PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Seasonal variation and trend in hospital admissions for stroke in patients with atrial fibrillation in Denmark and New Zealand: analysis of hospital discharge data from 1977 to 2008
AUTHORS	Christensen, Anette Luther ; Rasmussen, Lars Hvilsted; Baker, Michael; Lip, Gregory; Dethlefsen, Claus; Larsen, Torben Bjerregaard

VERSION 1 - REVIEW

REVIEWER	Lars Frost, Section of Cardiology Department of Medicine Silkeborg Hospital Denmark
REVIEW RETURNED	16-May-2012

THE STUDY	The authors report on seasonal variation and trend in hospital admission and mortality for stroke in patients with atrial fibrillation (AF) in Denmark and New Zealand. I find it a confusing that a) seasonality is reported together with outcomes such as b) trend in hospitalization with AF, c) trend in risk of stroke in AF, and d) trend in mortality in stroke with AF. Seasonality should be reported in a separate paper. AF and stroke cases recorded in the first study period are a mix of prevalent and incident cases. Please omit the first 3-5 years of the study period, but use that period to ensure that only true incident cases are included afterwards. Please add information about how comorbidity was sampled. Which ICD codes did you use? Table 2. I think that %-distribution of comorbidity has been inter-changed between Denmark and New Zealand. Please consult BMJ 2011;342:d124. This paper gives information on comorbidity in Danish AF patients. The expected proportion of diabetes is approximately 10%, not 19.0% as indicated in the present manuscript. The percentage of patients with at least one comorbid disorder does not correspond with the percentages of specific comorbid disorders mentioned in the table. Seasonality: Please add stratified analyses on sex and comorbidity. Please stratify on early versus late study period, because thee introduction of Diagnosis Related Groups taxation system in Denmark in 2000 may have introduced a seasonality bias. Abstract result section: The incidence rates for AF stratified by age 65 do not correspond to the incidence rates seen in Figure 1. Discussion: It is mentioned that stroke affects 15% of AF patients. What do you mean by that? Please give incidence rates of stroke. An absolute number does not make sense, because the cumulated incidence depends on time at risk. Reference #21 needs an URL.

RESULTS & CONCLUSIONS	The authors report on seasonal variation and trend in hospital admission and mortality for stroke in patients with atrial fibrillation (AF) in Denmark and New Zealand. I find it a confusing that a) seasonality is reported together with outcomes such as b) trend in hospitalization with AF, c) trend in risk of stroke in AF, and d) trend in mortality in stroke with AF. Seasonality should be reported in a separate paper. AF and stroke cases recorded in the first study period are a mix of prevalent and incident cases. Please omit the first 3-5 years of the study period, but use that period to ensure that only true incident cases are included afterwards. Please add information about how comorbidity was sampled. Which ICD codes did you use? Table 2. I think that %-distribution of comorbidity has been inter-changed between Denmark and New Zealand. Please consult BMJ 2011;342:d124. This paper gives information on comorbidity in Danish AF patients. The expected proportion of diabetes is approximately 10%, not 19.0% as indicated in the present manuscript. The percentage of patients with at least one comorbid disorder does not correspond with the percentages of specific comorbid disorders mentioned in the table. Seasonality: Please add stratified analyses on sex and comorbidity. Please stratify on early versus late study period, because thee introduction of Diagnosis Related Groups taxation system in Denmark in 2000 may have introduced a seasonality bias. Abstract result section: The incidence rates for AF stratified by age 65 do not correspond to the incidence rates seen in Figure 1. Discussion: It is mentioned that stroke affects 15% of AF patients. What do you mean by that? Please give incidence rates of stroke. An absolute number does not make sense, because the cumulated incidence depends on time at risk. Reference #21 needs an URL.

REVIEWER	Spengos, Konstantinos University of Athens Medical School
REVIEW RETURNED	02-Jun-2012

GENERAL COMMENTS	Excellent work that can be published without any further changes.

REVIEWER	Moineddin, Rahim University of Toronto
REVIEW RETURNED	26-Jun-2012

GENERAL COMMENTS	Comments on 'Seasonal variation and trend in hospital admissions for stroke in patients with atrial fibrillation in Denmark and New Zealand: analysis of hospital discharge data from 1977 to 2008' manuscript. Authors aimed to use hospital discharge data from Denmark and New Zealand to study the trend and seasonality of admissions for stroke in patients with AF. The methodology used is log-linear Poisson regression model. It is not clear why authors used weekly data instead of monthly.

