Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study

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ABSTRACT: We investigated the impact of season relative to other determinants of chronic obstructive pulmonary disease (COPD) exacerbation frequency in a long-term international study of patients with FEV_1 <60% predicted. **Methods:** COPD exacerbations were defined by worsening symptoms requiring systemic corticosteroids and/or antibiotics (moderate) or hospital admission (severe). Seasonality effect was calculated as the proportion of patients experiencing an exacerbation each month. **Results:** Exacerbations in the Northern and Southern regions showed an almost two-fold increase in the winter months. No seasonal pattern ~~was observed~~ occurred in the Tropics. Overall, 38% of exacerbations were treated with antibiotics only, 19% with systemic corticosteroids only and 43% with both, while 20% required hospital admission irrespective of the season. Exacerbation frequency was associated with older age, lower body mass index, lower FEV_1 %predicted, and history of prior exacerbations. Women and patients with worse baseline breathlessness by MRC score exacerbated more often (rate ratio (RR) male *versus* female 0.7, 95% confidence interval (CI): 0.7, 0.8; p<0.001; RR MRC dyspnoea grade 3 versus 1+2 combined 1.1, 95% CI: 1.1, 1.2; p<0.001). The effect of season was independent of these risk factors. **Conclusion:** COPD exacerbations and hospitalisations are more frequent in winter.
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INTRODUCTION

Patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) experience on average two to three exacerbation episodes per year [1, 2]. Hospitalisation and COPD-associated mortality account for substantial treatment and healthcare resource utilisation costs [2–4]. COPD exacerbations contribute to a worsening of health-related quality of life over time [1, 2, 5] and their occurrence predicts the likelihood of dying [6].

Factors predicting the frequency and slow resolution of an exacerbation include increasing age, more severe airflow obstruction and a history of prior exacerbations [7–10]. These data come from studies of differing size and duration of follow-up that report annualised exacerbation rates. Less attention has been paid to the influence of time of year on exacerbation occurrence and management. There is evidence of a seasonal variation in the rate of hospital admissions for COPD, more exacerbations occurring during the winter months compared with summer [11–13]. Exacerbations are also associated with cooler temperatures [14, 15]. This seasonal variation has been reported predominantly in countries in northern regions [16, 17], with little or no similar information available for either the southern regions or the tropics [18 - 20]. Furthermore, there is a paucity of information about seasonal variation in exacerbation rates and its importance compared with other factors predicting exacerbations. The current analysis was designed to test the impact of seasonal variation on reported exacerbations in relation to other risk factors, using data from the prospective 3-year TOwards a Revolution in COPD Health (TORCH) study involving 6,112 patients from the Northern and Southern regions and the Tropics [21].

METHODS

Patients

Outpatients aged 40 to 80 years with a diagnosis of COPD, defined in accordance with the European Respiratory Society Consensus Statement [22]; current or ex-smokers with at least 10-years pack history were recruited. They had a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) <60% predicted with reversibility to 400 mcg salbutamol <10% of predicted FEV_1 and FEV_1/forced vital capacity ratio ≤70% after bronchodilator. Exclusion criteria have been previously described [21] and included long-term oxygen therapy at start of the study or an exacerbation requiring systemic corticosteroids or hospitalisation during the run-in period.

Study design

TORCH was a multicentre, randomised, double-blind, parallel-group, 3-year study conducted in 42 countries around the world [21]. Eligible patients were stratified by smoking status and were randomised to receive placebo, salmeterol 50 mcg, fluticasone propionate 500 mcg or salmeterol/fluticasone propionate combination 50/500 mcg via the Diskus™/Accuhaler™ inhaler (one inhalation twice daily) for 3 years. All patients visited the clinic at 12-weekly intervals during which specific enquiry was made regarding exacerbations or events that required change in treatment or hospitalisation by asking the standard questions "Have you had any (other) medical problems since your last visit/assessment?" and "Have you taken any new medications, other than those given to you within this study since your last visit/assessment?". Exacerbations were recorded as moderate (defined by worsening symptoms requiring treatment with antibiotics and/or systemic corticosteroids) or severe (defined as those requiring hospitalisation), and were

documented by the investigator as an adverse event or serious adverse event. Treatment with short courses of systemic corticosteroids and/or antibiotics as reported by the patient was recorded in the patient's case report form. ~~Moderate exacerbations were defined by worsening symptoms requiring treatment with antibiotics and/or systemic corticosteroids, and severe exacerbations were defined as those requiring hospitalisation~~. All patients gave written informed consent and the study was approved by local ethical review boards and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Statistical analysis

