugs, aged 18–44 years, identified in Statistics Denmark during 1997–2005. Individual information on education and income was used as measures of SES. Education was categorised into basic school/high school, vocational training, and higher education, and income was categorised into low, middle, and high income. Associations between ICS use and SES were estimated by logistic regression models.
Results: High levels of education and income were independently associated with ICS use, education demonstrating the strongest association. Using basic school/high school and low income as baselines, the adjusted odds ratios (ORs) of ICS use for higher education were 1.46 (95% CI 1.40–1.51) and 1.10 (95% CI 1.06–1.14) for high income. Higher education was a nearly constant factor associated with ICS use throughout the observation period, but high income did not demonstrate any association before 2001 with increasing ORs observed each year hereafter. All associations became more pronounced when restricting to 35-44 year-olds.

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Conclusion: High levels of SES were positively associated with ICS use in young adult asthmatics. To encourage ICS use, special attention should be paid to asthmatics with low educational level and low income. Further studies are needed to elucidate underlying mechanisms for this socioeconomic inequality.

Introduction

The goal of asthma management is to achieve and maintain clinical control by minimising symptoms and exacerbations, maintain normal activity and lung function, and avoid medication side effects.[1,2] Inhaled corticosteroids (ICS) are the mainstay of asthma controller therapy and are indicated for all levels of persistent and uncontrolled asthma.[1,2] Despite an increasing prevalence of ICS use,[3,4] ICS are still used suboptimally[5,6] leading to an increased risk of asthma morbidity and mortality.[7]

During the past decade, it has become evident that low socioeconomic status (SES) is related to increasing prevalence and incidence of chronic diseases.[8–10] Often socioeconomic factors like education, occupation, and income are considered as key measures of SES. Studies on adult asthmatics have observed both positive[11–14] and no associations[15,16] between low SES and asthma prevalence and incidence. However, evidence on the association between SES and the quality of anti-asthmatic treatment with ICS is sparse.[17–20] As treatment principles have changed[21] concurrently with the introduction of new anti-asthmatic drugs[4] and change in copayment rules,[22] longitudinal studies are warranted to clarify the link between SES and ICS use over time. Knowledge about SES may guide the clinicians about which patients should have most attention.

In a previous study we investigated trends in ICS use in a population of young Danish adult asthmatics.[4] Based on a similar longitudinal dataset, the aim of the present study was to analyse to what extent socioeconomic factors, i.e. education and income, influenced ICS use.

Methods

Study design

The present study is an observational longitudinal study based on annual repeated cross-sectional analyses. We used population-based register data to identify all users of anti-asthmatic drugs in Denmark in the period 1997 to 2005.

Data sources

Data for this study were retrieved from four different registers in Statistics Denmark. Statistics Denmark contains detailed longitudinal information at an individual level for the entire Danish population (5.41 million in 2005).[23]

Data on pharmacotherapy were extracted from the Register of Medical Product Statistics comprising information on every medical product sold on prescription by Danish pharmacies since 1994. Each prescription record includes the patient's identifier, the identification code of the prescriber, the date of dispensing, the brand name, the manufacturer, quantity, form of the drug, code of reimbursement etc. Information on substances and quantities are classified according to World Health Organisation (WHO) anatomical-therapeutic-chemical (ATC) system and defined daily doses (DDD) methodology.[24] Data on education and income were retrieved from the Education Register and the Register of Family Income Statistics, and data on gender, year of birth, residence, and date of death or of migrations were obtained from the Population Register. All data were linked by using the unique person identifier, the civil registration number, which is shared among all other health-related registers in Denmark.

Study subjects

We identified all subjects who had redeemed drugs with ATC code R03 (drugs for obstructive airway diseases) during 1 January 1997 to 31 December 2005. We analysed annual cross-sections of this population with 1 January as index date. Thus, index dates were 1 January each year in 1998–2006. Only subjects alive and resident in Denmark during the past year were included.

