

# Association of Oral Glucocorticoid Use With an Increased Risk of Acute Pancreatitis

## A Population-Based Nested Case-Control Study

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**Importance:** Oral glucocorticoid use has been suggested to cause acute pancreatitis in several case reports. However, no epidemiological study has investigated this association.

**Objective:** To conduct a nationwide population-based case-control study to investigate the potential association between oral glucocorticoid use and acute pancreatitis.

**Design:** In this population-based case-control study, all individuals aged 40 to 84 years who developed a first episode of acute pancreatitis between 2006 and 2008 in Sweden were identified.

**Setting:** Population-based, nationwide, register-based study.

**Participants:** A total of 6161 cases with a first episode of acute pancreatitis and 61 637 controls were included in the final analyses. Cases were all patients diagnosed as having a first episode of acute pancreatitis during the study period, defined by the diagnosis code K85 in the *International Statistical Classification of Diseases, 10th Revision (ICD-10)*. Controls were randomly selected from the source population at risk of developing acute pancreatitis. For each case, 10 controls, matched for age, sex, and calendar period, were randomly selected from the general population. Oral glucocorticoid use was assessed from the Swedish Prescribed Drug Register. Current, recent, and former users were defined as patients who collected their glucocorticoid prescription within 30,

31 to 180, and after 180 days before the index date, respectively

**Main Outcome Measures:** Unconditional logistic regression was performed to calculate the odds ratios (ORs) with 95% confidence intervals for the association between oral glucocorticoid use and acute pancreatitis. Multivariable adjustment was made for potential confounders including, among others, alcohol abuse, diabetes, and concomitant drug use.

**Results:** The study included 6161 cases of acute pancreatitis and 61 637 controls. The risk of acute pancreatitis was increased among current users of oral glucocorticoids compared with nonusers (OR, 1.53; 95% CI, 1.27-1.84). This risk was highest 4 to 14 days after drug dispensation (OR, 1.73; 95% CI, 1.31-2.28) and attenuated thereafter. There was no association between oral glucocorticoid use and acute pancreatitis immediately after drug dispensation. There was no increased risk of acute pancreatitis among recent or former users of glucocorticoids compared with nonusers.

**Conclusions and Relevance:** Current oral glucocorticoid use is associated with an increased risk of acute pancreatitis.

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**A**CUTE PANCREATITIS IS THE most common pancreatic disorder. In 10% to 20% of patients, the disease progresses into a potentially life-threatening condition, associated with multiple-organ failure or death. While most cases of acute pancreatitis are attributed to excess alcohol consumption or gallstone disease,<sup>1</sup> the etiology is not fully understood,<sup>2</sup> and in 20% of cases it remains

unknown.<sup>3,4</sup> Drug-induced acute pancreatitis has previously been considered as a rare cause of acute pancreatitis,<sup>5</sup> but recent reports have indicated that drug-induced acute pancreatitis might be the third most common cause of the disease, accounting for 3% to 5% of all cases.<sup>6,7</sup>

Oral glucocorticoids are one of the most common groups of drugs, used in approximately 1% of the population.<sup>8,9</sup> These drugs have several well-known ad-

verse effects including osteoporosis, diabetes mellitus, and peptic ulcer.<sup>10</sup> In addition, several case reports have described induction of acute pancreatitis in patients treated with glucocorticoids.<sup>11-16</sup> In 2 of these case reports, there was a positive rechallenge with oral dexamethasone<sup>14</sup> and prednisone.<sup>16</sup> Importantly, some indications of glucocorticoid therapy, eg, inflammatory bowel disease,<sup>17</sup> systemic lupus erythematosus,<sup>18</sup> and Wegener granulomatosis,<sup>19</sup> could be risk factors for acute pancreatitis resulting in confounding by indication. To our knowledge, no pharmacoepidemiological study has investigated the association between oral glucocorticoid use and the risk of developing acute pancreatitis.

Therefore, a nationwide population-based case-control study was conducted to investigate the potential association between oral glucocorticoid use and acute pancreatitis.