	Generally weekly data has higher variation and less reliable. The weekly data may exhibit cyclical patterns with different periods. If there is no clinical rational for using weekly rates I recommend authors to consider monthly data instead. Did authors test their models for overdispersion? Authors should report goodness of fits for all their regression models. The weekly or monthly data are correlated with each other (serial correlation). How authors did take into account the serial correlation? Authors wrote 'A logit-linear logistic regression model was fitted to mortality data, assuming a logit-linear trend'. Do authors by logit-linear trend mean a linear trend in logistic regression model? If this is the case how did authors take into account the nonlinearity of the trend over time? Authors used splines to estimate the trend. How trends are modelled in the regression models? When trends are not linear reporting increase/decrease incidence rates are incorrect (see page 7). It is somewhat difficult to follow methods section and how it applies to specific models estimated on these datasets. I think it would be useful to completely and transparently all GLM's (Poisson or logistic) used and all covariates adjusted for and the possibly non-linear ways they enter the model (e.g. adjust for overall trend, sinusoid components, splines etc.). Why is the Peak2Trough package not available on CRAN anymore? What has the statistical community thought of the article: A. L. Christensen, S. Lundbye-Christensen and C. Dethlefsen. Poisson regression models outperform the geometrical model in estimating the peak-to-trough ratio of seasonal variation: a simulation study. Submitted, 2011. Does peak to trough ratio vary as a function of: - Data analytic method (Poisson model versus geometrical model) - Resolution of the underlying series (Quarterly, Monthly, Weekly) - Timeframe of cohort analysis (Figure 1 shows a non-stationary series)…what are annual peak to trough ratios – is there variability in these annual estimates? Are these estimates changing as the underlying mean/variance of the stochastic process are concurrently changing? What does this mean? Are global inferences, averaged over the entire 30 year series valid/meaningful?

VERSION 1 – AUTHOR RESPONSE

Response To Lars Frost:

---I find it a confusing that a) seasonality is reported together with outcomes such as b) trend in hospitalization with AF, c) trend in risk of stroke in AF, and d) trend in mortality in stroke with AF. Seasonality should be reported in a separate paper.

>>>We agree that when investigating seasonal variation in incidence rates of diseases, one should focus on this and not include several other analyses. However, since this paper focuses on the seasonal variation in two different countries, we feel that a description of the underlying epidemiology has to be presented in order to compare results. We have no experience whether hospitalisation rates of AF in New Zealand have been published, hence we have to provide these data ourself. We would respectfully maintain that the additional analyses on seasonality are necessary in this paper.

---AF and stroke cases recorded in the first study period are a mix of prevalent and incident cases. Please omit the first 3-5 years of the study period, but use that period to ensure that only true incident cases are included afterwards.

>>> This is a good point and we have made these changes for both cohorts, such that only stroke in AF patients from 1980 to 2008 are analysed in Denmark and from 1991 to 2008 in New Zealand. This restriction only changes the estimate of the peak-to-trough ratio in Denmark slightly from 1.21 to 1.22. We included the sentences:
***To avoid including prevalent cases of both AF and stroke in AF patients, identified cases before 1980 were excluded from the analyses for the Danish cohort.
…. after the second paragraph in Methods section, and

***To avoid including prevalent cases of both AF and stroke in AF patients, identified cases before 1991 were excluded from the analyses for the New Zealand cohort.
…. after the third paragraph.

---Please add information about how comorbidity was sampled. Which ICD codes did you use?

>>> We have supplemented a paragraph at the of the 'Study period and study population' section with the wording:
***Comorbidities were assessed by identifying hospitalizations with either congestive heart failure (ICD8: 427.09, 428, ICD9: 428, ICD10: I11.09, I50), hypertension (ICD8: 400-404, ICD9: 401-405, ICD10: I10-I13, I15), diabetes (ICD8: 249, 250, ICD9: 250, ICD10: E11, E14), acute myocardial infarction (ICD8: 410, ICD9: 410, ICD10: I21, I22), peripheral artery disease (ICD8: 440.2, 443, 444, ICD9: 440, 443, 444, ICD10: I70.2, I73.9, I74.5), or coronary artery disease (ICD8: 412, ICD9: 414, ICD10: I25.1). One subject may have more than one comorbidity.

