ORIGINAL ARTICLE

Epidemiology of Allergic Disease

WILEY

Academic achievement of adolescents with asthma or atopic disease

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Summary

Background: Over a fifth of children and adolescents suffer with asthma or atopic disease. It is unclear whether asthma impacts academic performance in children and adolescents, and little is known about the association of eczema, food allergy or hayfever and academic performance.

Objective: To examine whether asthma, eczema, food allergy or hayfever impacts on adolescent academic performance and to assess the role of unmeasured confounding.

Methods: This study used the Childhood and Adolescent Twin Study of Sweden cohort born 1992-1998. At age 9-12 years, parents reported on their child's ever or current asthma, eczema, food allergy and hayfever status (n = 10 963). At age 15, linked national patient and medication register information was used to create current and ever asthma definitions including severe and uncontrolled asthma for the same children. Academic outcomes in Grade 9 (age 15-16 years) included: eligibility for high school (Grades 10-12), and total mark of the best 16 subject units, retrieved from the Grade 9 academic register. Whole cohort analyses adjusted for known covariates were performed, and co-twin control analyses to assess unmeasured confounders.

Results: There were no associations found for asthma or food allergy at 9-12 years and academic outcomes in adolescence. In addition, at age 15, there were no statistically significant associations with current, ever, severe or uncontrolled asthma and academic outcomes. Eczema and hayfever at age 9-12 years were found to be positively associated with academic outcomes; however, co-twin control analyses did not support these findings, suggesting the main analyses may be subject to unmeasured confounding.

Conclusion and clinical relevance: Having asthma or an atopic disease during childhood or adolescence does not negatively impact on academic performance. This information can be used by clinicians when talking with children and parents about the implications of living with asthma or atopic disease.

KEYWORDS
asthma, atopic dermatitis, epidemiology, food allergy, quality-of-life, rhinitis

1 | INTRODUCTION

Asthma, eczema, allergic rhinitis (hayfever) and food allergy are genetically related inflammatory diseases[1] often caused by a hypersensitivity to external stimuli such as allergens. They often co-occur, and constitute the most common chronic illnesses in children, affecting absenteeism, quality of life and sleep behaviours.[2-4] Therefore, it seems plausible that asthma and atopic diseases may also impact cognitive learning and academic performance.

Although asthma has been shown to be associated with increased absenteeism[5,6] and in turn absenteeism has been shown to be associated with reduced academic performance,[5,6] the direct association between asthma and academic performance is unclear. Several studies have found a negative association between asthma and academic performance,[7-9] while others have found none.[5,10] This could be because of the heterogeneity of asthma and that most cases are mild and controlled which may not influence learning and cognition, where as other phenotypes of asthma such as uncontrolled, severe or late onset asthma may have a more obvious impact on learning and performance.[6,9] Another reason for a lack of consistency between study findings could be due to heterogeneity of the confounding factors adjusted for and the impact of possible unmeasured confounding. Unmeasured or residual confounders are variables that may affect both atopic disease status and academic performance but are either unrecognized and therefore not measured, or are recognized but are difficult or not possible to measure, for example severity of viral illnesses. One way to reduce unmeasured confounding is to compare an affected and non-affected twin since they share the same family environment and genetic background.

Furthermore, despite the fact that hayfever, eczema and food allergy are also common childhood diseases, affecting quality of life for the sufferers and their families,[11,12] very little has been studied to date on the effects of these diseases on academic performance.[7,13]

In this study, we will use a population-wide twin cohort to look at the associations of asthma, eczema, hayfever or food allergy at ages 9-15 with academic performance. In addition, we will investigate the associations for different definitions of asthma including severe and uncontrolled asthma and control for factors that occur at a family level such as socio-economic status by using a co-twin control approach.

2 | METHODS

2.1 | Study population

All twins in Sweden born between July 1992 and December 1998 were included (n = 14 992).[14,15] After exclusion of those twins who died or emigrated before recruitment, whose parents were not fluent in Swedish, or who had a disability, 14 520 twins were eligible to be included in the Childhood and Adolescent Twin Study in Sweden (CATSS) at ages 9-12 years. Parents were interviewed about their children's health status via a telephone questionnaire. There was a 79.5% participation rate (n = 11 546) of whom 10 963 had complete information for all covariates used in the current study. The information from CATSS was linked by personal identity number to nationwide registers held in Sweden by the National Board of Health and Welfare and Statistics Sweden.[16] All data was de-identified prior to analyses.