## METHODS

### STUDY DESIGN

This was a population-based case-control study conducted in Sweden using validated and nationwide databases.<sup>20</sup> The source population was all Swedish residents aged 40 to 84 years during the study period (January 1, 2006, through December 31, 2008). From this source population, the Swedish Patient Register was used to identify cases with a first episode of acute pancreatitis. The Swedish Register of the Total Population was used to identify randomly selected controls. The exposure to glucocorticoids was assessed through the Swedish Prescribed Drug Register, and data on covariates were retrieved from other nationwide registers in Sweden. Linkage between registers was performed using the personal identity number, uniquely identifying each resident in Sweden.<sup>21</sup>

### SOURCES OF DATA

The Swedish Patient Register comprises information on all inpatient care and outpatient specialist care in Sweden.<sup>22</sup> Each record includes, among others, diagnosis codes and information on performed surgical procedures. The register has complete national coverage on all inpatient care since 1987 and outpatient specialist care since 2001. The diagnosis of acute pancreatitis in the Swedish Patient Register has recently been validated by our group, revealing a high positive predictive value (98%).<sup>23</sup>

The Swedish Register of the Total Population contains individual characteristics, including age, sex, country of birth, marital status, and place of residence, on all Swedish residents since 1968.<sup>24</sup>

The Swedish Prescribed Drug Register holds information on all prescribed and dispensed drugs since July 1, 2005, covering the entire Swedish population.<sup>25</sup> The register includes information on drug substances according to the Anatomical Therapeutic Chemical (ATC) classification,<sup>26</sup> the quantity of drug dispensed, and date of expenditure.

The Swedish Causes of Death Register contains information on date of death for all deceased Swedish residents since 1952, and data on cause-specific death is 99.2% complete.<sup>27</sup>

The Swedish Cancer Register has information on all newly diagnosed cancers in Sweden since 1958. Both clinicians and pathologists are required to report new cases of cancer to the register, resulting in an estimated overall completeness of a minimum of 96%.<sup>28</sup>

The Swedish Register of Education, established in 1985 by Statistics Sweden, annually updates information on the highest level of formal education attained (from elementary to postgraduate level) by each Swedish resident.<sup>29</sup>

### CASE AND CONTROL IDENTIFICATION

Cases were all patients diagnosed as having a first episode of acute pancreatitis during the study period, defined by the diagnosis code K85 in the *International Statistical Classification of Diseases, 10th Revision (ICD-10)*.

Controls were randomly selected from the source population at risk of developing acute pancreatitis. Person-time was calculated for all individuals in the source population. To identify when a person was no longer at risk of acute pancreatitis or at a biased risk, censoring was made at date of death, emigration, or diagnosis of cancer (not including nonmelanoma cancers of the skin), whichever occurred first. For each case, 10 controls at risk of acute pancreatitis were randomly selected from the source population, using incidence density sampling.<sup>30</sup> The probability of becoming a control was proportional to the time at risk during the study period.<sup>31</sup> The controls were frequency matched for age, sex, and calendar period.

The exposure was considered in relation to an index date assigned to each case and control. For cases, the index date was set as the date of admission for acute pancreatitis. For controls, the index date was a randomly assigned date during the calendar year. Individuals who had a diagnosis of cancer (apart from nonmelanoma cancers of the skin) recorded in the Swedish Cancer Register before the study period, or any pancreatic disease (*ICD-10* codes K85-K87; *International Classification of Diseases, Ninth Revision [ICD-9]* code 577) recorded in the Swedish Patient Register before the study period were not included in the sampling of cases and controls. In total, 4 cases and 13 controls with incomplete personal identity numbers were excluded after sampling of the study population.

### EXPOSURE TO GLUCOCORTICOIDS

Dispensed drug prescriptions of oral glucocorticoids were identified using the corresponding ATC code (H02AB) in the Swedish Prescribed Drug Register. By having access to information on the brand and the administration route, no patient with intravenous, intramuscular, intra-articular, or subcutaneous administration route of glucocorticoids ( $n=517$ ) was defined as having been exposed to oral glucocorticoids. Only prescriptions dispensed before the index date were considered. Current, recent, and former users of glucocorticoids were defined as patients who filled their prescription for glucocorticoids within 30 days, 31 to 180 days, and after 180 days before the index date, respectively. Patients with no filled prescriptions for glucocorticoids in the register were defined as nonusers. To assess the role of confounding by indication in the association between oral glucocorticoid use and acute pancreatitis, the time since drug dispensation was further categorized among current and recent users. Current oral glucocorticoid use was categorized into immediate, early, or late use, corresponding to 0 to 3 days, 4 to 14 days, or 15 to 30 days since drug dispensation, respectively. Recent use was defined as early (31-60 days) or late use (61-180 days).

