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**Hospitalization of and mortality from bleeding peptic ulcer  
in Sweden. A nation-wide time-trend analysis.**

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5 **Hospitalization of and mortality from bleeding peptic ulcer in Sweden. A**  
6 **nation-wide time-trend analysis.**  
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19 data, drafting of the manuscript.

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21 the manuscript.  
22

23 Yunxia Lu: Study design, acquisition of data, statistical analysis

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**Abstract**

*Background and aims:* Time-trend analyses of incidence and mortality in bleeding peptic ulcer show divergent results. This study is the first detailed national analysis of hospitalization of and mortality from bleeding peptic ulcer in Sweden.

*Method:* Data from all hospitalizations at departments with primary responsibility for patients with bleeding ulcer in Sweden, with main- or co-diagnosis of bleeding ulcer from 1987-2005 were retrieved from the Hospital Discharge Register. A validation study was performed due to an uncertainty in diagnostic setting after the introduction of ICD-10 in 1997. Annual hospitalization rates per 100 000 inhabitants in relation to gender, age and ulcer location was calculated as well as age-standardized 30-day mortality rates.

*Results:* Hospitalizations for bleeding ulcer decreased from 63.9 to 35.3 per 100 000 inhabitants per year during the study period. The decrease was greater among men (men 80.4 to 40.9; women 47.7 to 29.7) and in younger age groups. Bleeding gastric ulcer decreased in both sexes and bleeding duodenal ulcer decreased most among men but was stable in a subgroup of elderly women. Median age increased from 70 to 76 years. Standardized 30-day mortality increased from 5.3 to 6.2 per cent. The increased mortality was found in those over the age of 65 years and with duodenal ulcer disease, whereas mortality was unchanged in those with bleeding gastric ulcer.

*Conclusion:* Hospitalization rates for bleeding peptic ulcer have markedly decreased in Sweden in all age groups. The 30-day mortality is low compared to other nationwide studies in the western world but has increased among patients with duodenal ulcer disease.

**Keywords:** peptic ulcer, bleeding, incidence, mortality.

## Introduction

Hospitalization rates for peptic ulcer have declined in most Western countries from the 1950's (1-6) probably due to a cohort phenomenon with decreasing prevalence of *Helicobacter pylori* (*H. pylori*) infection (7, 8) and modern ulcer treatment with histamin-2-receptor antagonists and proton pump inhibitors as well as eradication therapies against *H. pylori*.

However, during the last two decades, the prescriptions of low dose aspirin (ASA) and other non-steroidal anti-inflammatory drugs (NSAIDs) as well as selective serotonin reuptake inhibitors (SSRIs) have increased several fold in our country (9) These drugs interfere with the defense mechanisms of the gastric mucosa and/or influence with the haemostasis and may therefore promote peptic ulcer bleeding (10, 11).

There are divergent results in nation-wide population-based time-trend analyses of incidence of and mortality from peptic ulcer bleeding during the last decades. In Finland (1972-1992) (12) and England (1989-1999) (13) hospitalization rates increased for ulcer hemorrhage, especially among the elderly. In Scotland (1982-2002) (3) a general declining trend was found, but among the elderly the admission rates increased, especially for duodenal ulcer (DU) hemorrhage. In the Netherlands (1980-2003) (5) a gender difference was seen as female gastric ulcer (GU) and DU bleeding increased, whereas among men bleeding from DU decreased and GU bleeding was stable. In not nation-wide but regional population based studies from Denmark (1993-2002) (14), the Netherlands (1993-2000) (15) and Germany (1990-2000) (16) the incidence of ulcer hemorrhage was found unchanged.

Mortality rates from bleeding ulcer have been reported as being stable (15, 17, 18). In Scotland case fatality rates were decreasing after GU bleeding and increasing after DU hemorrhage (3) . Mortality rates have ranged between 5 and 15 per cent in different studies from the last decades (3, 15, 17-19). This study is the first detailed nation-wide analysis of

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3 mortality and hospitalization rates due to peptic ulcer hemorrhage in Sweden during the last  
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5 two decades.  
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## 10 **Method**