The number of patients reporting a new exacerbation was expressed as the proportion of patients on treatment during the month in which the exacerbation started. The pattern of exacerbations was analysed according to geographical location based on the location of participating centres. Similar analyses were conducted for all deaths occurring during the 3-year study period. Study populations were grouped into the Northern region (Canada, China, 26 Eastern and Western European countries, and the USA), the Southern region (Argentina, Australia, Brazil, Chile, New Zealand and South Africa), and the Tropics (countries lying between the tropics of Capricorn and Cancer: Hong Kong, Malaysia, Mexico, Philippines, Singapore, Taiwan and Thailand).
For seasonal comparisons, in the Northern region we defined summer as June to August inclusive and winter as December to February, with the reverse for the Southern region. Recruitment began in September 2000 and the study ended in November 2005. Our investigation of seasonality of exacerbations was restricted to a 4-year period (April 2001 to March 2005) when sufficient numbers of patients were on treatment to reduce the amount of random variation. For all other analyses, all data were used.
The number of exacerbations experienced by a patient during the study was expressed as a rate per year to account for the differing times on treatment. Exploratory analysis of the association between exacerbation rates during treatment and baseline characteristics was performed by modelling the exacerbation rates using the Negative Binomial distribution (to account for patient variability) using the logarithm of time on treatment as an offset variable. Smoking status, gender, region, treatment, exacerbations in the year prior to study entry (as recalled retrospectively by the patients or investigators at study entry), body mass index (BMI), Medical Research Council (MRC) dyspnoea score, age and baseline percentage predicted FEV_1 were included in the model. Rate ratios (RR) with 95% confidence intervals (CI) were calculated for each covariate with all other covariates included in the model.

RESULTS

Demographic and baseline characteristics of the study population are shown in table 1. Mean standard deviation (SD) age was 65 (8) years and post-bronchodilator FEV_1 was 1.23 (0.4) L. Males comprised the majority of the study population and over 40% of all patients were current smokers. Nearly 60% of patients had at least one exacerbation in the year prior to study entry; half of these had ≥2 exacerbations.

TABLE 1 Patient demographics and baseline characteristics by region

	ITT (efficacy) (n=6,112)	Northern (n=4,849)	Southern (n=622)	Tropics (n=641)
Mean age, years (SD)	65.0 (8.3)	64.8 (8.3)	65.5 (8.5)	66.5 (7.3)
Male gender, %	76	75	72	89
Current smoker, %	43	45	36	36
Mean post-bronchodilator FEV_1, L (SD)	1.23 (0.4)	1.26 (0.4)	1.16 (0.4)	1.01 (0.4)
Mean post-bronchodilator FEV_1, % predicted (SD)	44.3 (13.4)	45.1 (13.2)	42.4 (13.2)	40.3 (14.3)
Reversibility, as % of predicted FEV_1 (SD)	3.7 (3.7)	3.6 (3.8)	4.0 (3.5)	3.5 (3.7)
Mean BMI, kg/m^2 (SD)	25.4 (5.2)	26.0 (5.1)	24.6 (4.9)	21.7 (4.1)
Mean exacerbation rate* (SD)	1.2 (1.6)	1.2 (1.5)	1.2 (1.6)	1.6 (2.3)
Patients (%)* with				
0 exacerbations	43	43	42	40
1 exacerbation	25	25	24	24
$\geq$2 exacerbations	32	32	33	36

*In the 12 months prior to study entry.

BMI: body mass index; FEV_1: forced expiratory volume in 1 second; ITT: intent-to-treat.

Seventy-nine per cent of the study population was recruited from the Northern region, 10% from the Southern region and 11% from the Tropics.

Overall rates of exacerbations

Overall exacerbation rates per year (moderate or severe) are shown in figure 1. The distribution was highly skewed; the majority of patients had between 0 to 2 exacerbations per year, but a few had much higher rates. In total, there were approximately 13,000 exacerbations. The annual rate for moderate or severe exacerbations was 1.13 in the placebo group, 0.97 in the salmeterol

50mcg group, 0.93 in the fluticasone propionate 500mcg group and 0.85 in the salmeterol/fluticasone propionate 50/500mcg group.