The annual group of asthma patients was defined for each index date as all subjects who fulfilled the following inclusion criteria: 1) age 18–44 years, 2) *at least* 2 redeemed prescriptions on inhaled beta-2-agonists (IBA) within 365 days before the index date, and 3) current IBA use defined as *at least* 1 redeemed prescription of IBA 180 days before the index date. IBA referred to inhaled short-acting beta-2-agonists (SABA) (ATC R03AC02, R03AC03, R03AC04, and R03AC05), inhaled long-acting beta-2-agonists (LABA) (ATC R03AC12, and R03AC13), fixed combinations of SABA with anticholinergics (ATC R03AK03 and R03AK04), or LABA with ICS (ATC R03AK06 and R03AK07). A subject could be included on multiple index dates, if he or she fulfilled the inclusion criteria. However, the annual group of eligible asthma patients was changeable since age, number of IBA prescriptions, and current IBA use at each index date influenced inclusion or exclusion that particular year (Fig. 1).

Socioeconomic variables

To measure SES at an individual level, we retrieved individual information on education and disposable income for each year. Education was categorised according to the highest attained educational level as basic school/high school (7–12 years of primary, secondary and grammar school education), vocational training (10–12 years of education), and higher education (≥13 years of education).[25] Disposable income was defined as income for a single family member after taxation and adjusted for the number of family members.[23] On the basis of quartiles of disposable income according to each year, we categorised subjects in low (1st quartile), medium (2nd and 3rd quartile), and high

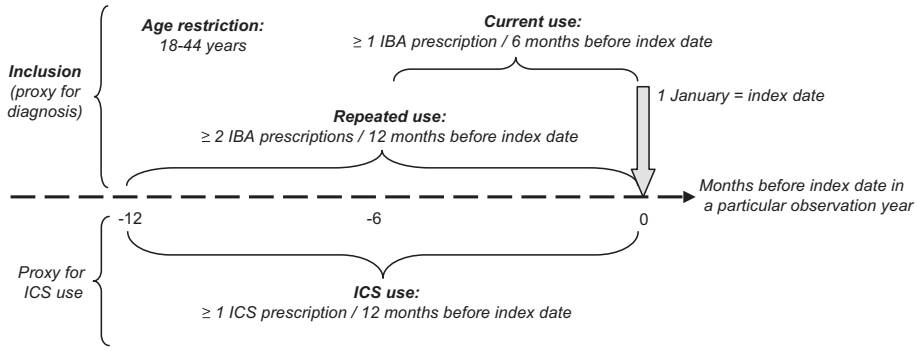

Figure 1 Inclusion criteria. This figure has been published in Respiratory Medicine.[4] Abbreviations: IBA = inhaled beta-2-agonists. ICS = inhaled corticosteroids.

income (4th quartile) recipients.[25] We excluded subjects for whom information on education or disposable income was missing (2.1% and 0.1%, respectively).

Drug use variables

Prevalent use of any drug was defined as *at least* one redeemed prescription during the year preceding the index date. Use of ICS referred both to ICS in non-combination inhalers (ATC R03BA01, R03BA02, R03BA03, R03BA05, and R03BA07), and fixed dose combination inhalers (FDCs) with ICS and LABA (ATC R03AK06 and R03AK07). Thus, use of FDCs was considered both as IBA and ICS use. Other drugs included were systemic glucocorticosteroids (ATC H02AB), leukotriene receptor antagonists (ATC R03DC), intranasal drugs for rhinitis (ATC R01A), drugs for specific immune therapy (ATC V01), inhaled short acting anticholinergics (ATC R03BB01 and R03BB02), oral long acting beta-2-agonists (ATC R03CC), oral methylxanthines (ATC R03DA), and oral chromones (ATC R03BC). Anti-IgE (ATC R03DX) was not included as this drug category has restricted delivery to hospitals. Also, we did not include inhaled long-acting anticholinergics (ATC R03BB04) as this drug category has its primary indication to patients with COPD.