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12 Health care in Sweden is provided to all citizens by public funding at public hospitals under  
13 the audit of the National Board of Health and Welfare. Discharge data are registered for all  
14 patients in the National Hospital Discharge Register as well as cause of death data in the  
15 Cause of Death Registry. Every citizen has an individual ten-digit personal identification  
16 number which facilitates registration and follow-up in the national registries.  
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24 All hospitalizations in Sweden from 1987 to 2005 at departments with primary responsibility  
25 for patients with peptic ulcer hemorrhage (main- or co-diagnosis at discharge) were retrieved  
26 from the Swedish Hospital Discharge Register. Patients with gastrointestinal bleeding have  
27 traditionally always been admitted to Departments of Surgery and surgeons are doing the  
28 great majority of all diagnostic and therapeutic endoscopic procedures in bleeding ulcer  
29 patients in Sweden as medical gastroenterologists, although increasing, still are few in  
30 numbers. In order to make an updated identification of the hospital departments with primary  
31 responsibility for peptic ulcer bleeding a questionnaire was sent to all emergency hospitals in  
32 Sweden in December 2005. In 60 out of totally 63 emergency hospitals in Sweden at that  
33 time, patients with bleeding ulcer were handled at Departments of Surgery. In only three  
34 hospitals bleeding ulcer patients were hospitalized at another department (Department of  
35 Medicine, Gastroenterology and Emergency conditions, respectively). This search strategy  
36 thus included all significant ulcer bleeds in all emergency hospitals in Sweden during the time  
37 period.  
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57 The study period started in 1987 as this was the first year the Swedish Hospital Discharge  
58 Register had a 100 per cent national coverage. The cohort consisted of totally 129 687  
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3 hospitalizations for peptic ulcer of which 58 445 hospitalizations were coded as bleeding  
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5 ulcer.  
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8 The 9th and 10th revision of International Classification of Diseases were used to identify the  
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10 ulcer cohort in the Swedish Hospital Discharge Registry and the following diagnoses were  
11  
12 included; bleeding gastric ulcer (GU); 531A, 531E, K25.0, K25.4, bleeding duodenal ulcer  
13  
14 (DU); 532A, 532E K26.0, K26.4, bleeding gastroduodenal ulcer (without specified location);  
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16 533A, 533E, K27.0, K27.4, perforated gastric ulcer 531B, 531C, 531F, 531G, K25.1, K25.2,  
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18 K25.5, K25.6, perforated duodenal ulcer 532B, 532C, 532F, 532G, K26.1, K26.2, K26.5,  
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20 K26.6, perforated gastroduodenal ulcer 533B, 533C, 533F, 533G, K27.1, K27.2, K27.5,  
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22 K27.6, unspecified (not bleeding, not perforated) gastric ulcer (UNS) 531D, 531H, 531X,  
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24 K25.3, K25.7, K25.9, duodenal ulcer UNS 532D, 532H, 532X, K26.3, K26.7, K26.9 and  
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26 gastroduodenal ulcer UNS 533D, 533H, 533X, K27.3, K27.7, K27.9. Ulcers classified as  
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28 both bleeding and perforated were assigned to the perforated ulcers. Gastrojejunal ulcers 534  
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30 and K28 were not included in this study.  
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37 In the preliminary calculations we found a sudden increase of hospitalizations for ulcer UNS  
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39 after 1997, and at the same time point there was a large drop in hospitalizations for bleeding  
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41 and perforated ulcers. These changes in hospitalization rates coincided with the introduction  
42  
43 of the ICD-10 classification system in Sweden. A validation study was performed and data  
44  
45 extrapolated according to the results from that study (please see online chapter Validation  
46  
47 study).  
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51 Annual hospitalization rates per 100 000 inhabitants of total ulcer, bleeding ulcer, perforated  
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53 ulcer and ulcer UNS were calculated. Further calculations of bleeding ulcer were performed  
54  
55 with reference to ulcer location, gender and age groups. Bleeding ulcer fatality rate within 30  
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57 days after admission date was calculated by Life table method and standardized to the gender  
58  
59 and age distribution of total bleeding hospitalization episodes in Sweden from 1987 to 2005.  
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3 Linear regression model was used to test secular trends of hospitalization and mortality rates.  
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5 Negative binomial regression model was used to compare hospitalization and mortality rates  
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7 among sub-groups. Logarithm of the number at risk (population in hospitalization rate and  
8  
9 effective sample size in mortality) was used as offset. Validity of negative binomial  
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11 regression models were justified by deviance value divided by degree of freedom.  
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15 The study was approved by the Regional Ethical Review Board, Lund, Sweden.  
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## 20 **Results**

