QUESTION 2

**Use of antiinflammatory therapy and asthma mortality in Japan**

ABSTRACT:

Asthma treatment guidelines were introduced in Japan in the 1990s, insisting as elsewhere, on the importance of anti-inflammatory therapy. The present study assessed whether use of anti-inflammatory medications was associated with a decrease in asthma mortality in Japan, the first country to use leukotriene receptor antagonists.

A population-based ecological study was conducted, spanning the period 1987 to 1999, among people aged 5 to 34 yrs in Japan. The association between the yearly rate of asthma death and sales of inhaled corticosteroids and leukotriene receptor antagonists was estimated using Poisson regression. The yearly asthma death rate was stable at 6 to 7 deaths per million before the introduction of leukotriene receptor antagonists in 1995 and decreased by __% thereafter, reaching 3.5 per million in 1999. The rate of asthma death was found to decrease with increasing use of both leukotriene receptor antagonists and inhaled corticosteroids. The rate ratio of asthma death was ___ per 1 million 25-day treatment courses of inhaled corticosteroids and ___for every 1 million 25-day treatment courses of leukotriene receptor antagonists, consumed per year in Japan. The increasing use of inhaled corticosteroids and leukotriene receptor antagonists may have contributed to the significant reduction in asthma mortality among young asthmatics in Japan. ***Eur Respir J 2003; 21: 101 to 104.***

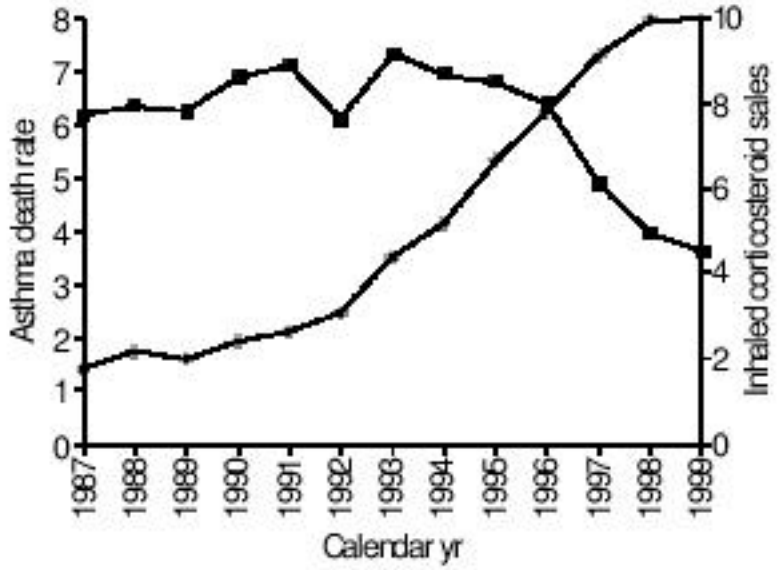


Fig. 1.– Yearly asthma death rate per million people aged 5–34 yrs in Japan over the period 1987–1999 (■) along with sales of inhaled corticosteroids in units of 1 million 25-day treatment courses (◆).

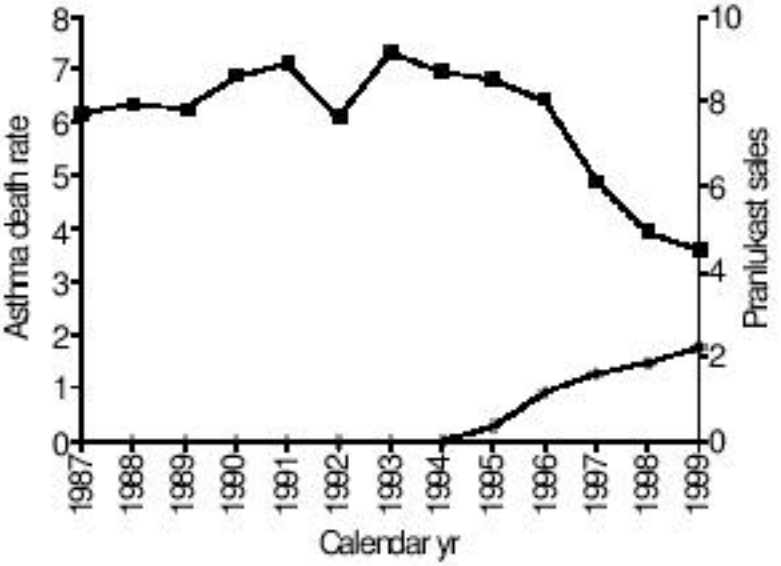


Fig. 2.– Yearly asthma death rate per million people aged 5–34 yrs in Japan over the period 1987–1999 (■) along with sales of leukotriene receptor antagonists in units of 1 million treatment episodes of 25 days with capsules of 112.5 mg of pranlukast (◆).