Pattern of new exacerbations

In the Northern and Southern regions, but not the Tropics, a seasonal pattern of exacerbations was seen with a higher proportion of patients exacerbating in the winter months, which was consistent over the 4-year period. Figures 2A and 2B show the raw data of the proportion of patients exacerbating in each month for the Northern and Southern regions and the Tropics, respectively. Figures 2C and 2D represent the same information averaged into one calendar year. The pattern of exacerbations in the Northern region is mirrored by the pattern of exacerbations in the Southern region (figs. 2A and 2C). A higher proportion of patients in the Southern region reported an exacerbation in any seasonally adjusted month compared with the Northern region (fig. 2C). In the Northern region, 5% of patients reported an exacerbation in the summer compared with 9% in the winter, while in the Southern region 7% of patients reported an exacerbation in the summer compared with 12% in the winter (fig. 2C). This seasonal pattern was seen in all four treatment arms.

Management of exacerbations

The proportion of patients with exacerbations treated with systemic corticosteroids alone, antibiotics alone or both in the Northern and Southern regions is presented in figure 3. Overall, 38% of exacerbations were treated with antibiotics only, 19% with systemic corticosteroids only and 43% with both. In the Northern region, more exacerbations in the winter (43%) were treated with antibiotics compared with those in the summer (37%). This pattern was reversed for exacerbations treated with systemic corticosteroids (15% in winter but 24% in summer). A clear seasonal treatment pattern was not seen in the Southern region, possibly due to the smaller number of patients.

The proportion of all patients who required hospitalisation for exacerbation in any given month was higher in the winter. For instance in the Northern region, the highest proportion in December (1.9%) was double that reported in the lowest month (August, 0.9%). However, the proportion of exacerbations requiring hospitalisation was similar year-round with a summer mean of 18.3% and a winter mean of 18.8%. This pattern was similar in the Southern region, but different in the Tropics with a higher proportion of events requiring hospitalisation (31.2%) than in the other regions (18.3% in the Northern region, 15.7% in the Southern region). Across all regions 20% of exacerbations required hospitalisation.

Factors affecting exacerbation rates

The effect of covariates on the rate of exacerbations during the study is shown in table 2. Season was a significant covariate with respect to exacerbation rate. In Northern and Southern regions there were more exacerbations in the winter compared to the summer. Patients ≥ 75 years of age compared with patients <55 years had 20% more exacerbations (RR 1.2, 95% CI: 1.0, 1.3; p=0.023). Compared with patients with a mean BMI of 20 to <25 kg/m^2 at baseline, patients with a BMI of ≥ 29 kg/m^2 had 10% fewer exacerbations (RR 0.9, 95% CI: 0.8, 0.9; p<0.001), while a low BMI (<20 kg/m^2) was associated with a 10% increased rate of exacerbations (RR 1.1, 95% CI: 1.0, 1.2; p=0.241).

TABLE 2 Effect of covariates on the rate of moderate and severe exacerbations

Factor	Comparison	Rate ratio	95% CI	p-value
Smoking Status	Current *versus* former	0.9	0.8, 0.9	<0.001
Age, years				0.064
	55–64 *versus* <55	1.1	1.0, 1.3	0.012
	65–74 *versus* <55	1.1	1.0, 1.3	0.020
	≥75 *versus* <55	1.2	1.0, 1.3	0.023
% predicted post-bronchodilator FEV$_1$				<0.001
	<30% *versus* ≥50%	1.9	1.7, 2.1	<0.001
	30 to <50% *versus* ≥50%	1.4	1.3, 1.5	<0.001
Gender	Male *versus* female	0.7	0.7, 0.8	<0.001
COPD exacerbations in the previous year				<0.001
COPD exacerbations in the previous year	1 *versus* 0	1.5	1.4, 1.6	<0.001
	≥2 *versus* 0	1.9	1.8, 2.1	<0.001
BMI, kg/m^2				<0.001
	<20 *versus* 20 to <25	1.1	1.0, 1.2	0.241
	25 to <29 *versus* 20 to <25	1.0	0.9, 1.0	0.262
	≥29 *versus* 20 to <25	0.9	0.8, 0.9	<0.001
MRC dyspnoea grade				<0.001
	3 *versus* 1+2	1.1	1.1, 1.2	<0.001
	4+5 *versus* 1+2	1.3	1.2, 1.4	<0.001
Region				<0.001