### 21 *Hospitalizations for peptic ulcer*

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23 Admission rates are expressed as hospitalizations per 100 000 inhabitants per year. The  
24  
25 hospitalization rate for peptic ulcer in total decreased from 102.1 to 54.8 during the study  
26  
27 period 1987 to 2005. Hospitalizations for bleeding ulcer decreased from 63.9 to 35.3, for  
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29 perforated ulcer from 11.9 to 7.7 and for ulcer UNS from 26.3 to 11.8 (All rates  $p < 0.0001$ )  
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31  
32 (Figure 1).  
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36 The declining trend of bleeding ulcer from 1987 to 2005 was significant for both sexes  
37  
38 ( $p < 0.0001$ ) but more pronounced for men (80.4 to 40.9) than for women (47.7 to 29.7)  
39  
40 (Figure 2) and the male to female ratio decreased from 1.69 to 1.37 during the study period.  
41  
42 Median age increased for both men (67 to 73 years) ( $p < 0.0001$ ) and women (74 to 78 years)  
43  
44 ( $p < 0.0001$ ). The hospitalization rates were much higher among the elderly and the decrease in  
45  
46 hospitalization rates was lower among the elderly compared to that of the younger age groups  
47  
48 though the decrease was significant in all age groups ( $p < 0.0001$ ) (Table 1).  
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53 Hospitalization rates for gastric ulcer was higher than for duodenal ulcer hemorrhage during  
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55 the entire study period ( $p < 0.0001$ ). Both gastric and duodenal ulcer bleeding decreased from  
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57 1987 to 2005 (Figure 3). Admissions for gastric ulcer bleeding decreased among men from  
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59 35.6 to 20.2 and among women from 26.3 to 17.1 and the decrease was more pronounced  
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3 among younger people although hospitalization rates declined in all age groups ( $p < 0.0001$ )  
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5 (men over 85 years,  $p = 0.0002$ ) (Table 3 online). Hospitalizations for duodenal ulcer  
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7 hemorrhage decreased in males from 40.5 to 20.1 and in females from 18.9 to 12.3. The  
8  
9 hospitalization rates for duodenal ulcer hemorrhage decreased in all age groups ( $p < 0.0001$ )  
10  
11 except among women over 85 years of age where the rate was stable ( $p = 0.0942$ ) (Table 4  
12  
13 online). The male hospitalization rate was significantly higher than the female rate for both  
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15 gastric and duodenal ulcer bleeding during the whole study period ( $p < 0.0001$ ).  
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### 20 21 22 *Mortality from bleeding ulcer*

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24 Mortality rates are presented in text and tables as the means of 1987/1988 and 2004/2005 in  
25  
26 order to reduce the effects of inter-annual variations.  
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28  
29 Standardized total mortality within 30 days after admission for an episode of bleeding ulcer  
30  
31 increased during the study period from 5.3 to 6.2 percent (Figure 4) mostly due to an  
32  
33 increased mortality after duodenal ulcer bleeding. Table 2 presents 30-day mortality by  
34  
35 gender and age. Men had an overall higher mortality than women ( $p = 0.0023$ ) and mortality  
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37 increased in both sexes from 1987 to 2005.  
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41 After gastric ulcer bleeding the mortality was stable from 1987 to 2005 (Table 2) but men had  
42  
43 a higher mortality than women during the entire study period ( $p = 0.0071$ ). Mortality in  
44  
45 duodenal ulcer bleeding increased among both men and women and in most age groups  
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47 during the study period (Table 2). The mortality rate after duodenal ulcer bleeding among  
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49 men was not different from that among women. Mortality was not higher after an episode of  
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51 duodenal ulcer than gastric ulcer hemorrhage during the entire study period.  
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### 56 57 **Discussion**

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3 In this nation wide study covering all emergency hospitals in Sweden we found a highly  
4  
5 significant decrease in hospital admissions due to bleeding ulcers between 1987 and 2005.

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8 The greatest decrease in our study appears between the years 1992 to 1999. During the years  
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10 before and after this period the curves are fairly stable. The decline approximately coincides  
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12 in time when you could expect a more wide spread effect of the introduction of proton pump  
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14 inhibitors and eradication therapies against *H. pylori*.

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17 For bleeding ulcer we found decreasing admission rates for both GU and DU hemorrhage,  
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19 among both men and women and in every age-group except in the oldest women (>85 years)  
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21 with bleeding duodenal ulcer where the hospitalization rate was stable. The decrease was  
22  
23 greater in young people and lesser in the elderly. This might be explained by lower prevalence  
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25 of *H. pylori* infection in the younger population (7, 8) and the influence of low dose aspirin,  
26  
27 other NSAIDs and SSRI more and more commonly prescribed to the elderly (9).

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30 Decreased incidence of peptic ulcer complications after 1988 in Sweden has recently been  
31  
32 published (20) and the same trend has been shown in a local hospital study from Southern  
33  
34 Sweden (21). Declining admission rates for bleeding ulcers are previously only found in  
35  
36 Scotland (3). In most other countries with studies of time trend for bleeding ulcer during the  
37  
38 last decades the admission rates have been stable or have increased (5, 12-16). Although the  
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40 studies are all from Western Europe they still show quite different results. There could be  
41  
42 several reasons to this finding. The prevalence of *H. pylori* differ between countries (22).