2.2 | Exposures

2.2.1 | Asthma

At 9-12 years, CATSS parent-report questions were used to define asthma. Parents/guardians were asked about the child ever having asthma (*parent-report ever asthma 9-12*) and still having asthma (*parent-report current asthma 9-12*). The asthma questions in CATSS have been shown to have good agreement with register-based definitions.[17]

At age 15, register-based data was used to define asthma for the same population. Inpatient and specialist diagnoses came from the National Patient Register (NPR), and prescriptions were taken from the Swedish Prescribed Drug Register (SPDR). *Register-based ever Asthma 15* was defined as fulfilling one of the following criteria: (a) two or more dispenses of preventer medications since 2005, that is either; inhaled corticosteroids (ICS, ATC code R03BA), leukotriene receptor agonists (LTRA, ATC code R03DC03) or fixed combinations of β2-agonists and corticosteroids (β2-ICS, ATC code R03AK); (b) two dispenses of β2- adrenoreceptor agonists (ATC code R03AC), and either a third dispense of a β2- adrenoreceptor agonist or of a preventer medication (ICS, LTRA, β2-ICS) in any 12 month period; (c) an asthma diagnosis in the NPR after the age of 4.5 years.[18] *Register-based current Asthma 15* was defined as having *register-based ever asthma* before age 15 years, AND either a dispensed medication or an asthma diagnosis recorded within 18 months of their 15th birthday. *Uncontrolled asthma 15* was defined using a combination of European Respiratory Society (ERS)/American Thoracic Society (ATS)[19] and the Global Initiative for Asthma (GINA) guidelines[20] as applicable to our data. One of the following criteria had to be met in the last 12 months: (a) hospitalization for asthma (NPR); (b) unplanned visit to the hospital or general practitioner for asthma (NPR); (c) two persistent asthma symptoms in the last 12 months (self-reported by adolescent in CATSS)—difficulty in breathing >once per week, waking from asthma > twice per month, or disturbance of daily activities due to asthma > sometimes; (d) >four dispenses of a short-acting β2 agonist in the last 12 months (SPDR). *Severe asthma 15* was defined according to the ERS/ATS guidelines as a prescription of high dose ICS in the last year plus a second controller or systemic corticosteroid (regardless of whether the asthma was controlled or uncontrolled).[19] High dose ICS was determined by GINA guidelines.[20] Equal to and more than the adult high dose recommendation was included to allow for adolescent participants that may not have reached their full adult growth (rather than just greater than, as is recommended in the guidelines).

2.2.2 | Sub-analysis age 15

Additionally at age 15, the original CATSS 9-12 participants and their parents were invited for interview again. Of those interviewed at ages 9-12, n = 4664 (42.5%) agreed to participate in CATSS 15. Parents were asked if their child still had asthma (*parent-report current asthma 15*) and adolescents self-reported on whether they still had asthma (*self-report current asthma 15*).

2.2.3 | Eczema, hayfever and food allergy

At 9-12 years, CATSS parent-report questions were used to define eczema, hayfever and food allergy. Parents/guardians were asked about the child *ever* having each of these diseases and still having them (*current*). We chose not to include register-based definitions for these illnesses at age 15 due to possible under-utilization of health care for these particular illnesses.[18]

2.3 | Academic outcomes

In Grade 9 of school in Sweden, all children (age 15-16 years) are assessed in each subject based on national criteria. Prior to 2011, *Eligibility for high school* (Grades 10-12) was achieved if the child passed Swedish, English and Mathematics in Grade 9. From 2011 onwards, eligibility was achieved if the child also passed five additional subjects. *Total mark* is defined as the total of the best 16 subject units during Grade 9 (range 0-320 points, each unit can add up to 20 points). All data was retrieved from the National Grade 9 pupil register (AK9), held by Statistics Sweden.