Subjects were categorised according to their annual cumulative IBA consumption in DDD (1—99, 100—199, 200—399, and ≥400 DDD/year) as used in previous studies.[4,26] The DDD is not a dose recommendation, but a measure to aggregate drugs that have different potency.[24] The DDD represents the assumed average maintenance dose per day for a drug used for its main indication in adults.[24] As an example, the DDD for inhaled terbutaline is 2.0 mg and for inhaled salbutamol 0.8 mg. Thus, according to guidelines[1] a well-controlled asthma patient using less than two inhalations of reliever therapy a week corresponds to an annual use of less than 26 DDD with a 0.5 mg inhaler device. In comparison, a person using 400 DDD/year would have an average use of 4.38 inhalations daily.

Data analysis

Our outcome was use of ICS, defined as *at least* one redeemed prescription of ICS during the year preceding the index date. Data were analysed as annual cross-sections at each of the nine index dates. To analyse variables associated with ICS use, adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated by means of multivariate logistic regression models. To account for possible dependence of repeated measurements within subjects, we adjusted for clustering using robust estimates. Our primary independent variables were educational level and disposable income. Other independent variables considered as factors associated with ICS use and potential confounders were gender, age, calendar year, IBA use category, and prevalent use of anti-asthmatic drugs, or other drugs associated with asthma. Age was stratified into three categories: 18—24 years, 25—34 years, and 35—44 years.

We first analysed factors associated with ICS use for *the entire observation period for all subjects*. We supplemented with an analysis *restricted to 35-44 year-olds*. This analysis was performed because students enrolled at higher education institutions in Denmark, who have not yet attained an educational degree, may be classified as having low disposable income and being lower educated on the basis of register information. Though this classification may be formally correct, it does not necessarily reflect their true SES. Consequently, it was assumed that subjects in age category 35—44 years would generally have finished their higher education and would have found their ultimate rank of income. Secondly, we investigated possible interactions between educational level and disposable income *for all subjects* for *the entire observation period* by stratifying on educational level and disposable income, respectively. Thirdly, to investigate time trends for socioeconomic factors, we performed separate analyses for *each year* of the observation period *for all subjects*. Finally, we tested for *time trends* of ICS use using the interaction term between year and education, and the interaction term between year and disposable income. We then repeated all analyses with the threshold for ICS use set to *at least* two redeemed prescriptions during the year preceding the index date.

All analyses were performed using Stata Release 11.0 (StataCorp, College Station, TX, USA). A p-value < 0.05 was considered statistically significant.

Results

A total of 97 665 subjects (54.3% women) met the inclusion criteria during 1997—2005, corresponding to 308 335 observations. Overall, 74 511 subjects were prescribed ICS

(76.3%) during the observation period. The mean number of observations per subject was 5.3 (SD 2.9). Other baseline characteristics at the year of the subjects' *first inclusion* are presented in Table 1.

Factors associated with ICS use

Table 2 shows selected factors associated with ICS use for all subjects and subjects aged 35–44 years throughout the entire observation period. Increasing ORs for ICS use were observed for vocational training and higher education compared to basic school/high school. This association was more pronounced among 35-44 year-olds with adjusted ORs of 1.15 (95% CI 1.10–1.20) and 1.52 (95% CI 1.44–1.60) for vocational training and higher education, respectively. The extent of disposable income was positively associated with ICS use in subjects with middle and higher disposable income compared to subjects with low disposable income. Again, a stronger association was observed when restricting to 35-44 year-olds, adjusted OR of 1.15 (95% CI 1.09–1.20) for middle income, and 1.24 (95% CI 1.17–1.31) for high income. In the last year of the observation period (2005), the one year prevalence of ICS use among 35-44 year-olds was 72.5% (95% CI 71.3–73.6) among subjects with basic school/high school versus 81.4% (95% CI 80.3–82.5) among higher educated subjects, and 70.0% (95% CI 68.1–71.9) among low disposable income subjects versus 79.6% (95% CI 78.6–80.7) among subjects with high disposable income.

Table 3 shows the association between categories of educational level and ICS use, stratified on disposable income. Despite a less pronounced association between higher education and ICS use in the high income category, we found higher education to be strongly associated with ICS use in all categories of disposable income.

Table 4 shows the association for categories of disposable income with ICS use stratified on educational level. We found that the impact of increasing disposable income was most pronounced among lower educated subjects (basic school/high school), adjusted OR for high disposable income of 1.18 (95% CI 1.13–1.24).