---Table 2. I think that %-distribution of comorbidity has been inter-changed between Denmark and New Zealand. Please consult BMJ 2011;342:d124. This paper gives information on comorbidity in Danish AF patients. The expected proportion of diabetes is approximately 10%, not 19.0% as indicated in the present manuscript. The percentage of patients with at least one comorbid disorder does not correspond with the percentages of specific comorbid disorders mentioned in the table.

>>> We appreciate this comment as we have not been totally clear in which percentages were presented. The percentages actually represents the proportion of subject having comorbidities with congestive heart failure, hypertension etc. We have changes the figures such that we instead present percentages with a given comorbidity of the entire cohort.

---Seasonality: Please add stratified analyses on sex and comorbidity. Please stratify on early versus late study period, because thee introduction of Diagnosis Related Groups taxation system in Denmark in 2000 may have introduced a seasonality bias.

>>> This comment is well appreciated, since sex and comorbidities may be a potential effect modifier on the seasonal variation. However, since the primary interest of this paper is to estimate the seasonal variation in two countries, results from stratified analyses on sex and comorbidities may be exhaustive and confuse the primary interest. Thus we consider such analyses to be beyond the scope of this paper, and will serve better as primary interest in a separate paper.
Regarding the introduction of Diagnosis Related Groups taxation system in Denmark in 2000 we do not believe that this would affect the seasonal variation of incidence rates of stroke in AF patients. A possible effect would rather be seen in the trend, which actually does seem to change around the year 2000. Consequently we have added the sentence to the discussion after the fourth paragraph:

***This may be due to the introduction of Diagnosis Related Groups taxation system in Denmark in 2000.

---Abstract result section: The incidence rates for AF stratified by age 65 do not correspond to the incidence rates seen in Figure 1.

>>>We apologise for the confusing wording, as we do not report incidence rates merely changes in incidence rates. Therefore there is no immediate correspondence to figure.

---Discussion: It is mentioned that stroke affects 15% of AF patients. What do you mean by that? Please give incidence rates of stroke. An absolute number does not make sense, because the cumulated incidence depends on time at risk.

>>> This comment makes a good point, as Lars Frost emphasizes the impact of time on such a figure. We agree that the 15% is dependent on time for follow-up, and we have erased the sentence. The estimated incidence rates of stroke in AF patients are shown in Figure 2.

---Reference #21 needs an URL.

>>> According to R guidelines for referencing R-packages only title, author, year and version of package are stated.

Response To Rahim Moineddin:

---It is not clear why authors used weekly data instead of monthly. Generally weekly data has higher variation and less reliable. The weekly data may exhibit cyclical patterns with different periods. If there is no clinical rational for using weekly rates I recommend authors to consider monthly data instead.

>>>The reason why we analyse weekly counts is that we find it crucial to have a high density of data meanwhile keeping the complexity of the model low. If we analysed daily data, we would need to adjust for a weekday effect, which is not of interest for the study. If we analysed monthly data we feel that we loose some information regarding the pattern of seasonality. Furthermore, we do not suspect any cyclic pattern within the months, as with the weeks.

---Did authors test their models for overdispersion?

>>>This is a good point, as if overdispersion is present in data, we need to estimate robust variances. However, we believe that we explain as much variance as possible by including both an overall trend and a seasonal variation component. In fact, a test for overdispersion by use of the odTest from the R-package pscl did not show any evidence of overdispersion for any of the Poisson regression models. Neither was overdispersion present in the logistic regression model. We have stated assessment of overdispersion at the end of the results section:

***All models were assessed for overdispersion and revealed no indication of such.

---Authors should report goodness of fits for all their regression models.

>>>We considered goodness-of-fit (GoF) and corresponding tests as nuisance in this paper, as the figures would not be interpreted, since we do not perform model selection or statistically compare two different models on the same data.