There are no reports indicating any association between the use of inhalation glucocorticoids and acute pancreatitis, and since the systemic uptake of inhalation glucocorticoids is negligible, no association between inhalation glucocorticoids and acute pancreatitis was expected. Therefore, to further validate the results for the association between oral glucocorticoid use and acute pancreatitis, we also analyzed the risk of acute pan-

**Table 1. Distribution of Characteristics Among Cases with Acute Pancreatitis Occurring Between 2006 and 2008 and the Frequency-Matched Population Controls**

| Characteristic                 | No. (%)             |                          |
|--------------------------------|---------------------|--------------------------|
|                                | Cases<br>(n = 6161) | Controls<br>(n = 61 637) |
| Age, median (range), y         | 63 (40-84)          | 63 (40-83)               |
| Sex                            |                     |                          |
| Women                          | 2774 (45.0)         | 27 745 (45.0)            |
| Men                            | 3387 (55.0)         | 33 892 (55.0)            |
| Married                        |                     |                          |
| Yes                            | 3427 (55.6)         | 37 593 (61.0)            |
| No                             | 2680 (43.5)         | 23 872 (38.7)            |
| Missing                        | 54 (0.9)            | 172 (0.3)                |
| Educational level              |                     |                          |
| Elementary                     | 2464 (40.0)         | 21 896 (35.5)            |
| Secondary school               | 2455 (39.9)         | 24 016 (39.0)            |
| University                     | 1099 (17.8)         | 14 769 (24.0)            |
| Missing                        | 143 (2.3)           | 956 (1.5)                |
| Comorbidities                  |                     |                          |
| Alcohol abuse                  | 563 (9.1)           | 1507 (2.4)               |
| Ischemic heart disease         | 972 (15.8)          | 5988 (9.7)               |
| Peripheral vascular disease    | 273 (4.4)           | 1169 (1.9)               |
| COPD                           | 278 (4.5)           | 1328 (2.2)               |
| Obesity                        | 144 (2.3)           | 533 (0.9)                |
| Hyperlipidemia                 | 418 (6.8)           | 2614 (4.2)               |
| Diabetes                       | 564 (9.2)           | 3759 (6.1)               |
| Gallstone disease              | 1084 (17.6)         | 2595 (4.2)               |
| No. of drugs used <sup>a</sup> |                     |                          |
| 0                              | 876 (14.2)          | 17 363 (28.2)            |
| 1-2                            | 1196 (19.4)         | 14 715 (23.9)            |
| 3-4                            | 1081 (17.6)         | 10 375 (16.8)            |
| 5-8                            | 1861 (30.2)         | 13 665 (22.2)            |
| ≥9                             | 1147 (18.6)         | 5519 (9.0)               |

Abbreviation: COPD, chronic obstructive pulmonary disease.

<sup>a</sup>Concomitant drugs dispensed within 6 months from index date.

creatitis in relation to the use of inhalation glucocorticoids using the corresponding ATC code (R03BA).

### STATISTICAL ANALYSES

Unconditional logistic regression was used to estimate the odds ratios (ORs) and the corresponding 95% confidence intervals for the association between oral (and inhalation) glucocorticoid use and acute pancreatitis. Owing to the small number of strata relative to the total sample size, it was appropriate to use unconditional logistic regression.<sup>32</sup> The following 3 statistical models were constructed:

- Model 1 (“crude model”) included adjustment for the matching variables only (age, sex, and calendar period).
- Model 2 was additionally adjusted for educational level (categorized as elementary school, secondary school, or university), marital status (married or not married), and underlying comorbidities. The comorbidities were determined by hospitalizations recorded in the Swedish Patient Register since 1987, outpatient care in the Swedish Patient Register since 2001, or a dispensed prescription between July 1, 2005, and the index date. The included comorbidities were as follows: alcohol abuse, identified as having a history of excessive alcohol consumption, alcohol-related disease, or use of medication for treating alcohol dependency (recorded as ICD-9 codes 291, 303, 305A, 357F, 425F, 535D, 571A to 571D, or 980; ICD-10 codes E244, F10, G312, G621, G721, I426, K292, K70, O354, or T51; or ATC code N07BB); chronic obstructive pulmonary

disease (recorded as ICD-9 codes 491-492 or 496; or ICD-10 codes J41-J44); ischemic heart disease (recorded as ICD-9 codes 410-413, 414A, or 414W; or ICD-10 codes I20-I25); obesity or medication for treating obesity (recorded as the ICD-9 code 278A; ICD-10 code E66; or ATC code A08A); peptic ulcer disease (recorded as ICD-9 codes 531-534; or ICD-10 codes K25-K28); diabetes or antidiabetic medication (recorded as ICD-9 code 250; ICD-10 codes E10-E14; or ATC code A10); gallstone disease or cholecystectomy (recorded as ICD-9 codes 574 or 575A-575B; ICD-10 codes K80-K81; or the procedure codes 5350-5359 before 1997 or codes JKA20-JKA21 occurring in 1997 or thereafter [based on the Swedish Classification of Surgical Procedures]). For the analyses of inhalation glucocorticoids, no adjustment was made for chronic obstructive pulmonary disease.

- Model 3 was additionally adjusted for number of drugs (unique 7-digit ATC codes) dispensed within 6 months before the index date (0, 1-2, 3-4, 5-8, and ≥9).

For oral glucocorticoid use, stratified analyses were performed for the type of the drug. The statistical analyses were performed using Stata v.11.2 statistical software (StataCorp).

## RESULTS

### STUDY PARTICIPANTS

A total of 6161 cases with a first episode of acute pancreatitis and 61 637 controls were included in the final analyses. The frequency matching of the control participants resulted in similar age and sex distribution between cases and controls (**Table 1**). The median age of the study population was 63 years, and 55.0% were men. Cases were less likely to be married (43.5%) or have a university education (17.8%) compared with controls (38.7% and 24.0%, respectively). The comorbidities were more common in cases, who also used more concomitant drugs (Table 1). Overall, 10.9% of the cases and 6.9% of the controls had ever received oral glucocorticoid therapy during the study period (**Table 2**). In both cases and controls, the most commonly used glucocorticoid drugs were prednisolone and betamethasone (63.7% and 33.6%, respectively). Inhalation glucocorticoids were used as frequently in cases (5.3%) as in controls (4.1%), and budesonide was the most commonly used type.

### GLUCOCORTICOIDS AND RISK OF ACUTE PANCREATITIS

In current users of oral glucocorticoids, the risk of acute pancreatitis was increased 2-fold (OR, 2.37; 95% CI, 1.99-2.82 [model 1]) compared with nonusers (**Table 3**). This association attenuated after adjustment for confounders (OR, 1.96; 95% CI, 1.63-2.37 [model 2]) and when further adjusting for concomitant drugs (OR, 1.53; 95% CI, 1.27-1.84 [model 3]) but remained statistically significantly increased in all analyses. This risk was not present among recent and former users of oral glucocorticoids. There was no apparent association between the use of inhalation glucocorticoids and the risk of acute pancreatitis compared with nonusers, irrespective of the time since drug dispensation (Table 3).

There was no association between oral glucocorticoid use and acute pancreatitis immediately (0-3 days) after drug dispensation (OR, 1.01; 95% CI, 0.60-1.70 [model 3]) (**Table 4**). However, this risk was 73% (OR, 1.73; 95% CI, 1.31-2.28 [model 3]) increased between 4 and 14 days after drug dispensation and attenuated gradually with time thereafter.