2.4 | Covariates

Data on sex, birth weight, gestational age, maternal age at delivery and maternal smoking during pregnancy were retrieved from the Medical Birth Register. Parental education and country of birth data were retrieved from and the Longitudinal Integration Database for health insurance and labour market studies. Socio-economic status was defined as a combination of both parent's level of education at the time of the telephone interview (both parents ≤Grade 9, one or both parents completed Grade 12, one or both parents completed at least 2 years of graduate education).

2.5 | Statistical analysis

Logistic regression models were used to estimate the odds ratios (OR), and 95% confidence intervals (95% CI) of *eligibility for high school* for each of the different atopic exposures at each time point. Similarly, the difference in *total mark* and 95% CI were estimated for those with and without each atopic exposure using linear regression models. A sandwich estimator was used to account for correlation caused by clustering of observations within twin pairs. Potential confounders were assessed using directed acyclic graphs and analyses were then adjusted for the following: sex, birth weight, gestational

age, maternal age at delivery, maternal smoking, mother's and father's birth countries and parental education. Effect modification by sex and age (9 or 12 years) was tested by including an interaction term in each model.

A co-twin control analysis compared twins with atopic disease with their non-affected twin to reduce the risk of bias caused by confounding (shared environment or genetic).[21] This was only done for the total mark analysis as the twin pairs were much more likely to be discordant on a continuous outcome such as total mark rather than a binary outcome such as eligibility for high school.

Data management and statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., USA) and STATA 15.1 (StataCorp, USA).

This study was approved by the Regional Ethical Review board in Stockholm, Sweden.

3 | RESULTS

The demographic characteristics for the CATSS cohort population for the whole population and by academic outcome are shown in Table 1. The characteristics for the cohort for the sub-analysis at age 15 can be found in Table S1.

The prevalence of parent-report current asthma at 9-12 years was 9.3%, and at age 15 years current asthma prevalence ranged from 4.4% for self-report asthma to 7.1% for parent-report and register-based asthma. Severe asthma was identified in 65 adolescents (8.3% of the register-based current asthma cases, 0.6% of the total population), and uncontrolled asthma was identified in 89 adolescents (11.4% of register-based current asthma cases, 0.9% of the total population). The prevalence of other parent-reported current atopic diseases at 9-12 years was 7.8% eczema, 7.3% hayfever and 8.1% food allergy.

Analysis of various definitions of asthma at ages 9-12 and 15 with academic performance in Grade 9 is shown in Table 2. None of the parent-report or register-based current or ever asthma definitions at any of the ages had statistical associations with eligibility for high school or a change in total mark (for example: parent-report ever asthma 9-12 years and eligibility for high school: adjusted OR 1.11, 95% CI: 0.89, 1.40; register-based ever asthma 15 years and difference in average total mark 0.1 (95% CI: −3.2, 3.4). Although those with uncontrolled or severe asthma had a slightly lower average total mark than those with no asthma, this was not significant (Table 2) and in fact they were more likely to be eligible for high school (non-significant trend, Table 2). No evidence was found for differences in associations between sexes or ages using interaction terms (results not shown).

Having ever or current eczema was positively associated with a higher chance of being eligible for high school (*current eczema*: adjOR 1.48, 95% CI: 1.04, 2.10), and ever eczema with higher total mark (eg *ever eczema*: +3.0, 95% CI: 0.4, 5.7). Having ever or current hayfever was also positively associated with a higher chance of being eligible for high school (*current hayfever 9-12*: adjOR 1.57, 95% CI: 1.12, 2.19) and a higher total mark (*current hayfever 9-12*: +6.4, 95% CI: 2.4,

TABLE 1 Demographic characteristics for CATSS twins whole population, those eligible for high school and by average total mark (95% CI)