The actual figures are:
Log-linear Poisson model for incidence rates of AF for age <65: GoF = 391, p<0.001
Log-linear Poisson model for incidence rates of AF for age >=65: GoF = 3703, p<0.001

Log-linear Poisson model for incidence rates of stroke in AF patients in Denmark: GoF = 1726, p<0.001
Log-linear Poisson model for incidence rates of stroke in AF patients in New Zealand: GoF = 984, p<0.001

Logit-linear logistic model for 30-days case fatality risk: GoF = 38400, p=0.001

---The weekly or monthly data are correlated with each other (serial correlation). How authors did take into account the serial correlation?

>>>Please see answer to the last comment below.

---Authors wrote ‘A logit-linear logistic regression model was fitted to mortality data, assuming a logit-linear trend’. Do authors by logit-linear trend mean a linear trend in logistic regression model? If this is the case how did authors take into account the nonlinearity of the trend over time?

>>>We apologize for this wording as we meant a linear trend in a logit-linear logistic model. The emphasis on this secondary analysis is only to assess whether the incidence rates are increasing or decreasing, rather than providing a thorough description of the behaviour of the trend. For that reason we have modelled the trend as linear.

---Authors used splines to estimate the trend. How trends are modelled in the regression models?

>>>We specified the overall trend in incidence rates of stroke in AF patients as a restricted cubic spline with five knots by use of the function rcs() implemented in the R-package rms.

---When trends are not linear reporting increase/decrease incidence rates are incorrect (see page 7).

>>>We did in fact model the trend in 30-days case fatality risk as linear, hence we report a decrease in Denmark and an increase in New Zealand. The reason for modelling the trend as a linear function is the same as the answer above.

---It is somewhat difficult to follow methods section and how it applies to specific models estimated on these datasets. I think it would be useful to completely and transparently all GLM's (Poisson or logistic) used and all covariates adjusted for and the possibly non-linear ways they enter the model (e.g. adjust for overall trend, sinusoid components, splines etc.).

>>>We have rewritten the methods section in order to clarify the analyses performed by use of the suggestions of this comment, as the clarity of this section is of high importance.

***We define three effect measures for analyses. First, incidence rates of AF, defined as the annual number of hospitalizations with AF divided by the annual population size. Second, weekly incidence rates of stroke in AF patients defined as the weekly number of first time hospitalizations with stroke having previous hospital admissions for AF divided by the weekly person-time at risk i.e. for a given week the number of AF patients with no previous stroke. Third, 30-days case fatality risk, defined as the annual number of death among stroke patients having AF divided by the annual number of stroke patients having AF.
A log-linear Poisson regression model was fitted to incidence rates of AF, adjusting for a linear trend and modeling an interaction between trend and country. The analysis was stratified on age groups (<65 and ≥ 65 years of age). Only annual incidence rates from 1991 to 2008 were analyzed.
A log-linear Poisson regression model was fitted to weekly incidence rates of stroke in AF patients adjusted for a non-linear trend and a seasonal variation component. The seasonal variation component was specified as a sum of four sinusoids with frequencies one to four [18]. The overall trend was specified as a restricted cubic spline with five knots [19]. As a measurement of the seasonal variation we estimated the peak-to-trough ratio, which is an incidence rate ratio.
A logit-linear logistic regression model was fitted to 30-days case fatality risks, adjusting for a linear trend and modeling an interaction between trend and country.
Assessments of statistically significant interaction between trend and countries were performed by a likelihood ratio test. Tests for overdispersion of Poisson models and goodness of fit, including tests for all models were performed.
P-values less than 5% were considered statistically significant. All analyses were performed in R version 2.15.1 [20] using the package Peak2Trough [21].

---Why is the Peak2Trough package not available on CRAN anymore?

>>>This was due to changes in another package, which the Peak2Trough package was dependent on. This is corrected now, and the package is now available as an updated version.

---What has the statistical community thought of the article:
A. L. Christensen, S. Lundbye-Christensen and C. Dethlefsen. Poisson regression models outperform the geometrical model in estimating the peak-to-trough ratio of seasonal variation: a simulation study. Submitted, 2011.
Does peak to trough ratio vary as a function of:

- Data analytic method (Poisson model versus geometrical model)
- Resolution of the underlying series (Quarterly, Monthly, Weekly)
- Timeframe of cohort analysis (Figure 1 shows a non-stationary series)…what are annual peak to trough ratios – is there variability in these annual estimates? Are these estimates changing as the underlying mean/variance of the stochastic process are concurrently changing? What does this mean? Are global inferences, averaged over the entire 30 year series valid/meaningful?