North *versus* South	0.8	0.7, 0.9	<0.001
Tropics *versus* South	0.9	0.8, 1.0	0.045

Rate ratios (RR) with 95% confidence intervals (CI) were calculated for each covariate with all other covariates included in the model. Multivariate negative binomial model (each variable adjusted for all the others). BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; MRC: Medical Research Council.

Low FEV_1 was also associated with an increased rate of exacerbation (<30% predicted FEV_1 compared with ≥50%, RR 1.9, 95% CI: 1.7, 2.1; p<0.001). Patients who reported one exacerbation in the year prior to study entry had a 50% higher rate of exacerbations while on treatment (RR 1.5, 95% CI: 1.4, 1.6; p<0.001) and those reporting two or more exacerbations in the year prior to study entry had nearly double the rate (RR 1.9, 95% CI: 1.8, 2.1; p<0.001) compared with patients who reported no exacerbations.
Males had a 30% lower exacerbation rate than females (RR 0.7, 95% CI: 0.7, 0.8; p<0.001). Increasing severity of dyspnoea, based on baseline MRC dyspnoea grade, was associated with a greater rate of exacerbations, a grade of 3 having an exacerbation RR of 1.1 (95% CI: 1.1, 1.2; p<0.001) and grades of 4+5 having a RR of 1.3 (95% CI: 1.2, 1.4; p<0.001), compared with grades of 1+2.
Current smoking was associated with a 10% lower rate of reported exacerbations than former smoking (0.9 RR, 95% CI: 0.8, 0.9; p<0.001), after adjusting for other covariates.
The reporting of exacerbations differed according to the region of the world, with the rate in the Northern region being 20% lower than in the Southern region (RR 0.8, 95% CI: 0.7, 0.9; p<0.001).
The seasonal influence on exacerbation pattern was evident in all the patient sub-groups studied. This is illustrated in figure 4 for FEV_1 percentage predicted and MRC dyspnoea grade.

Mortality

There were more deaths in the 3 months of winter than the 3 months of summer. In the Northern region 625 of the 4,849 patients died and 180 (29%) of these deaths occurred during the 3 months of winter in the 3-year study period while 135 (22%) occurred in the summer. In the Southern region 113 of the 622 patients died, 42 (37%) during winter compared with 16 (14%) during the summer.
These differences in seasonal mortality were more evident for COPD-related deaths, which accounted for 41% of all deaths in TORCH. In the Northern region, 79 (34%) of the 235 COPD-related deaths occurred during winter while 48 (20%) occurred in the summer. In the Southern region, 27 (55%) of these deaths occurred during winter and four (8%) during the summer.

DISCUSSION

COPD patients and their doctors know that exacerbations occur commonly in the winter months, but data to establish the size of this effect have been lacking. Exacerbations defined by healthcare use as proposed recently by the ATS/ERS Task Force [23] were commoner during

winter. These patterns were consistent from year to year over the study period and accounted for an almost two-fold increased risk of exacerbation in winter, in Northern and Southern region countries, but not in the Tropical countries.

~~Our findings of~~ Thus far, data supporting a seasonal pattern in COPD exacerbations ~~support and extend data~~ derives from smaller studies conducted mainly in Europe [12–14, 16, 17] where a seasonal effect has been reported as part of other analyses. The TORCH study population comprises data collected over 3 years from patients in 42 countries, and as such provides sufficient power to extend and support the previously reported findings. COPD hospital admissions and deaths increase dramatically in the winter months, as do general practice visits for respiratory tract infections [14–17]. Factors potentially contributing to this include increased exposure to viral infections, increased host susceptibility, greater time spent indoors, reduced physical activity, and temperature-related reduction in lung function. These patterns also relate to lower weekly mean temperatures, as well as influenza activity and personal cold exposure factors [24]. The mechanisms by which greater risk of respiratory infections occurs in winter are complex, and include the interaction of temperature and humidity, changes in human behaviour, exposure to colder air indoors and outdoors [14–17, 25–28], air pollution and greater vulnerability of local host defence [20, 29].