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45 Immigration patterns vary a lot between the European countries and immigrants in Western  
46  
47 countries are shown to have high *H. pylori* infection rates (7, 23-25). Socio-economic  
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49 differences might also play a role as low socio-economic class and crowded living conditions  
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51 in childhood are shown to be related to *H. pylori* infection (25-27). Prescription patterns of  
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53 both ulcer healing and ulcer promoting drugs could be a factor, as well as compliance to  
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55 medication due to costs for medication for the patient.  
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3 Most studies have evaluated the admission rates for peptic ulcer, and varying medical  
4 traditions and probably more importantly differences in reimbursement for hospitalizations  
5 may affect differences in indications for hospital admission, though this probably is a minor  
6 problem when studying ulcer complications. Finally, differences in diagnostic efforts cannot  
7 be ruled out nor those of diagnostic coding.

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10 The standardized 30-day mortality in bleeding ulcer increased in our study from 5.3 to 6.2 per  
11 cent despite the supposed improvements in the care of these patients with both new  
12 endoscopic and pharmacologic treatments as well as better intensive care during the last  
13 decades. Other population-based studies have reported of higher in-hospital or 30-day  
14 mortality between 10 to 14 per cent after ulcer bleeding (14, 15, 19). The difference in  
15 mortality seen for ulcer hemorrhage **might be** due to variations in case mix with different  
16 proportions of elderly and co-morbid patients with different nutritional and socio-economic  
17 backgrounds in the studies. The lower mortality in Sweden may reflect a better general health  
18 situation in the population in our country. Variations in quality of therapy and care could also  
19 play a role.

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22 Thirty-day mortality after bleeding ulcer was higher in the older age groups which is in line  
23 with other reports (3, 15, 17, 19) and to be expected due to probably higher co-morbidity and  
24 medicine usage among the elderly. The mortality was also increasing during the study period  
25 among the elderly patients while it was stable among patients younger than 65 years. **We**  
26 **found an increased mortality among men compared to woman. This might reflect a worse**  
27 **general health condition among men which could be attributed to several factors for example**  
28 **a higher frequency of smoking and smoking related diseases and higher alcohol consumption.**

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31 In contrast to the findings by Rockall et al. (19), we did not find a higher mortality among  
32 patients already hospitalized for another reason at the start of bleeding in comparison to those  
33 who started to bleed at home. However register studies are not an appropriate setting to

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3 investigate this issue as there is a lack of control for patients who start to bleed at the  
4 department with primary responsibility for gastrointestinal bleeding, although they are  
5 admitted for something else.  
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10 In our study we found 30-day mortality to be stable after gastric ulcer bleeding but it  
11 increased after duodenal ulcer hemorrhage, which is in line with the findings in the Scottish  
12 study where case fatality rates after gastric ulcer declined but it increased after duodenal ulcer  
13 hemorrhage (3). Most bleeding ulcer patients are subjected to endoscopic procedures  
14 nowadays and most bleedings cease on endoscopic treatment. Duodenal ulcers are often more  
15 difficult to reach for the endoscopist with optimal therapy and the rebleeding rate is higher,  
16 especially if the ulcer has eroded the gastroduodenal artery, which might explain the  
17 increasing mortality rate for duodenal ulcers. For these cases emergency surgery is the rescue  
18 therapy and mortality after surgery in these situations is high. As elective ulcer surgery has  
19 virtually vanished during the last two decades the impact of decreased experience among  
20 surgeons cannot be ruled out.  
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36 The strength of our study is the large national sample size covering all significant ulcer  
37 bleedings in the country. This was reached by analyzing all hospitalizations with a discharge  
38 diagnosis of bleeding ulcer from the departments with primary responsibility of  
39 gastrointestinal bleeding, validated by a questionnaire to all emergency hospitals in Sweden.  
40 Another strength is that we noted the misclassification problem of bleeding ulcer as ulcer  
41 UNS after the introduction of ICD-10 and conducted a validation study with a very high  
42 response rate of 96.8 per cent. The extrapolation of the results from the validation study to the  
43 ulcer cohort during the analyzed years 1993/1994 and 1999/2000 is thus considered to be  
44 fairly accurate. The accuracy of the extrapolation may however decline with time from the  
45 index years, and individual annual hospitalization rates must therefore be interpreted with  
46 caution although we believe that the overall trends are correct.  
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3 A weakness of the study includes the problems with potential errors in registry data though  
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5 we believe that the Swedish Hospital Discharge Register do not contain more errors than  
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7 similar National Registers in other countries. The Swedish individual ten-digit personal  
8  
9 identification number facilitates registration and follow-up and all emergency hospitals are  
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11 under public control and audit and patients living within the hospital catchment area are in a  
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13 very high percentage referred to their local hospital.  
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17 In summary, the hospitalization rate for bleeding peptic ulcer has decreased by more than 40  
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19 per cent in Sweden from 1987 to 2005. This is probably due to a decreasing prevalence of *H.*  
20  
21 *pylori* in the population. An increase in 30-day mortality after peptic ulcer bleeding was  
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23 observed during the same time period mostly due to an increased mortality after duodenal  
24  
25 ulcer bleeding. This might reflect more frequent serious co-morbidity in the elderly  
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27 population with corresponding increased use of ulcer and bleeding promoting drugs, but  
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29 differences in care cannot be ruled out.  
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Figure 1. Annual hospitalisation rates for ulcer in Sweden, 1987 - 2005