QUESTION 2

a Refer to the SAS statements, and the output, for "analysis a"

- *Interpret the parameter estimate* `5.8104`. • *Comment.*

b Refer to the SAS statements, and the output, for "analysis b"

- *Fill in the blanks (indicated by* ***????????*** *) in the SAS program and output*
- *Interpret the parameter estimate* `1.8929`.
- *Why is the* `0.0194` so small? (hint: what would it be in Quebec?)
- *Interpret the* `p = 0.0001` and say why it is silly in this analysis.

c Refer to the SAS statements, and the output, for "analysis c"

- *Use these to fill in the blanks in the author's text below (show your work):*

  "The rate ratio for the [5-year] intra-LTRA period relative to the [8-year] pre-LTRA period was ____
  ( ____% reduction in the rate of asthma death; 95% CI ____% to ____%).
  This decrease corresponds to a reduction of (approx) ____ deaths per million per year after this introduction.

- *Why is the* `Deviance` *so high in analysis c, compared with analysis b? (above graphs from article may help)*

d The authors, in the methods section, say that

> "Poisson regression models were used for all analyses. (...) To correlate yearly drug consumption with the corresponding yearly rate of asthma death a loglinear relative risk model was used to estimate rate ratios and a ***linear excess risk*** model was used to estimate rate differences associated with LTRAs and inhaled corticosteroid usage"

- *Explain in detail how you would set up the data in SAS and what statements you would use in GENMOD to fit the "linear excess risk" model. Also, specify and explain which fitted parameter(s) from the output you would use to report and interpret your findings.*

e Examine Table 2, the text following it, and analyses e1.a, e1.b and e2

Table 2. – Rate ratio and rate difference of asthma death, among subjects aged 5–34 yrs in Japan during 1987-1999, associated with leukotriene receptor antagonist (LTRA) and inhaled corticosteroid use

| | RR | 95% CI | RD | 95% CI |
|---|---|---|---|---|
| Inhaled corticosteroids | 0.96 | 0.95 to 0.97 | –0.29 | –0.35 to –0.23 |
| Leukotriene receptor antagonists | 0.80 | 0.76 to 0.83 | –1.29 | –1.51 to –1.07 |

"Table 2 shows that the rate ratios of asthma death were ____ for every 1 million treatment courses of inhaled corticosteroids sold per year and ____ for every million treatment courses of LTRAs sold per year. Table 2 also indicates that every additional million treatment courses of LTRAs is associated with a reduction of ____ asthma deaths per million people per year and that every additional million units of inhaled corticosteroid is associated with a reduction of ____ asthma deaths per million people per year.

- *Fill in the 4 ____ 's in the above statements.*
- *From **which** analysis (e1.a / e1.b / e2) and **how** did the authors get the 0.96?*
- *In light of e1.a and e1.b, how do you interpret the results of analysis e2 ?*

f Although not included in analyses a-e below, the analyses performed by the authors *"included an adjustment for extra-Poisson year-to-year variability"*

- *Explain **what** they mean by "**extra**-Poisson year-to-year variability", **why** it might occur, and the **effect** on parameter estimates/SE's of adjusting for it.*

g The authors state that "These results must be interpreted with caution. Population-based epidemiological studies based on ecological designs are inherently weak because they _____. The "ecological fallacy" can result from this limitation and that is why ecological studies are employed primarily to generate hypotheses.

- *Fill in some words (not more than 20) to complete the above sentence. Then give a concrete example of how the results could lead to a wrong conclusion from this study*

h See analyses h.

- *What caused the error message for analysis h1?*
- *What modification was used to produce analysis h2?*
- *What does* exp[-11.9226] *represent?*
- *Why is the* -11.9226 *different from the* 1.8929 *in analysis b ?*

i In Table 1 of the article it was reported that in the 8 year period before the introduction of leukotriene receptor antagonists (LTRAs), t*he asthma death rate (per million inhabitant-years) was 6.64; 95% CI 6.39 to 6.89*. The paper did **not** report (a) *how many deaths* there were in this 8-year period, or (b) the *number of inhabitants aged 5–34 yrs* in an 'average' year. But, *just from this rate, and its associated CI, it **is** possible, without any further information,* to derive these two numbers.