The seasonal variation was not seen in tropical countries that are characterised by relatively constant temperatures with a mean of 18°C (64°F) or higher, all year round. In tropical regions there is background influenza activity throughout the year [30, 31], which may contribute to a more stable pattern of exacerbations throughout the year as noted in the present study. Seasonal variations occur with some infections in the tropics, but may be more closely related to the wet season, air pressure and relative humidity rather than temperature alone [17, 18, 20]. Other factors include outdoor pollution [30–32], and its interaction with cooler temperatures. The tropical countries in TORCH differ in distance from the equator and meteorological characteristics which produce different seasonal patterns of respiratory illness between countries [33].

The seasonal variation in the number of exacerbation events was accompanied by a variation in the treatment of exacerbations. Antibiotics were used alone or in combination with steroids more frequently in the winter months compared with summer in the Northern region. The treatment difference may reflect differences in the way exacerbation patients present in the winter, but data about seasonal variation in the microbiology of COPD patients are lacking. In contrast, in the Southern region both antibiotic and systemic corticosteroids use increased in the winter and there was a strong tendency for both to be used in combination. The reason for these differences cannot be determined here and requires further study.

More patients were hospitalised due to COPD in the winter months, although in absolute terms, the proportion of cases where this occurred was low. However almost 20% of exacerbations in our large worldwide population required hospitalisation and this was consistent between the seasons and very similar to that reported in a smaller US study [34]. Moreover, the relative proportion of events leading to hospital admission was unaffected by season, suggesting that the colder weather increased the number rather than the overall severity of exacerbations.

Like other researchers, we found that older age, having a lower BMI, a lower FEV_1 and a higher incidence of exacerbations in the previous year all significantly increased the risk of exacerbations [7–10]. In addition, we found that gender and MRC dyspnoea grade at study entry and smoking status are risk factors. Women report more breathlessness for similar levels of airflow obstruction and are more likely to receive treatment for COPD than men [35, 36]. They

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may therefore be more likely to be classified as having an exacerbation. However, there are also data indicating that women are at higher risk of being hospitalised for exacerbations [37], which is unlikely to be due solely to differential symptom reporting. A higher MRC dyspnoea grade may identify patients more likely to receive exacerbation treatment when they present with worsening symptoms. However, MRC grade also relates to exercise performance and the degree of activity normally undertaken is a predictor of the risk of exacerbation [7, 38]. The paradoxical observation that current smokers were less likely to exacerbate compared with ex-smokers may not be a chance finding. Potential explanations may be a healthy survivor effect or the possible beneficial effect of smoking on sputum clearance [39, 40].

Our data differ in the magnitude of some of the associations from those reported by Hurst et al for ECLIPSE [10]. We identified almost twice as many exacerbations as that observational study, which included more patients with moderate COPD who were taking more medication than in our clinical patient population. Moreover, our study was not confined to Europe, North America and New Zealand and, unlike ECLIPSE, we did not record the presence of reflux symptoms. While these factors help explain some of the differences in predictive capacity, it is reassuring to see the considerable agreement in the determinants of exacerbation risk, irrespective of the composition of the study population. Notably, the seasonal effect on exacerbations occurred independently of all the identified risk factors.

Winter mortality from pre-existing respiratory disease was the single strongest predictor of excess deaths in a large general practice based UK study, [41] and pre-existing respiratory disease increased mortality from cardiovascular but not respiratory causes. Several other studies have demonstrated excess all-cause, cardiovascular and respiratory mortality in winter, which is greater in women than men [25–27]. Somewhat paradoxically, vulnerability to death is increased to a greater extent for a given fall of temperature, in regions with warmer winter temperatures. This appears to relate to greater personal cold exposure, lack of indoor heating, failure to dress appropriately for the cold, and reduced outdoor physical activity [27, 28]. In our population, possibly due to the limited number of events especially in the Southern region, we did not see a clear seasonal pattern in mortality.