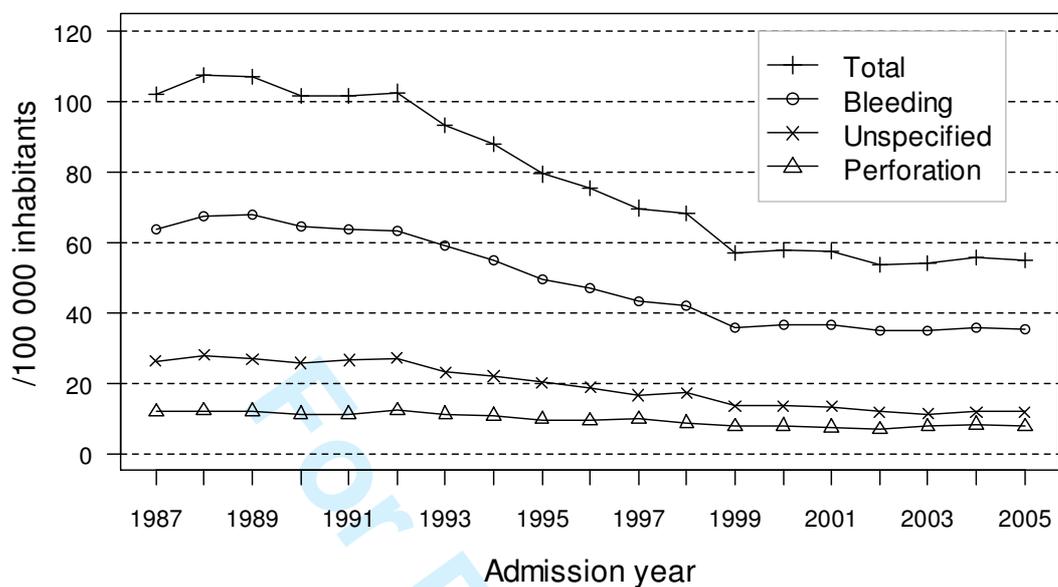
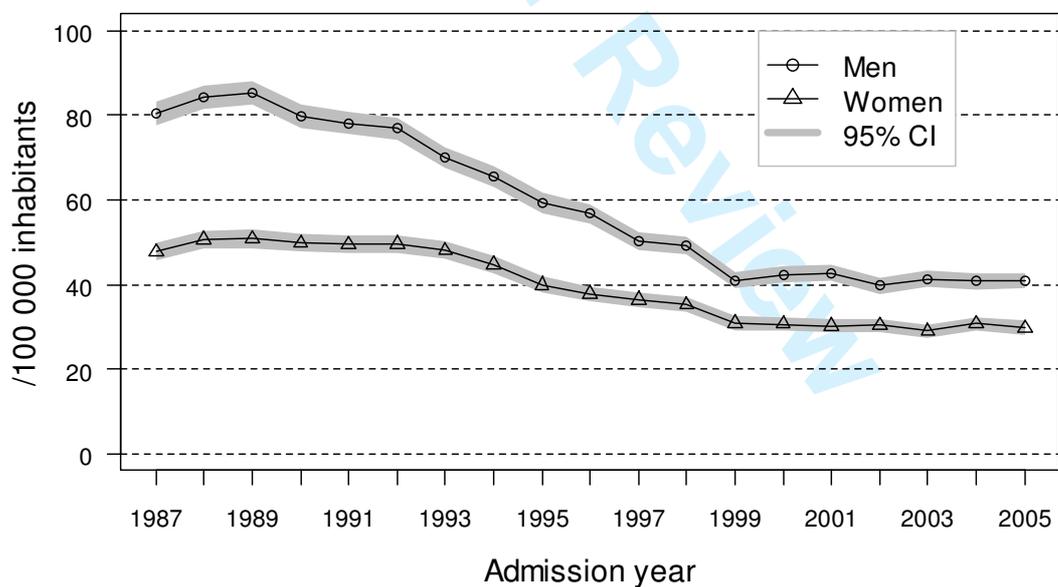
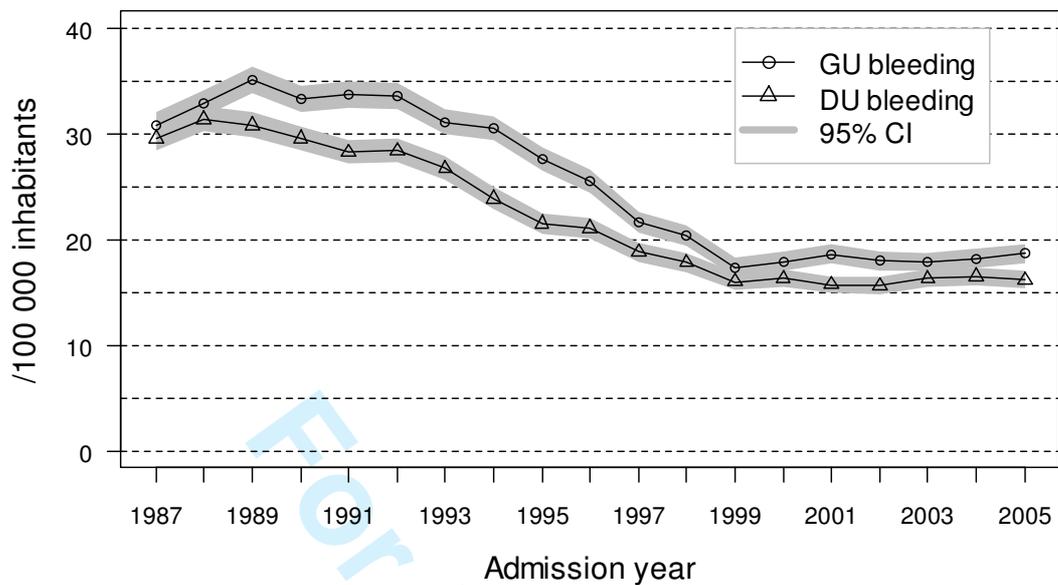