The results were stratified for the 2 most common types of oral glucocorticoids, betamethasone and prednisolone (**Table 5**). The use of betamethasone was associated with a more than 3-fold (OR, 3.53; 95% CI, 1.93-6.46) transient increased risk of acute pancreatitis 4 to 14 days after drug dispensation compared with nonusers. The corresponding risk among users of prednisolone was a 41% (OR, 1.42; 95% CI, 1.03-1.95) increased risk. This risk reached its highest level (OR, 1.70; 95% CI, 1.24-2.34) 15 to 30 days after drug dispensation and attenuated thereafter.

### COMMENT

In the present study, current use of oral glucocorticoids was associated with an increased risk of acute pancreatitis. The results were supported by the early increase in the risk of acute pancreatitis after initiation of the medication, followed by rapid attenuation of the risk to levels comparable with nonusers. There was low probability of confounding by indication on the population level, as illustrated by the lack of association of glucocorticoid use and acute pancreatitis within the first 3 days of drug dispensation.

Strengths of this study include the population-based design, the large sample size, and the complete national coverage on the drug exposure and the outcome. The prospectively collected data counteract recall and selection bias, and the access to information on comorbidities and complete information on concomitant drug use made it possible to perform robust adjustments for potential confounders. However, there are also some methodological limitations. A dispensed prescription does not necessarily imply actual use of the drug. However, such misclassification is not expected to be related to the development of acute pancreatitis and therefore will not dilute the true associations. In addition, the Swedish Prescribed Drug Register does not provide any information on in-hospital use of drugs or the indication for the medication. However, the lack of any association immediately after oral glucocorticoid use and development of acute pancreatitis reduces the likelihood of influence of in-hospital use and confounding by indication. Misclassification of the outcome might be a problem when using register-based data only.<sup>33</sup> Rise in the level of pancreatic amylase has been shown among patients receiving intravenous methylprednisolone.<sup>34</sup> Such rise in the level of pancreatic amylase might be misinterpreted as acute pancreatitis. However, the rise in the pancreatic amylase levels was well below 3 times higher than the upper normal level. Furthermore, as validated by our research group, the diagnosis of acute pancreatitis based on hospital discharge records in Sweden is highly valid.<sup>23</sup> As presented by this study, 603 patient medical records were reviewed, of which 442 (83%) were de-

**Table 2. Glucocorticoid Use Among Cases With Acute Pancreatitis Occurring Between 2006 and 2008 in Sweden and the Frequency-Matched Population-Based Controls**

| Glucocorticoid Use                | No. (%)             |                          |
|-----------------------------------|---------------------|--------------------------|
|                                   | Cases<br>(n = 6161) | Controls<br>(n = 61 637) |
| <b>Oral glucocorticoids</b>       |                     |                          |
| <b>User</b>                       |                     |                          |
| Nonuser                           | 5491 (89.1)         | 57 368 (93.1)            |
| Current, 0-30 d                   | 159 (2.6)           | 682 (1.1)                |
| Recent, 31-180 d                  | 257 (4.2)           | 1544 (2.5)               |
| Former, >6 mo                     | 254 (4.1)           | 2043 (3.3)               |
| <b>Type</b>                       |                     |                          |
| Betametasone, H02AB01             | 225 (33.6)          | 1612 (37.7)              |
| Dexamethasone, H02AB02            | 2 (0.3)             | 1 (0)                    |
| Methylprednisolone, H02AB04       | 1 (0.1)             | 6 (0.2)                  |
| Prednisolone, H02AB06             | 427 (63.7)          | 2609 (61.1)              |
| Prednisone, H02AB07               | 5 (0.8)             | 9 (0.2)                  |
| Hydrocortisone, H02AB09           | 10 (1.5)            | 34 (0.8)                 |
| Cortisone, H02AB10                | 0                   | 1 (0)                    |
| <b>Inhalation glucocorticoids</b> |                     |                          |
| <b>User</b>                       |                     |                          |
| Nonuser                           | 5836 (94.7)         | 59 130 (95.9)            |
| Current, 0-30 d                   | 59 (1.0)            | 465 (0.8)                |
| Recent, 31-180 d                  | 138 (2.2)           | 1114 (1.8)               |
| Former, >6 mo                     | 128 (2.1)           | 928 (1.5)                |
| <b>Type</b>                       |                     |                          |
| Beclomethasone, R03BA01           | 7 (2.2)             | 88 (3.5)                 |
| Budesonide, R03BA02               | 290 (89.2)          | 2140 (85.2)              |
| Fluticasone, R03BA05              | 22 (6.8)            | 154 (6.1)                |
| Mometasone, R03BA                 | 6 (1.8)             | 129 (5.1)                |