There are strengths and limitations of our data. We recorded data in a standardised way in a large patient population and carefully identified the time and cause of death [42]. This approach provided adequate statistical power to test for differences due to region or risk factors. Although we excluded subjects with known serious co-morbidities, including those dependent on oxygen therapy at entry, we do not believe the study population and setting biases our main findings. ~~Although~~ We recognise that ours was a treatment intervention trial and not an epidemiological study and acknowledge the inherent differences between these two study types. However, the lack of ~~there was no~~ interaction between any of the treatments used in this study and the factors identified as predicting exacerbation ~~and so we were able to~~ allowed us to pool all ~~our~~ the data for this analysis enabling analysis from more than 6,000 patients.

CONCLUSION

In the TORCH trial the major burden of exacerbations fell in the winter months of both Northern and Southern regions of the world, which aligns with the perceptions of COPD patients and their doctors. ~~Based on the~~ Furthermore, the risk factors identified in this study (which, it must be considered, was an interventional study)~~,~~ may make it ~~may be~~ possible to prospectively profile an individual's risk of exacerbating and thus allow ~~to optimise~~ optimisation of care to reduce this risk. Further studies to establish the feasibility of such an approach are warranted.

SUPPORT STATEMENT

STATEMENT OF INTEREST

C.J. has received consulting fees from Altana, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline and Novartis; speaking fees from Altana, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline and Novartis; and grant support from GlaxoSmithKline. **B.C.** has received consulting fees from Altana, AstraZeneca, Boehringer-Ingelheim and GlaxoSmithKline; speaking fees from Altana, AstraZeneca, Boehringer-Ingelheim and GlaxoSmithKline; and grant support from Boehringer-Ingelheim and GlaxoSmithKline. **J.A.A.** is employed by and holds stock in GlaxoSmithKline. **G.T.F.** has received consulting fees from Astra Zeneca, Boehringer-Ingelheim, GlaxoSmithKline and Novartis; speaking fees from Boehringer-Ingelheim, GlaxoSmithKline and Pfizer; and grant support from Boehringer-Ingelheim, Forrest, GlaxoSmithKline and Novartis. **P.W.J.** has received consulting fees from Almirall, AstraZeneca, GlaxoSmithKline, Novartis, Roche and Spiration; speaking fees from AstraZeneca and GlaxoSmithKline; and grant support from GlaxoSmithKline. **J.V.** has received consulting fees from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Hoffman-LaRoche and Nycomed; speaking fees from AstraZeneca, Boehringer-Ingelheim and GlaxoSmithKline; and grant support from GlaxoSmithKline. **J.C.Y.** is employed by and holds stock in GlaxoSmithKline. **P.M.A.C.** has received consulting fees from AstraZeneca, GlaxoSmithKline, Novartis, Nycomed and Pfizer; speaking fees from GlaxoSmithKline and Nycomed; and grant support from Boehringer-Ingelheim and GlaxoSmithKline.