Figure 2. Annual hospitalisation rates for bleeding ulcer by gender in Sweden, 1987 - 2005

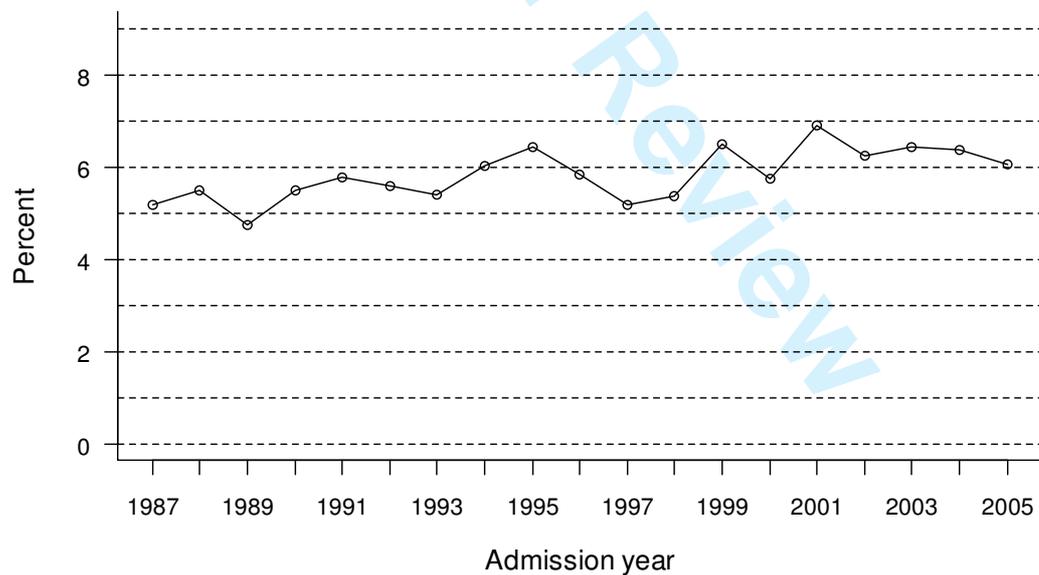


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**Figure 3. Annual hospitalisation rates for bleeding gastric and duodenal ulcer in Sweden, 1987 - 2005**



**Figure 4. Standardised 30-day mortality rates after bleeding ulcer in Sweden, 1987 - 2005\***



\* Standardised to the gender and age distribution of total bleeding ulcer hospitalisation episodes in Sweden, 1987 - 2005.

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Table 1. Hospitalization rates for bleeding ulcer / 100 000 inhabitants / year and difference in per cent between 1987 and 2005.

	1987	1996	2005	% diff	
<b>Men</b>					
<45 years	20.0	10.5	4.7	-77	*
45-54 years	84.2	45.1	28.5	-66	*
55-64 years	131.4	80.8	62.2	-53	*
65-74 years	219.0	172.9	97.4	-56	*
75-84 years	363.6	268.9	214.5	-41	*
>84 years	428.8	433.4	343.1	-20	*
<b>Women</b>					
<45 years	6.6	3.9	2.7	-59	*
45-54 years	39.5	23.8	15.4	-61	*
55-64 years	60.0	34.7	26.3	-56	*
65-74 years	113.0	78.6	63.2	-44	*
75-84 years	205.4	177.9	139.2	-32	*
>84 years	242.3	242.2	189.2	-22	*
<b>Total</b>					
<45 years	13.4	7.3	3.7	-72	*
45-54 years	62.2	34.6	22.0	-65	*
55-64 years	94.8	57.6	44.3	-53	*
65-74 years	162.2	122.3	79.6	-51	*
75-84 years	269.6	215.3	170.9	-37	*
>84 years	301.0	301.8	239.0	-21	*

p value for trend by linear regression from 1987 to 2005

\* <0.0001

Table 2. 30 day mortality (%) after ulcer bleeding.