defined as definitive acute pancreatitis and 80 cases (15%) were defined as probable acute pancreatitis, leaving only 8 (2%) as wrongly diagnosed. The diagnosis was based on clinical signs in combination with elevated pancreatic amylase 3 times above the upper normal limit and/or specific radiological findings.

Although the analyses were controlled for potential confounders, there were no direct measures on factors such as alcohol abuse,<sup>35</sup> smoking,<sup>36</sup> abdominal adiposity,<sup>37</sup> or dietary factors,<sup>38</sup> which have all been shown to be associated acute pancreatitis. However, chronic diseases, eg, cardiovascular diseases and chronic obstructive pulmonary disease, are more common among individuals with these lifestyle factors. Therefore, analyses were controlled for occurrence of disease history in the Swedish Patient Register and any medication for such diseases as assessed in the Swedish Prescribed Drug Register, in an attempt to reduce residual confounding.

To our knowledge, this is the first epidemiological study that has investigated the relation between glucocorticoid use and acute pancreatitis. Several case studies have reported development of acute pancreatitis linked with oral glucocorticoid use.<sup>11-16</sup> In 2 case reports, acute pancreatitis recurred following readministration of dexamethasone<sup>14</sup> and prednisone.<sup>16</sup> However, more epidemiological studies are warranted before the association can be established.

The mechanism by which oral glucocorticoid treatment might induce acute pancreatitis is unknown and



**Table 3. Odds Ratios (ORs) and 95% Confidence Intervals for the Association Between Oral and Inhalation Glucocorticoid Use and the Risk of Acute Pancreatitis by Time Since Glucocorticoid Use**

| Glucocorticoid Use         | OR (95% CI)          |                      |                      |
|----------------------------|----------------------|----------------------|----------------------|
|                            | Model 1 <sup>a</sup> | Model 2 <sup>b</sup> | Model 3 <sup>c</sup> |
| Oral glucocorticoids       |                      |                      |                      |
| Current, 0-30 d            | 2.37 (1.99-2.82)     | 1.96 (1.63-2.37)     | 1.53 (1.27-1.84)     |
| Recent, 31-180 d           | 1.69 (1.48-1.94)     | 1.44 (1.25-1.66)     | 1.12 (0.97-1.29)     |
| Former, >6 mo              | 1.25 (1.10-1.43)     | 1.12 (0.97-1.29)     | 0.98 (0.85-1.12)     |
| Inhalation glucocorticoids |                      |                      |                      |
| Current, 0-30 d            | 1.27 (0.97-1.67)     | 1.17 (0.88-1.55)     | 0.90 (0.68-1.19)     |
| Recent, 31-180 d           | 1.24 (1.04-1.49)     | 1.12 (0.93-1.35)     | 0.89 (0.74-1.08)     |
| Former, >6 mo              | 1.39 (1.15-1.67)     | 1.29 (1.06-1.57)     | 1.15 (0.95-1.41)     |

<sup>a</sup>Model 1: Accounting for age, sex, and calendar year.

<sup>b</sup>Model 2: Further adjusted for educational level, marital status, alcohol abuse, obesity, hyperlipidemia, diabetes, chronic obstructive pulmonary disease (for the analyses of oral glucocorticoids), ischemic heart disease, peripheral vascular disease, and gallstone disease.

<sup>c</sup>Model 3: Additionally adjusted for concomitant drug use.