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FIGURE LEGENDS
FIGURE 1. Distribution of exacerbation rates per patient per year during the study. Note: The very high calculated exacerbation rates (≥10) were primarily due to premature drop out of frequent exacerbators with <6 months follow-up time.
FIGURE 2. Proportion of patients reporting an exacerbation in the Northern and Southern regions (A) and in the Tropics (B) over 4 years, and reporting an exacerbation in the Northern and Southern regions (C) and in the Tropics (D) averaged over one calendar year.
FIGURE 3. Proportion of patients reporting an exacerbation and treatment received in the Northern (A) and Southern (B) region.
FIGURE 4. Proportion of patients reporting an exacerbation in the Northern region by forced expiratory volume in 1 s percentage predicted (A) and by Medical Research Council dyspnoea grade (B).
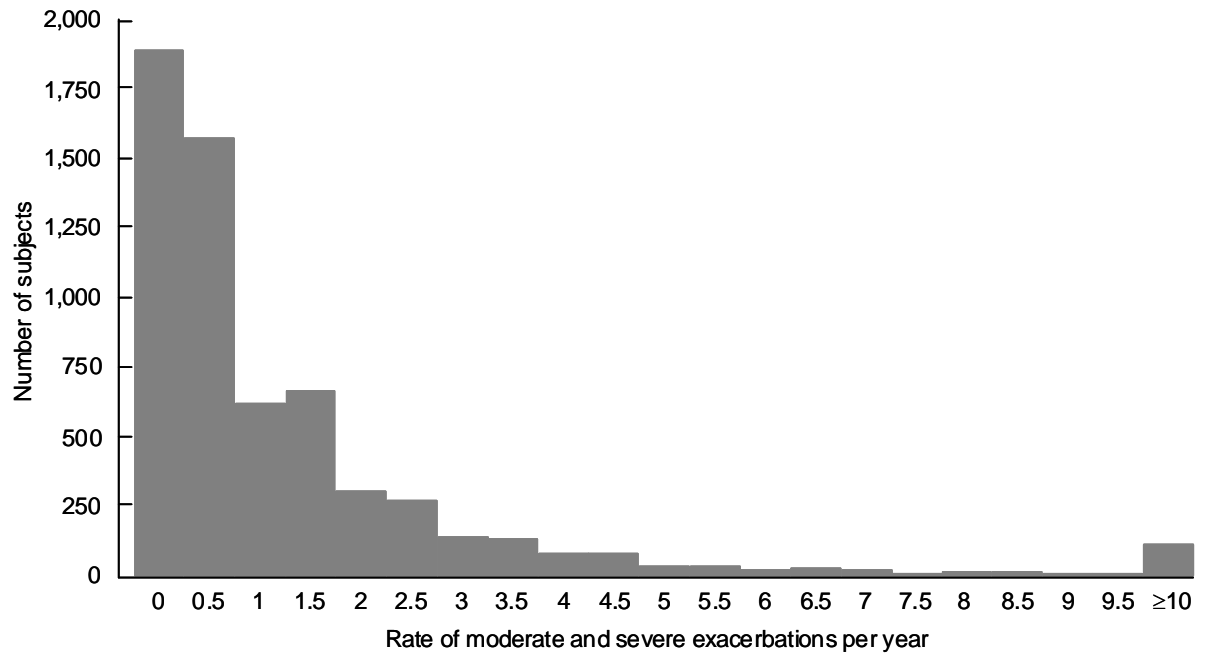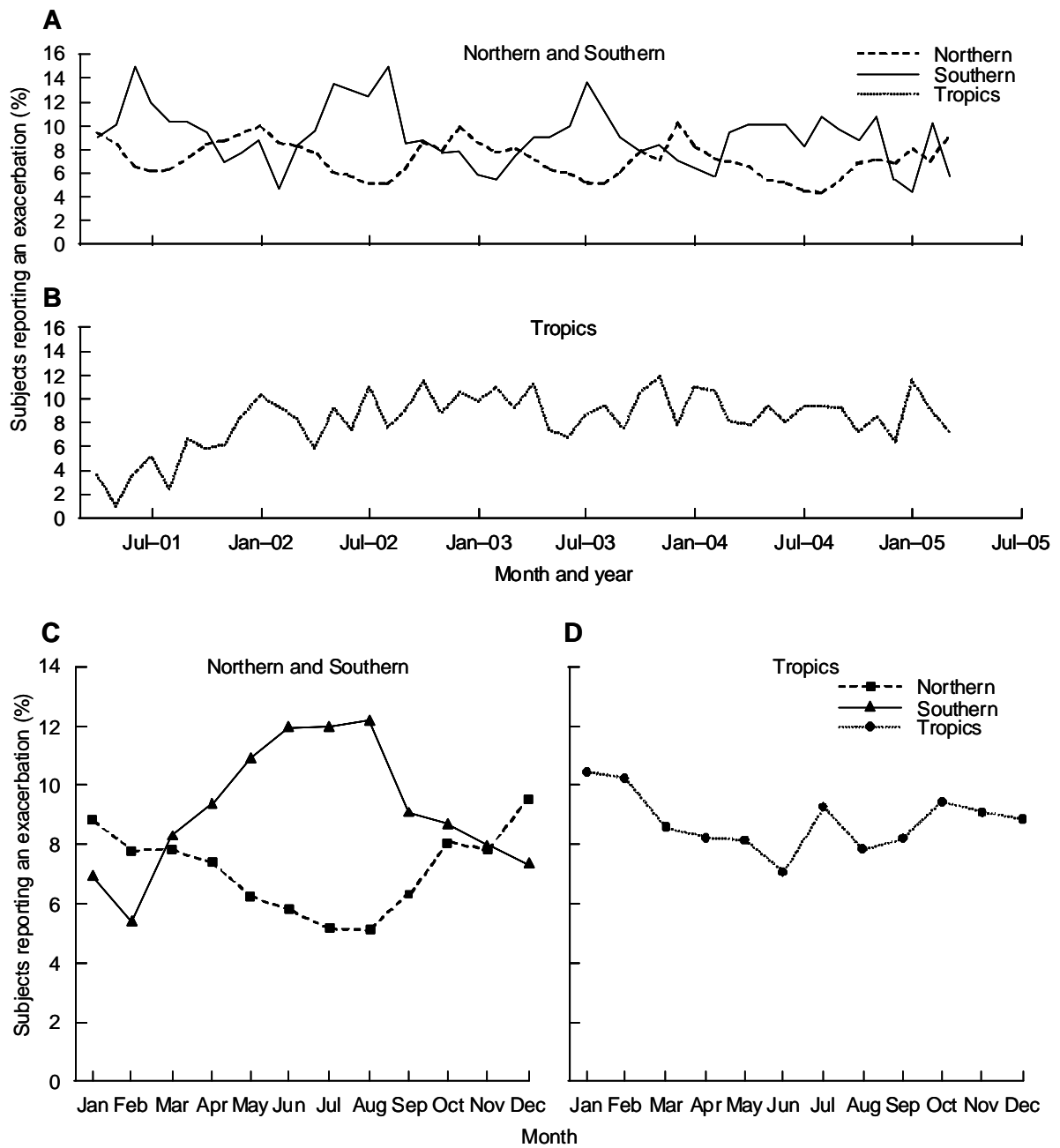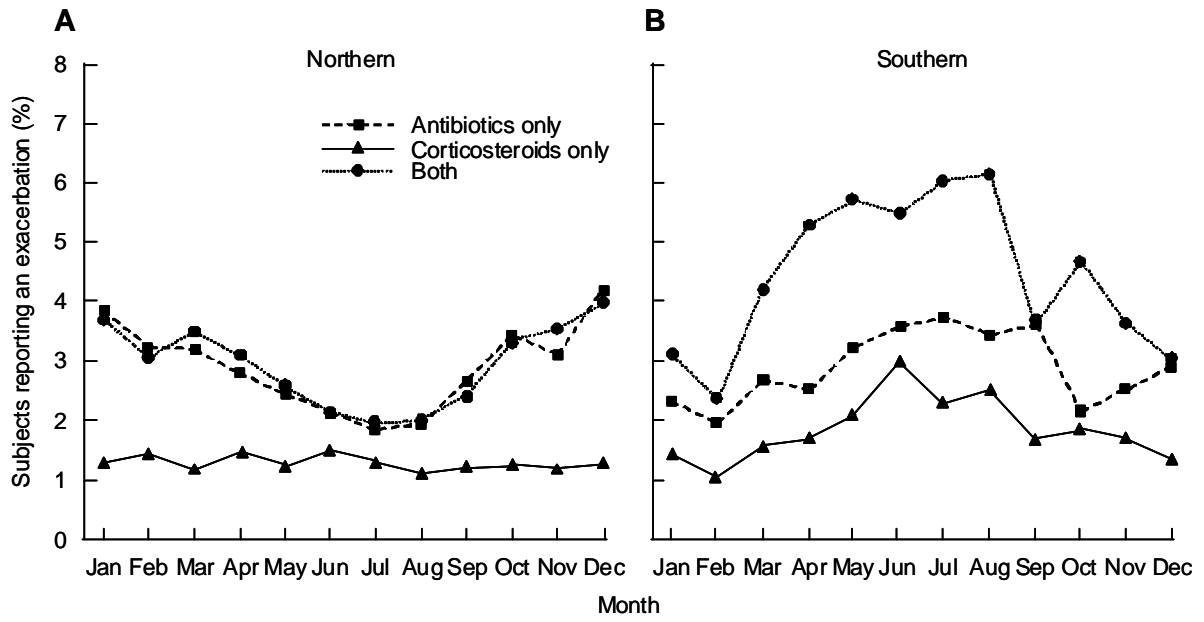
Figure 1.

Figure 2.

Figure 3.

Figure 4.