>>>The mentioned paper was accepted for publication in 2011 and so far has no citations which we interpret as no disagreements from the statistical society. The issues addressed in this comment are highly interesting and problematic in modelling seasonal variation in incidence rates. We are working on an ongoing project, introducing a methodology, which explicitly handles the issues. However, this methodology is somewhat unfamiliar to epidemiologists, and we consider it to be beyond the scope of this paper.

VERSION 2 – REVIEW

REVIEWER	Lars Frost Associate Professor, MD, PhD, DMSc Head of Cardiology Department of Medicine Silkeborg Hospital Denmark
REVIEW RETURNED	20-Jul-2012

GENERAL COMMENTS	The manuscript has improved significantly, but I had to work (hard) to fully understand it. To facilitate readers understanding please: In general: Present in same priority in all sections: 1) seasonality, 2) incidence and trend in AF, 3) incidence and trend in stroke with AF, 4) incidence and trend in mortality in stroke with AF. Or consider not using a hierarchy in outcomes (this is not at randomised study). The most straightforward presentation would be a) Incidence and trend in AF, b) incidence and trend in stroke with AF, c) incidence and trend in mortality in stroke with AF, d) seasonality. Consider changing title to: Seasonality, incidence and prognosis in atrial fibrillation and stroke in Denmark or New Zeeland, or Incidence, prognosis and seasonality in atrial fibrillation and stroke in Denmark and New Zeeland. Specifically: Abstract: I do not think that readers in general are familiar with "annual incidence rate ratio" which is not defined in the abstract. Please delete this from the abstract or report straight forward: The incidence rate of atrial fibrillation increased in Denmark and New Zeeland by 5.0% and 2.6% annually in those aged above 65 years and by 5.4% and 0.2% annually in those younger than 65 years. Materials and methods: "To avoid including prevalent cases" should be changed to "To reduce inclusion of prevalent cases".

VERSION 2 – AUTHOR RESPONSE

Response To Lars Frost:

***Present in same priority in all sections: 1) seasonality, 2) incidence and trend in AF, 3) incidence and trend in stroke with AF, 4) incidence and trend in mortality in stroke with AF. Or consider not using a hierarchy in outcomes (this is not at randomised study). The most straightforward presentation would be a) Incidence and trend in AF, b) incidence and trend in stroke with AF, c) incidence and trend in mortality in stroke with AF, d) seasonality.

>>>We have ensured the same order in reporting the results in all sections with the following order: 1) Trend in AF, 2) Seasonal variation in stroke in AF patients, 3) trend in stroke in AF patients, 4) 30-days case fatality risk. The order of reports of seasonal variation and trend in stroke in AF patients is chosen since the results are obtained from one analysis – one model fit – where time of year for hospitalisation is considered to be the exposure and the association between exposure and outcome, ie hospitalisation with stroke having AF is merely adjusted for an overall trend. We believe the manuscript is now easier to understand, as the order is the maintained during the entire manuscript.

***Consider changing title to: Seasonality, incidence and prognosis in atrial fibrillation and stroke in Denmark or New Zeeland, or Incidence, prognosis and seasonality in atrial fibrillation and stroke in Denmark and New Zeeland.

>>>The title is now changed to ‘Seasonality, incidence and prognosis in atrial fibrillation and stroke in Denmark and New Zealand’, which we believe captures the scope of the paper.

***Specifically:
Abstract: I do not think that readers in general are familiar with “annual incidence rate ratio” which is not defined in the abstract. Please delete this from the abstract or report straight forward: The incidence rate of atrial fibrillation increased in Denmark and New Zeeland by 5.0% and 2.6% annually in those aged above 65 years and by 5.4% and 0.2% annually in those younger than 65 years.

>>>We appreciate this comments, as if the slightest confusing about results may arise, we should be more explicit in our phrasing. The abstract is now changed such that only percentages of annual increase are reported.

***Materials and methods:
“To avoid including prevalent cases” should be changed to “To reduce inclusion of prevalent cases”.

>>>We highly agree with this distinction in wording, so we have changed the sentence.