Trends in ORs for socioeconomic factors associated with ICS use

Fig. 2 shows the adjusted ORs with CIs for the four socioeconomic factors associated with ICS use for each year during the observation period for all subjects. Vocational training was a factor associated with ICS use throughout the observation period with adjusted OR estimates ranging from 1.03 (95% CI 0.97–1.09) in 1997, 1.11 (95% CI 1.05–1.18) in 2001, and 1.09 (95% CI 1.02–1.16) in 2005 (Fig. 2A). Higher education showed a nearly constant effect through all observation years (adjusted ORs of 1.48 (95% CI 1.38–1.59) in 1997 compared to 1.47 (95% CI 1.37–1.57) in 2001, and 1.49 (95% CI 1.39–1.60) in 2005) (Fig. 2B). From 1999 a small but nearly constant association was observed for middle disposable income with adjusted ORs of 1.05 (95% CI 0.98–1.11) in 1999, and 1.08 (95% CI 1.01–1.15) in 2005 (Fig. 2C). Increasing ORs were observed for all years for high disposable income from year 1999, adjusted ORs of 1.05 (95% CI 0.98–1.13) in 1999 compared to 1.15 (95% CI 1.06–1.24) in 2002, and 1.30 (95% CI 1.20–1.40) in 2005 (Fig. 2D).

Separate analyses indicated a temporal trend for the association between high disposable income and ICS use for all subjects (adjusted OR 1.02 per year (95% CI 1.01–1.03), $p < 0.001$) and for 35-44 year-olds (adjusted OR 1.05 per year (95% CI 1.03–1.07), $p < 0.0001$). Also, a similar trend effect was found between middle disposable income among 35-44 year-olds and ICS use (adjusted OR 1.03 per year (95% CI 1.01–1.05), $p < 0.001$). No statistically significant temporal trends were found between any of the different educational levels and ICS use, neither among all subjects nor restricted to 35-44 year-olds.

In all analyses with the threshold for ICS use set to at least 2 redeemed prescriptions during the year preceding index date, we found similar associations between calendar

Table 1 Baseline characteristics at the year of the subjects' first inclusion.

Characteristics		Number (%)	Prevalent ICS users (%)
Total number of subjects		97 665 (100.0)	64.9
(mean age ± SD, years)		*(30.9 ± 8.3)*	–
Women		53 050 (54.3)	67.7
(mean age ± SD, years)		*(31.3 ± 8.3)*	–
Men		44 615 (45.7)	63.4
(mean age ± SD, years)		*(30.5 ± 8.2)*	–
Age (years)	18–24	27 039 (27.7)	66.9
	25–34	32 497 (33.3)	61.7
	35–44	38 129 (39.0)	66.3
Highest attained educational level	Basic school/high school	53 532 (54.8)	64.4
	Vocational training	27 074 (27.7)	63.4
	Higher education	17 059 (17.5)	68.9
Disposable income	Low (1st quartile)	26 022 (26.6)	63.3
	Middle (2nd–3rd quartile)	47 267 (48.4)	64.8
	High (4th quartile)	24 376 (25.0)	67.0

Baseline characteristics of all included subjects based on individual records at *the first year* of inclusion during observation period from 1997–2005. Abbreviations: SD = standard deviation.

Table 2 ORs for different factors associated with ICS use.