Standardized by age and gender wherever applicable.

	1987/1988	2004/2005	p-value for trend
Total $\square$ #	5.3%	6.2%	0.0014
<65 years #	1.0%	2.8%	0.054
65-74 years #	3.7%	5.9%	0.020
>74 years #	9.4%	9.6%	0.0092
Men total $\square$	5.9%	6.1%	0.019
<65 years	0.8%	2.2%	0.24
65-74 years	3.8%	5.7%	0.046
>74 years	10.2%	9.7%	0.065
Women total $\square$	4.9%	6.6%	0.015
<65 years	1.4%	3.7%	0.069
65-74 years	3.6%	6.3%	0.048
>74 years	8.1%	9.4%	0.030
Men GU total $\square$	5.1%	5.2%	0.57
<65 years	0.8%	2.3%	0.72
65-74 years	3.5%	3.3%	0.54
>74 years	8.6%	9.1%	0.26
Women GU total $\square$	4.2%	5.5%	0.22
<65 years	0.5%	3.8%	0.27
65-74 years	2.6%	4.9%	0.16
>74 years	7.8%	6.9%	0.62
Men DU total $\square$	6.0%	6.1%	0.023
<65 years	0.6%	2.6%	0.042
65-74 years	2.8%	6.3%	0.030
>74 years	11.2%	9.1%	0.14
Women DU total $\square$	5.9%	7.6%	0.013
<65 years	1.9%	4.7%	0.010
65-74 years	4.8%	8.2%	0.16
>74 years	9.3%	10.3%	0.019

Linear regression was used to test for secular trend.

*Abbreviations:* GU=gastric ulcer, DU=duodenal ulcer $\square$  Standardized to the age distribution of bleeding ulcer hospitalizations in Sweden 1987-2005

# Standardized to the gender distribution of bleeding ulcer hospitalizations in Sweden 1987-2005

Table 3. Hospitalisation rates for bleeding gastric ulcer /  
100 000 inhabitants / year and difference in per cent  
between 1987 and 2005.

	1987	1996	2005	% diff	
<b>Men</b>					
<45 years	7.6	4.8	2.2	-72	*
45-54 years	35.2	22.1	14.9	-58	*
55-64 years	55.7	43.6	30.0	-46	*
65-74 years	98.5	83.7	47.2	-52	*
75-84 years	176.1	145.7	105.2	-40	*
>84 years	213.2	232.9	181.0	-15	**
<b>Women</b>					
<45 years	3.1	2.0	1.5	-53	*
45-54 years	19.1	13.4	8.4	-56	*
55-64 years	30.2	19.6	15.1	-50	*
65-74 years	68.4	44.5	35.6	-48	*
75-84 years	116.3	110.4	82.1	-29	*
>84 years	132.4	140.9	110.3	-17	*
<b>Total</b>					
<45 years	5.4	3.4	1.8	-67	*
45-54 years	27.3	17.8	11.7	-57	*
55-64 years	42.6	31.5	22.6	-47	*
65-74 years	82.4	62.7	41.1	-50	*
75-84 years	140.6	124.9	91.9	-35	*
>84 years	157.9	169.6	133.2	-16	*

p values for trend by linear regression from 1987 to  
2005

\* <0.0001, \*\* =0.0002

Table 4. Hospitalisation rates for bleeding duodenal ulcer / 100 000 inhabitants / year and difference in per cent between 1987 and 2005.

	1987	1996	2005	% diff	
<b>Men</b>					
<45 years	11.4	5.6	2.4	-79	*
45-54 years	44.9	22.7	13.6	-70	*
55-64 years	66.1	37.7	32.6	-51	*
65-74 years	110.3	88.2	48.9	-56	*
75-84 years	166.8	123.3	104.3	-38	*
>84 years	190.9	196.4	152.7	-20	*
<b>Women</b>					
<45 years	3.1	1.6	1.0	-66	*
45-54 years	19.4	10.2	6.6	-66	*
55-64 years	26.2	14.8	10.7	-59	*
65-74 years	40.8	32.2	28.4	-30	*
75-84 years	76.7	64.1	55.9	-27	*
>84 years	89.2	95.6	77.5	-13	ns
<b>Total</b>					
<45 years	7.3	3.7	1.7	-76	*
45-54 years	32.3	16.5	10.1	-69	*
55-64 years	45.7	26.2	21.8	-52	*
65-74 years	73.0	58.1	38.2	-48	*
75-84 years	113.3	88.4	76.3	-33	*
>84 years	121.2	127.0	101.8	-16	*