- *Explain how these numbers could be back-calculated just from the 6.64 and the 95% CI 6.39 to 6.89. (if you don't remember the exact form of a formula, that's fine, but do explain the principles, and any assumptions, you would use)*

```
DATA a; /* [ obtained from one of the authors ]

pop:    population aged 5-34 yrs (millions)

InhCo6: # Tx courses of inhaled corticosteroids (millions)
LTRA6:  # Tx courses of leukotriene receptor antagonist (millions)

INPUT
Obsn  Year  deaths  pop      rate     InhCo6    LTRA6   post;
LINES;
 1    1987    317   51.312   6.177    1.7830    0.00000    0
 2    1988    323   50.974   6.336    2.2050    0.00000    0
 3    1989    317   50.736   6.248    2.0240    0.00000    0
 4    1990    347   50.312   6.896    2.4110    0.00000    0
 5    1991    356   50.067   7.110    2.6410    0.00000    0
 6    1992    304   49.889   6.093    3.0980    0.00000    0
 7    1993    364   49.632   7.333    4.4180    0.00000    0
 8    1994    342   49.271   6.941    5.1820    0.00000    0
 9    1995    331   48.758   6.788    6.6670    0.37394    1
10    1996    310   48.467   6.396    7.8000    1.15929    1
11    1997    235   48.117   4.883    9.1510    1.58748    1
12    1998    190   47.800   3.974    9.9836    1.86794    1
13    1999    171   47.500   3.600   10.0314    2.22614    1
;
RUN;
```

**>>>> analysis a <<<<**

```
proc genmod data=a;
 model deaths = / dist = poisson link=log ;
 where (post=0) ;
run;
```

The GENMOD Procedure Model Information

| Description | Value |
|---|---|
| Data Set | WORK.A |
| Distribution | POISSON |
| Link Function | LOG |
| Dependent Variable | DEATHS |
| Observations Used | 8 |

Criteria For Assessing Goodness Of Fit

| Criterion | DF | Value | Value/DF |
|---|---|---|---|
| Deviance | 7 | 9.6299 | 1.3757 |
| Scaled Deviance | 7 | 9.6299 | 1.3757 |
| Pearson Chi-Square | 7 | 9.6344 | 1.3763 |
| Scaled Pearson X2 | 7 | 9.6344 | 1.3763 |
| Log Likelihood | . | 12843.7472 | . |

Analysis Of Parameter Estimates

| Parameter | DF | Estimate | Std Err | ChiSquare | Pr>Chi |
|---|---|---|---|---|---|
| INTERCEPT | 1 | **5.8104** | 0.0194 | 90141.1528 | 0.0001 |

**>>>> analysis b <<<<**

```
proc genmod data=a;
 model deaths = /
    dist = poisson link=log  ?????????????? ;
 where (post=0) ;
```

Model Information

| Description | Value |
|---|---|
| Distribution | POISSON |
| Link Function | LOG |
| Dependent Variable | DEATHS |
| **??????????????** | **??????** |
| Observations Used | 8 |

Criteria For Assessing Goodness Of Fit

| Criterion | DF | Value | Value/DF |
|---|---|---|---|
| Deviance | 7 | 12.1821 | 1.7403 |
| Scaled Deviance | 7 | 12.1821 | 1.7403 |
| Pearson Chi-Square | 7 | 12.2195 | 1.7456 |
| Scaled Pearson X2 | 7 | 12.2195 | 1.7456 |
| Log Likelihood | . | 12842.4711 | . |

Analysis Of Parameter Estimates

| Parameter | DF | Estimate | Std Err | ChiSquare | Pr>Chi |
|---|---|---|---|---|---|
| INTERCEPT | 1 | **1.8929** | **0.0194** | 9566.8661 | 0.0001 |

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**>>>> analysis c <<<<**

```
proc genmod data=a;
 model deaths = post / dist = poisson link=log ?????????;
```

Model Information

| Description | Value |
|---|---|
| Distribution | POISSON |
| Link Function | LOG |
| Dependent Variable | DEATHS |
| Offset Variable | ?????? |
| Observations Used | 13 |

Criteria For Assessing Goodness Of Fit

| Criterion | DF | Value | Value/DF |
|---|---|---|---|
| Deviance | 11 | 88.2099 | 8.0191 |
| Scaled Deviance | 11 | 88.2099 | 8.0191 |
| Pearson Chi-Square | 11 | 88.0281 | 8.0026 |
| Scaled Pearson X2 | 11 | 88.0281 | 8.0026 |
| Log Likelihood | . | 18425.4574 | . |