	Whole population n (%)	Eligible for high school n (%)	Total mark Grade 9 average (SD)
	N = 10 963	N = 10 066	218.7 (60.1)
Sex			
Male	5602 (51.1)	5102 (50.7)	208.5 (58.5)
Female	5361 (48.9)	4964 (49.3)	229.4 (59.9)
Birth weight			
<2499 g	4061 (37.3)	3666 (36.7)	217.0 (60.8)
2500-2999 g	3870 (35.5)	3580 (35.8)	219.2 (59.7)
>3000 g	2958 (27.2)	2750 (27.5)	220 (59.6)
Gestational age			
<244 d	2035 (18.6)	1827 (18.2)	216.2 (60.8)
245-272	6494 (59.2)	5972 (59.3)	219.0 (60.2)
>273	2434 (22.2)	2267 (22.5)	220.0 (59.1)
Mother smoked in pregnancy			
Yes	1799 (17.5)	1503 (17.5)	186.5 (65.8)
Mother's age at delivery			
≤24	1205 (11.0)	1049 (10.4)	200.0 (59.8)
25-29	3600 (32.8)	3295 (32.7)	215.0 (58.6)
30-34	3979 (36.3)	3690 (36.7)	223 (59.4)
≥35	2179 (19.9)	2032 (20.2)	227 (61.3)
Mother's country of birth			
Sweden	9866 (90.0)	9082 (90.2)	219.0 (59.9)
Other	1097 (10.0)	984 (9.8)	215.9 (61.6)
Father's country of birth			
Sweden	9830 (89.7)	9071 (90.1)	219.4 (59.8)
Other	1133 (10.3)	995 (9.9)	213.1 (62.6)
Parent's highest level of education			
Grade 9 or below	382 (3.6)	281 (2.8)	168.5 (69.5)
Grade 12 for one or both parents	5248 (48.9)	4657 (47.1)	202.1 (58.8)
>2 y tertiary for one or both parents	5104 (47.6)	4943 (50.0)	240.5 (51.6)

CATSS, Childhood and Adolescent Twin Study in Sweden.

11.0; Table 3). Ever and current food allergy showed no associations with academic performance variables. No evidence was found for a difference between sexes or ages for any of the associations using interaction terms (results not shown).

The co-twin control analysis did not find any significant differences in Grade 9 total marks for any of the asthma definitions at any age nor for eczema, hayfever or food allergy, (Tables 4 and 5).

4 | DISCUSSION

Overall, this study has found that asthma during childhood or adolescence does not have a negative impact on academic performance.

Some positive associations were found for eczema and hayfever at ages 9/12 and academic outcomes. However, the co-twin control analyses found null results, implying that for hayfever and eczema some unmeasured confounding exists in the initial analyses (Table 5).

The strengths of this study are that it is a longitudinal analysis with exposures measured at both 9-12 and 15 years. At 9-12 years of age, we were able to obtain exposure data for not only asthma but also hayfever, eczema and food allergy, the last two which have rarely been investigated. In addition, the questionnaires and registers allowed several definitions for asthma and allergy exposures, improving the validity and robustness of our findings. At 9-12 years, we used ever and current reported disease definitions, and for the 15-year-old analyses we were able to assess validated register-based

TABLE 2 Asthma at ages 9-12, 15 y and academic performance in Grade 9 of school

	N	Proportion eligible for high school		Odds ratios (95% CI)[a]	Average total mark		Average difference in total mark (95% CI)[a]
		With asthma n (%)	Without asthma n (%)		With asthma (SD)	Without asthma (SD)	
Parent-report current asthma 9-12	10 963	942 (92.4)	9074 (91.8)	1.23 (0.94, 1.61)	214.0 (60.0)	219.2 (60.1)	−0.1 (−3.9, 3.7)
Parent-report ever asthma 9-12	10 963	1343 (91.4)	8649 (91.9)	1.11 (0.89, 1.40)	213.2 (60.9)	219.7 (59.9)	+0.3 (−3.1, 3.8)
Register-based current asthma 15	10 963	724 (92.9)	9367 (91.7)	1.26 (0.91, 1.75)	217.1 (58.6)	218.8 (60.2)	0.1 (−4.1, 4.4)
Register-based ever asthma 15	10 963	1306 (92.6)	8785 (91.7)	1.20 (0.94, 1.54)	216.2 (59.5)	219.1 (60.2)	0.1 (−3.2, 3.4)
Severe asthma 15	10 266[b]	64 (98.5)	9357 (91.7)	5.09 (0.72, 36.03)	218.7 (47.8)	218.4 (60.2)	−1.4 (−11.1, 8.3)
Uncontrolled asthma 15	10 281[b]	85 (95.5)	9349 (91.7)	2.36 (0.72, 7.71)	211.6 (58.0)	218.8 (60.2)	−2.6 (−15.1, 10.0)
Sub-analysis							
Parent-report current asthma 15	4516	306 (95.6)	3949 (94.3)	1.53 (0.84, 2.82)	227.3 (50.6)	232.1 (54.5)	−0.9 (−6.8, 5.0)
Self-report current asthma 15	4664	183 (95.8)	4144 (95.2)	1.11 (0.53, 2.36)	228.5 (53.0)	234.2 (53.0)	−3.0 (−11.0, 5.0)