Factors associated with ICS use		All subjects[a] (N = 97 665) OR (95% CI)	35-44 years[a] (N = 49 317) OR (95% CI)
Year	1997	1.00	1.00
	1998	1.00 (0.98–1.03)	1.00 (0.96–1.04)
	1999	0.98 (0.96–1.01)	0.99 (0.95–1.04)
	2000	0.98 (0.96–1.01)	0.95 (0.91–1.00)
	2001	1.12 (1.08–1.15)	1.07 (1.02–1.13)
	2002	1.26 (1.22–1.30)	1.17 (1.12–1.23)
	2003	1.38 (1.34–1.42)	1.27 (1.21–1.34)
	2004	1.55 (1.50–1.60)	1.42 (1.35–1.49)
	2005	1.65 (1.60–1.70)	1.52 (1.44–1.60)
Highest attained educational level	Basic school/high school	1.00	1.00
	Vocational training	1.06 (1.02–1.09)	1.15 (1.10–1.20)
	Higher education	1.46 (1.40–1.51)	1.52 (1.44–1.60)
Disposable income	Low (1st quartile)	1.00	1.00
	Middle (2nd–3rd quartile)	1.03 (1.00–1.06)	1.15 (1.09–1.20)
	High (4th quartile)	1.10 (1.06–1.14)	1.24 (1.17–1.31)
Gender	Women	1.00	1.00
	Men	0.66 (0.64–0.68)	0.70 (0.67–0.73)
Age (Years)	18–24	1.00	
	25–34	0.71 (0.68–0.73)	
	35–44	0.83 (0.80–0.86)	
IBA use (DDD/year)	1–99	1.00	1.00
	100–199	1.33 (1.30–1.37)	1.44 (1.38–1.50)
	200–399	1.98 (1.92–2.05)	2.16 (2.06–2.27)
	$\geq$ 400	2.02 (1.94–2.10)	2.21 (2.09–2.34)

Abbreviations: IBA = inhaled beta-2-agonists, ICS = inhaled corticosteroids. OR = odds ratio.
[a] Adjusted for highest attained educational level, disposable income, gender, age categories, IBA use categories, calendar years, and prevalent use of specific anti-asthmatic drug categories.

year, educational level, disposable income, and ICS use (data not shown).

Discussion

Principal findings and comparison with other studies

To our knowledge, this is the first longitudinal study to explore potential associations between SES and ICS use in a national population of young adult asthmatics. The key findings were that high levels of education and disposable income were independently associated with higher use of ICS. Overall, education was a stronger factor associated with ICS use than disposable income which only became significant from 2001. The impact of increasing disposable income on ICS use was most pronounced among lower educated subjects. The impact of education and disposable income was more pronounced in 35-44 year-olds, who could be assumed to have finished their education and found their ultimate level of income. This was supported by an absolute

Table 3 ORs for categories of highest attained educational level associated with ICS use stratified on level of disposable income.

Disposable income	Highest attained educational level	OR (95% CI)
Low (1st quartile)	Basic/high school	1.00
	Vocational training	1.11 (1.04–1.18)
	Higher education	1.48 (1.37–1.60)
Middle (2nd–3rd quartile)	Basic/high school	1.00
	Vocational training	1.06 (1.02–1.10)
	Higher education	1.52 (1.44–1.59)
High (4th quartile)	Basic/high school	1.00
	Vocational training	1.02 (0.96–1.08)
	Higher education	1.34 (1.25–1.43)

Each stratum of disposable income adjusted for gender, age categories, IBA use categories, calendar years, and prevalent use of specific anti-asthmatic drug categories. Abbreviations: IBA = inhaled beta-2-agonists, ICS = inhaled corticosteroids. OR = odds ratio.

Table 4 ORs for categories of disposable income associated with ICS use stratified on highest attained educational level.

Highest attained educational level	Disposable income	OR (95% CI)
Basic/high school	Low	1.00
	Middle	1.04 (1.01–1.07)
	High	1.18 (1.13–1.24)
Vocational training	Low	1.00
	Middle	1.02 (0.97–1.09)
	High	1.09 (1.02–1.16)
Higher education	Low	1.00
	Middle	1.07 (0.99–1.16)
	High	1.06 (0.97–1.15)

Each stratum of highest attained educational level adjusted for gender, age categories, IBA use categories, calendar years, and prevalent use of specific anti-asthmatic drug categories. Abbreviations: IBA = inhaled beta-2-agonists, ICS = inhaled corticosteroids. OR = odds ratio.

difference in one year prevalence of ICS use between low and high SES groups of approximately 10% in 2005 for this age category.