Analysis Of Parameter Estimates

| Parameter | DF | Estimate | Std Err | ChiSquare | Pr>Chi |
|---|---|---|---|---|---|
| INTERCEPT | 1 | 1.8929 | 0.0194 | 9566.8150 | 0.0001 |
| POST | 1 | -0.2558 | 0.0344 | 55.3004 | 0.0001 |

Model Information (all 3 **analyses, namely e1.a, e1.b and e2**)

| Description | Value | Description | Value |
|---|---|---|---|
| Distribution | POISSON | Dependent Variable | DEATHS |
| Link Function | LOG | Offset Variable | **???????** |
| Observations Used | 13 | | |

**>>>> analysis e1.a <<<<**

```
proc genmod data=a;
 model deaths = InhCo6  /
   dist = poisson link=log  ??????????? ;
```

| Criterion | DF | Value | Value/DF |
|---|---|---|---|
| Deviance | 11 | 75.0957 | 6.8269 |
| Pearson Chi-Square | 11 | 75.0763 | 6.8251 |
| Scaled Pearson X2 | 11 | 75.0763 | 6.8251 |
| Log Likelihood | . | 18432.0145 | . |

| Parameter | DF | Estimate | Std Err | ChiSquare | Pr>Chi |
|---|---|---|---|---|---|
| INTERCEPT | 1 | 2.0269 | 0.0304 | 4443.1982 | 0.0001 |
| INHCO6 | 1 | -0.0453 | 0.0055 | 68.0151 | 0.0001 |

**>>>> analysis e1.b <<<<**

```
proc genmod data=a;
 model deaths =  LTRA6 /
   dist = poisson link=log  ?????????? ;
```

| Criterion | DF | Value | Value/DF |
|---|---|---|---|
| Deviance | 11 | 33.4434 | 3.0403 |
| Pearson Chi-Square | 11 | 34.0678 | 3.0971 |
| Scaled Pearson X2 | 11 | 34.0678 | 3.0971 |
| Log Likelihood | . | 18452.8407 | . |

| Parameter | DF | Estimate | Std Err | ChiSquare | Pr>Chi |
|---|---|---|---|---|---|
| INTERCEPT | 1 | 1.9115 | 0.0184 | 10782.6883 | 0.0001 |
| LTRA6 | 1 | -0.2272 | 0.0223 | 103.3338 | 0.0001 |

**>>>> analysis e2 <<<<**

```
proc genmod data=a;
 model deaths = InhCo6 LTRA6  / corrb
   dist = poisson link=log ??????????? ;
```

| Criterion | DF | Value | Value/DF |
|---|---|---|---|
| Deviance | 10 | 22.1170 | 2.2117 |
| Pearson Chi-Square | 10 | 22.6470 | 2.2647 |
| Scaled Pearson X2 | 10 | 22.6470 | 2.2647 |
| Log Likelihood | . | 18458.5039 | . |

| Parameter | DF | Estimate | SE | Pr>Chi | Correlation Matrix | | |
|---|---|---|---|---|---|---|---|
| | | | | | INTERCEPT | INHCO6 | LTRA6 |
| INTERCEPT | 1 | 1.7647 | 0.0476 | 0.0001 | 1.00 | -0.92 | 0.75 |
| INHCO6 | 1 | 0.0456 | 0.0135 | 0.0007 | -0.92 | 1.00 | -0.90 |
| LTRA6 | 1 | -0.3906 | 0.0532 | 0.0001 | 0.75 | -0.90 | 1.00 |

**>>>> analysis h1 <<<<**

```
proc logistic data=a;
 model deaths/pop = ;
 where (post=0) ;
run;
```

NOTE: 8 observations were read.

**ERROR**: No valid observations due either to missing values in the response, explanatory, frequency, or weight variable, or to nonpositive frequency or weight values.

---

**>>>> analysis h2 <<<<**

```
proc logistic data=a ;
 model deaths/popln =  ;
 where (post=0) ;
run;
```

The LOGISTIC Procedure

Data Set: WORK.A
Response Variable (Events): DEATHS
Response Variable (Trials): POPLN
Number of Observations: 8
Link Function: Logit

Response Profile

| Ordered Value | Binary Outcome | Count |
|---|---|---|
| 1 | EVENT | 2670 |
| 2 | NO EVENT | 402190330 |

-2 LOG L = 69006.71

Analysis of Maximum Likelihood Estimates

| Variable | DF | Parameter Estimate | Standard Error | Wald Chi-Sq | Pr > Chi-Sq | Odds Ratio |
|---|---|---|---|---|---|---|
| INTERCPT | 1 | **-11.9226** | 0.0194 | 379533.8 | 0.0001 | . |