[a]Adjusted for: sex, gestational age, birth weight, mother smoked during pregnancy, maternal age of delivery, parent's birth country, parent's highest level of education

[b]Those with register-based current asthma that is not severe/uncontrolled have been excluded from analysis.

asthma definitions,[18] including severe and uncontrolled asthma based on ERS/ATS and GINA guideline definitions. In addition, we were able to do a sub-analysis on parent-report and self-report asthma at age 15 years. Furthermore, the outcome variables for academic performance were based on testing consistent with national curricula obtained from Swedish registers, therefore reducing bias due to recall or non-participation. Finally, we were able to control for unmeasured environmental and genetic confounding by including a co-twin control design.

One of the limitations in this study was that we were not able to test eczema, hayfever and food allergy at age 15 years. This would have been interesting to do especially for eczema and hayfever as we saw associations at age 9-12 years. Secondly, there may be some reporting bias from using only parent-report variables at age 9-12 years. We unfortunately could not obtain a register-based definition for asthma for this age group as the Prescribed Drug Register only began in 2005. Thirdly, it is important to put this research in perspective as Sweden has free health care for children and therefore in countries with health care disparities based on wealth differences results may be seen. Furthermore, 90% of those participating in CATSS had Swedish parents which could reduce generalizability to other nationalities, however, other research has shown that the genetic diversity within Sweden is substantial and comparable with diversity across Europe.[22]

The results for asthma support a 2005 review investigating asthma in children and academic performance concluding that any association was weak or nonexistent,[23] as well as the null findings of two subsequent studies: a Swedish study on adolescents,[10] and a US study on children aged 8-17.[5] However, two more recent studies have found an association between ever, school age[9] and diagnosed asthma[7] with worse academic performance. The larger of these studies by Kim et al[7] included 299 695 children from years 7-12, and although this is the largest study in this field to date, the limitation of this study was that the participants were voluntary and self-reported on both exposures and academic performance, hence increasing the risk for selection and measurement bias.

Despite the fact that children with severe asthma are more at risk of absenteeism[24] and decreased quality of life[25] there are only a few studies that we are aware of that have investigated severe or uncontrolled asthma with academic performance. Both Nilsson et al and Moonie et al[5,9] found a non-significant trend for children with persistent or uncontrolled asthma and worse academic performance. However, a study in New Zealand found no association between asthma severity and school performance during the first year of

TABLE 3 Parent-report eczema, hayfever and food allergy at ages 9-12 and academic performance in Grade 9 of school

	Proportion eligible for high school			Average total mark		
	With atopic disease n (%)	Without atopic disease n (%)	Odds ratios (95% CI)[a]	With atopic disease (SD)	Without atopic disease (SD)	Average difference in total mark (95% CI)[a]
Current eczema	802 (94.1)	9242 (91.6)	1.48 (1.04, 2.10)*	222.2 (55.9)	218.4 (60.4)	+2.0 (−1.9, 5.9)
Ever eczema	2219 (93.1)	7799 (91.5)	1.31 (1.07, 1.60)**	221.1 (58.5)	218.0 (60.5)	+3.0 (0.4, 5.7)*
Current hayfever	751 (94.5)	9284 (91.6)	1.57 (1.12, 2.19)**	221.8 (56.5)	218.5 (60.4)	+6.6 (2.4, 11.0)**
Ever hayfever	860 (93.9)	9102 (91.6)	1.36 (1.02, 1.81)*	220.4 (57.9)	218.4 (60.4)	+4.9 (0.4, 8.9)*
Current food allergy	824 (93.0)	9116 (91.7)	1.13 (0.83, 1.53)	221.7 (59.1)	218.3 (60.2)	+3.0 (−1.3, 7.2)
Ever food allergy	1383 (93.4)	8683 (91.6)	1.25 (0.97, 1.60)	221.9 (60.2)	218.2 (60.1)	+3.0 (−0.4, 6.4)

[a]Adjusted for: sex, age, gestational age, birth weight, mother smoked during pregnancy, maternal age of delivery, parent's birth country, parent's highest level of education.
*$P \leq 0.05$.
**$P \leq 0.01$.