**Table 4. Odds Ratios (ORs) and 95% Confidence Intervals for the Association Between Oral Glucocorticoid Use and the Risk of Acute Pancreatitis by Time Since Glucocorticoid Use<sup>a</sup>**

| Time Since Glucocorticoid Use | OR (95% CI)          |                      |                      |
|-------------------------------|----------------------|----------------------|----------------------|
|                               | Model 1 <sup>b</sup> | Model 2 <sup>c</sup> | Model 3 <sup>d</sup> |
| Current                       |                      |                      |                      |
| Immediate, 0-3 d              | 1.75 (1.07-2.84)     | 1.31 (0.78-2.22)     | 1.01 (0.60-1.70)     |
| Early, 4-14 d                 | 2.55 (1.96-3.31)     | 2.22 (1.69-2.94)     | 1.73 (1.31-2.28)     |
| Late, 15-30 d                 | 2.38 (1.83-3.09)     | 1.92 (1.45-2.54)     | 1.49 (1.13-1.97)     |
| Recent                        |                      |                      |                      |
| Early, 31-60 d                | 1.77 (1.40-2.23)     | 1.51 (1.18-1.93)     | 1.18 (0.92-1.51)     |
| Late, 61-180 d                | 1.64 (1.39-1.93)     | 1.38 (1.17-1.64)     | 1.08 (0.91-1.28)     |

<sup>a</sup>Time from glucocorticoid use was categorized in more detail.

<sup>b</sup>Model 1: Accounting for age, sex, and calendar year.

<sup>c</sup>Model 2: Further adjusted for educational level, marital status, alcohol abuse, obesity, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, ischemic heart disease, peripheral vascular disease, and gallstone disease.

<sup>d</sup>Model 3: Additionally adjusted for concomitant drug use.

**Table 5. Odds Ratios (ORs) and 95% Confidence Intervals for the Association Between Oral Glucocorticoid Use and the Risk of Acute Pancreatitis by Time Since Oral Glucocorticoid Use and the Type of Glucocorticoid**

| Time Since Oral Glucocorticoid Use | Type of Oral Glucocorticoid, OR (95% CI) |                           |
|------------------------------------|--|---------------------------|
|                                    | Betamethasone <sup>a</sup>               | Prednisolone <sup>a</sup> |
| Current                            |  |                           |
| Immediate, 0-3 d                   | 0.70 (0.20-2.51)                         | 1.10 (0.62-1.95)          |
| Early, 4-14 d                      | 3.53 (1.93-6.46)                         | 1.42 (1.03-1.95)          |
| Late, 15-30 d                      | 0.94 (0.51-1.73)                         | 1.70 (1.24-2.34)          |
| Recent                             |  |                           |
| Early, 31-60 d                     | 1.10 (0.66-1.84)                         | 1.19 (0.89-1.58)          |
| Late, 61-180 d                     | 0.97 (0.71-1.33)                         | 1.11 (0.90-1.36)          |

<sup>a</sup>The models were adjusted for age, sex, calendar year, educational level, marital status, alcohol abuse, obesity, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, ischemic heart disease, peripheral vascular disease, gallstone disease, and concomitant drug use.

needs to be investigated in future experimental studies. Although immediate nongenomic effects of glucocorticoids have been described,<sup>39</sup> the latency between drug dispensation and development of acute pancreatitis implies that the effect of glucocorticoids is primarily on gene

transcription.<sup>39</sup> The systemic effect of modern inhalation glucocorticoids has been shown to be negligible.<sup>40</sup> In line with this, inhalation glucocorticoids were not found to affect the risk of acute pancreatitis in the present study.

The type of oral glucocorticoid seemed to modify the risk of acute pancreatitis. Betamethasone is more potent than prednisolone in suppressing the endogenous production of cortisol by the adrenal cortex<sup>41</sup> and in promoting gene transcription in target organs.<sup>42</sup> Likewise, the risk of acute pancreatitis early after drug dispensation was stronger in users of betamethasone compared with prednisolone in our study. Unfortunately, the Swedish Prescribed Drug Register does not provide information about drug dosage or the indication of the medication. The potential modifying effect of these factors on the association between oral glucocorticoid use and acute pancreatitis need to be clarified in future studies.

In conclusion, this large and population-based case-control study with valid assessment of exposure, outcome, and covariates indicates that current use of oral glucocorticoids increases the risk of acute pancreatitis. Patients, particularly those at increased risk of acute pancreatitis such as those with high alcohol consumption or gallstones, might benefit from being monitored closely during the first month of oral glucocorticoid use.

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