p values for trend by linear regression from 1987 to 2005

\* <0.0001, ns =0.0942

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3 *Validation study*  
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5 In the preliminary calculations we found a sudden increase of hospitalizations for ulcer UNS  
6 after 1997, and at the same time point there was a large drop in hospitalizations for bleeding  
7 and perforated ulcers. We considered this finding to be medically doubtful, as the reason to  
8 hospitalization for ulcer disease in modern time in the majority of cases is because of ulcer  
9 complications (hemorrhage, perforation or obstruction). These changes in hospitalization rates  
10 coincided with the introduction of the ICD-10 classification system in Sweden. In the short  
11 alphabetic version of diagnostic codes published by the National Board of Health and  
12 Welfare, usually used by doctors, there was no longer a specification of 4<sup>th</sup> position of the  
13 diagnostic code. The fourth position is required to give information of the presence of  
14 bleeding or perforation and to retrieve this information after 1997 the more comprehensive  
15 systematic version had to be explored. An increased rate of misclassifications could thus be  
16 suspected. A validation study was therefore conducted in order to calculate the suspected rate  
17 of misclassified ulcer complications (bleeding and perforations) as ulcer UNS after 1997.  
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19 A random sampling of totally 400 emergency hospitalizations at Departments of Surgery,  
20 with a discharge diagnosis of ulcer UNS were drawn from the Swedish Hospital Discharge  
21 Register, 200 from the period 1993-1994 and 200 from 1999-2000. The sampling number was  
22 chosen after the following calculations: With an assumption of a base-line misclassification of  
23 diagnoses in the Swedish Hospital Discharge Register of around 10 per cent, 195 individuals  
24 in each group were required to detect an increase to around 20 per cent of misclassified ulcer  
25 complications as ulcer UNS after the introduction of ICD-10 (80 per cent power, two-sided  
26 test,  $\alpha= 0.05$ ).  
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54 In cooperation with the National Board of Health and Welfare, questionnaires were sent to the  
55 departments where the patients had been hospitalized, for evaluation of the medical records to  
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ascertain a potential misclassification of a perforated or bleeding ulcer. The response rate was 96.8 per cent (387/400). Data were unidentified before further processing and analyzing.

The criteria of a misclassified bleeding ulcer was either a) operation for bleeding ulcer or b) symptoms/history of bleeding at admission together with an endoscopically verified ulcer with no other bleeding source or c) an endoscopically verified bleeding ulcer. The criteria of a misclassified perforated ulcer were either operation for perforated ulcer or in another way verified perforated ulcer.

In the validation study the median age increased from 69 to 74 years ( $p=0.0132$ ). Symptoms or patient history of bleeding (hematemesis or melena) at time for admission increased by 53 per cent and was much more frequent in the latter period (52.3 per cent compared to 34.2 per cent,  $p=0.000047$ , Fisher's exact test). Diagnostic endoscopy was frequently performed during both periods (84.0 and 89.2 per cent, ns). The diagnosis of ulcer disease was verified (through surgery, endoscopy, radiology or autopsy) to a higher extent in the latter period (81.0 and 88.8 per cent respectively,  $p=0.033$ ). The verification of bleeding was made in about 20 per cent of patients (blood in stomach, ongoing bleeding, visible vessel, hematin coloured spot or blood clot covering ulcer base) and did not change between periods.

In summary, 65/190 patients met the criteria of a misclassified bleeding ulcer before the introduction of ICD-10 in comparison with 98/197 patients after the introduction of ICD-10, an increase from 34.2 to 49.7 per cent ( $p=0.002$ ). The misclassification of perforated ulcer increased from 1/190 (0.5 per cent) to 12/197 (6.1 per cent) ( $p=0.003$ ).

#### *Extrapolation of data*

The percentage of misclassified bleeding or perforated ulcers found in the validation study was subtracted from the crude rate of hospitalizations for ulcer UNS in the cohort. The result from the period 1993-1994 was used for 1987-1996 (before the introduction of ICD-10) and

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3 the result from 1999-2000 was used for 1997-2005 (after the introduction of ICD-10) (In one  
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5 Swedish region the introduction of ICD-10 took place in 1998). The number of  
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7 hospitalizations subtracted from the ulcer UNS cases was then added to the bleeding or  
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9 perforated ulcer cases in the cohort. Chi-square tests showed no difference regarding the  
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11 distribution in age, gender and ulcer location between the misclassified bleeding cases in the  
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13 validation study and the UNS cases in the cohort. The same extrapolation percentage was  
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15 therefore applied across all subgroups of age, gender and ulcer location.  
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For Peer Review