Concerning income, we used disposable income as economy measure, as this was thought to best represent the individual's purchasing power.[25] As ICS are expensive drugs (e.g. in 2005, 100 doses of powder inhalation of 400 μg budesonide cost 480 Danish Kroner (DKK) corresponding to about 64 Euro),[27] cost may be a barrier for their use in low income groups. The association between high disposable income and ICS use became stronger with time and was statistically significant from 2001. This relationship could be due to the introduction of fixed dose combination inhalers with ICS and LABA in 1999 and 2001.[4] Additionally, new copayment rules were introduced in March 2000 with full user payment for the first 500 DKK (∼ 67 Euro) spent per year.[22] Above the 500 DKK limit the proportion paid by the Regional Health Service would increase with increasing annual drug expenses for an individual.[22] These changes in copayment rules could be assumed to negatively affect purchase of anti-asthmatics for the low SES groups, as the barrier to buy expensive medication is expected to be higher for these groups compared to high SES groups. Cost of medicine as well as copayment have been identified as factors associated with non-adherence to medication.[28,29]

Regarding education, a consistent association between higher educational levels and ICS use was found for all calendar years. Several factors may be relevant: high education as a proxy of cognitive skills, SES levels' influence on adherence to ICS, or possibly the physician's attitude towards patients perceived as peers. The latter is not well elucidated in the literature. Cognitive skills may facilitate information on appropriate asthma treatment and may render the patient capable of transforming symptoms of

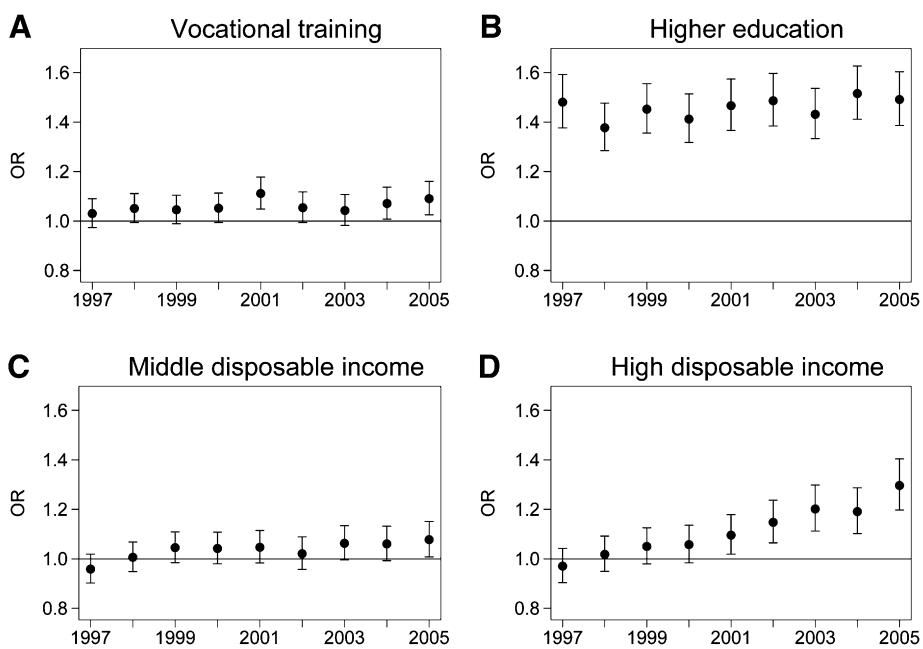

Figure 2 Trends in ORs for socioeconomic factors associated with ICS use. A and B: Basic school/high school is used as reference, adjusted for disposable income, gender, age categories, IBA use, and prevalent use of specific anti-asthmatic drugs. C and D: Low disposable income is used as reference, adjusted for highest attained educational level, gender, age categories, IBA use, and prevalent use of specific anti-asthmatic drugs. Abbreviations: OR = odds ratio, SES = socioeconomic status, ICS = inhaled corticosteroids.

asthma deterioration into initiating or enhancing controller therapy with ICS.[17]