TABLE 4 Co-twin control analysis for asthma age 9-12 and 15 y. Average difference in total mark in Grade 9 of school

	Number of discordant twin pairs (N)	Average difference in total mark (95% CI)[a]
Parent-report current asthma 9-12	703	−1.36 (−4.83, 2.10)
Parent-report ever asthma 9-12	874	−1.91 (−5.23, 1.40)
Register-based current asthma 15	563	0.83 (−3.08, 4.75)
Register-based ever asthma 15	947	0.08 (−2.95, 3.10)
Severe asthma 15	42	−4.50 (−17.28, 8.28)
Uncontrolled asthma 15	61	−2.77 (−11.17, 5.62)
Sub-analysis		
Self-report current asthma 15	126	0.11 (−7.35, 7.57)
Parent-report current asthma 15	226	4.44 (−1.35, 10.22)

[a]Adjusted for: sex, and birth weight.

school,[8] and a small study comparing 25 severe asthma children with controls also found no difference in school performance.[26] These authors concluded that children with severe asthma adapt well to living with asthma.[26] Our investigation supports this conclusion that severe or uncontrolled asthma does not lead to worse academic performance. Future larger studies could further assess the severe asthma group by separating hospitalized and non-hospitalized cases to test whether those with uncontrolled severe asthma are at risk of worse academic outcomes.

The current study found that those with hayfever (allergic rhinitis) were more likely to have a better academic performance, both for high school eligibility and for total mark in Year 9. Of the few studies that have investigated allergic rhinitis, interestingly two of them also found an increase in academic performance in those with allergic rhinitis compared to controls.[7,10] However, the null results for hayfever

and academic performance in the co-twin control analysis suggests that the initial analyses be influenced by confounding, that is, a factor that leads to increased hayfever risk also increases academic performance, such as parental socio-economic status.[27] In contrast to the direction of our results, a case control study by Walker et al[13] found that those who had dropped one or more grades were more likely to have suffered with seasonal allergic rhinitis during the examination period or on the days leading up to the examination period than those who had not dropped grades. However, they found no differences in academic performance for diagnosed allergic rhinitis or allergic rhinitis ever. In addition, a Swedish study found that those with severe nasal symptoms (defined as significant interference in daily activities by nasal symptoms in the last 12 months) were more likely to perform worse.[10] Taken together, this would suggest that having severe or acute allergic rhinitis on the days of testing may influence academic

	Number of discordant twin pairs (N)	Average difference in total mark (95% CI)[a]
Parent-report current eczema 9-12	589	–2.06 (–5.88, 1.76)
Parent-report ever eczema 9-12	1461	0.09 (–2.29, 2.48)
Parent-report current hayfever 9-12	535	0.08 (–3.76, 3.92)
Parent-report ever hayfever 9-12	598	0.67 (–2.92, 4.27)
Parent-report current food allergy 9-12	590	1.77 (–1.73, 5.27)
Parent-report ever food allergy 9-12	877	0.98 (–2.04, 4.00)

TABLE 5 Co-twin control analysis for eczema, hayfever and food allergy. Average difference in total mark in Grade 9 of school

[a]Adjusted for: sex and birth weight.

performance negatively, but that having allergic rhinitis or hayfever as a condition per se does not imply worse academic performance.

Similarly to hayfever, we found that those with eczema were more likely to have an improved academic performance; however, the co-twin control study did not support the main findings, suggesting rather, a null finding, and confounding of the original analysis by unmeasured factors. We are only aware of two other studies that have investigated eczema in children and academic performance, both of these had null findings.[7,10]

Finally, our study is the only study we are aware of that has looked at food allergy and academic performance. Our results suggest that having a food allergy does not negatively affect academic performance.

In conclusion, we find no evidence to support that having asthma, eczema, hayfever or food allergy during childhood or asthma during adolescence has a negative effect on academic performance. Unmeasured confounding may be playing a role in analyses of these type and should be considered in future studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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