Evidence on the relationship between anti-asthmatic treatment with ICS and SES is sparse. Nevertheless, our results agree with previous findings on asthmatics. Apter et al. showed that socioeconomic factors associated with non-adherence with ICS were less than 12 years of education and low household income.[17] Likewise, de Vries et al. found that low SES, defined by a combination of educational level and employment, was associated with poor asthma control.[19] Uncontrolled asthma could be a consequence of suboptimal asthma treatment. Conversely, Janson et al. demonstrated that ICS adherence was associated with high income, but they could not demonstrate an association between ICS adherence and educational level.[20] Common for the studies[17,19,20] mentioned is the fact that no uniform definition of SES was used and the studies were limited by relatively few participants. As no strict international definition of SES is available, comparing results between studies is a major challenge.[30]

In addition, we found an increased association between ICS use and high annual IBA use (Table 2). Overuse of IBA has been demonstrated to be strongly associated with ICS use and severity of asthma symptoms reflecting that subjects with high IBA use possess poor asthma control, and are therefore more likely to use ICS.[31] Moreover, other factors found to be positively associated with ICS use were calendar year from 2001, female gender, and low age (Table 2). These have been discussed in a previous publication.[4]

Strengths and limitations

Among the strengths of this study is the population-based approach based on national register data with high completeness and validity,[32–34] which renders our study less vulnerable to selection bias and recall bias. Using a model based on repeated annual cross-sections allowed us to examine longitudinal trends for different factors associated with ICS use. By our age restriction, we avoided subjects with anti-asthmatic drug use from other diagnoses than asthma (e.g. COPD). Furthermore, we have analysed the trend of disposable income on ICS use by two different approaches (separate annual analyses and analyses using interaction with time).

Exposure to ICS is extremely difficult to evaluate in real-life studies and may not be reflected adequately by the proposed proxy of ICS use defined as at least one redeemed prescription within a year. However, changing the ICS use threshold to at least two prescriptions within a year did not induce any considerable changes in the associations between education, income and ICS use. Adherence to ICS use is complex and difficult to measure, and may depend on many patient related factors, e.g. smoking, physical fitness, body composition, comorbidities, psychological traits, side effects, and educational support. It was a limitation in our study that our data sources could not account for these potential confounders of ICS use. Moreover, our analyses did not account for costs of inhalation drugs and inflation during the observation period. Nevertheless, only a minor increase in costs of inhalation medicine occurred during the observation period,[27] which was balanced by an increase in disposable income. The relative difference between high and low disposable income in both extremes of the observation period was almost unchanged (39% in 1997 and 43% in 2005), and consistent with previous findings from Denmark.[25] By categorising subjects according to the relative disposable income each year during the observation period (quartiles), we have rendered our analyses less sensitive to inflation. Furthermore, we have used data on redeemed prescriptions that do not allow us to distinguish between physician prescribing behavior and patient non-adherence, i.e. not purchasing a prescribed drug.

Conclusion

Our results demonstrate that high levels of education and disposable income are positively associated with ICS use in young Danish adult asthmatics. These results emphasise the fact that health care professionals should consider socioeconomic factors when providing information and education to asthma patients with special attention to subgroups with low educational level and low income. Additionally, as income had some considerable influence on ICS use among subjects with lower educational level, this could indicate that cost of ICS is a barrier for its use among lower educated subjects. Future studies should explore causal relations for the inequality between SES and ICS use by also including physician characteristics as potential factors associated with the quality of ICS treatment, e.g. variation between the constitution of practices, outpatient clinics, and hospital departments.

Ethical approval

Registry-based studies do not require an ethical approval in Denmark. Statistics Denmark and the Danish Medicines Agency gave permission to data access.

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Conflict of interest statement

All authors have completed the International Committee of Medical Journal Editors Unified Uniform Disclosure Form for Potential Conflicts of Interest (available on request from the corresponding author) and declare that: JRD has received a fee for organising education and travel funding to the ERS congress in 2009 from AstraZeneca. JS has participated in a study funded by a research grant from AstraZeneca. JH's research institution has received support from MSD for the submitted work, and JH has received fees for teaching from AstraZeneca, Nycomed, Pfizer and the Danish Association of the Pharmaceutical Industry, and research grants from Nycomed, Pfizer, MSD, and Alkabello. HCS has received payment for research from Asthmatx Inc.

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Appendix. Supplementary data

The supplementary data associated with this article can be found in the on-line version at doi:10.1016/j.rmed.2010.11.009.

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