

## ACETAMINOPHEN, ASPIRIN, AND CHRONIC RENAL FAILURE

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**ABSTRACT**

**Background** Several epidemiologic studies have demonstrated an association between heavy consumption of nonnarcotic analgesics and the occurrence of chronic renal failure, but it is unclear which is the cause and which is the effect.

**Methods** In a nationwide, population-based, case-control study of early-stage chronic renal failure in Sweden, face-to-face interviews were conducted with 926 patients with newly diagnosed renal failure and 998 control subjects, of whom 918 and 980, respectively, had complete data. We used logistic-regression models to estimate the relative risks of disease-specific types of chronic renal failure associated with the use of various analgesics.

**Results** Aspirin and acetaminophen were used regularly by 37 percent and 25 percent, respectively, of the patients with renal failure and by 19 percent and 12 percent, respectively, of the controls. Regular use of either drug in the absence of the other was associated with an increase by a factor of 2.5 in the risk of chronic renal failure from any cause. The relative risks rose with increasing cumulative lifetime doses, rose more consistently with acetaminophen use than with aspirin use, and were increased for most disease-specific types of chronic renal failure. When we disregarded the recent use of analgesics, which could have occurred in response to antecedents of renal disease, the associations were only slightly attenuated.

**Conclusions** Our results are consistent with the existence of exacerbating effects of acetaminophen and aspirin on chronic renal failure. However, we cannot rule out the possibility of bias due to the triggering of analgesic consumption by predisposing conditions. (N Engl J Med 2001;345:1801-8.)

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**A**NALGESIC nephropathy, first attributed to the habitual use of phenacetin-containing analgesics,<sup>1,2</sup> has also been described among users of excessive amounts of analgesic mixtures containing acetaminophen (paracetamol), aspirin, caffeine, or codeine.<sup>3,4</sup> The use of single-ingredient analgesics containing acetaminophen or aspirin has also been linked with chronic renal failure.<sup>5-8</sup>

Previous case-control studies evaluating analgesic use in relation to chronic renal failure have had methodologic shortcomings,<sup>9-12</sup> including a failure to identify patients early enough in the course of their disease to ensure that the disease itself had not led to

a change in the use of analgesics; a failure to specify diagnostic criteria; a failure to adjust for the use of other analgesics; incompleteness of data on exposure; and the use of proxy respondents. To investigate whether acetaminophen and aspirin affect the development of chronic renal failure, we conducted an analysis as part of a larger population-based case-control study in Sweden in which we tried to avoid such shortcomings.

**METHODS****Study Subjects**

The Swedish Population Register<sup>13</sup> provided a well-defined data base of all 5.3 million people born in Sweden, 18 to 74 years of age, who were living in the country during the period from May 20, 1996, through May 31, 1998 (the ascertainment period).

Eligible patients were men whose serum creatinine level exceeded 3.4 mg per deciliter (300  $\mu$ mol per liter) for the first time or women whose serum creatinine level exceeded 2.8 mg per deciliter (250  $\mu$ mol per liter) for the first time. To help us identify patients, medical laboratories provided monthly lists of serum creatinine measurements. Physicians who treated patients with renal disease determined patients' eligibility for the study by reviewing the medical records of patients with elevated serum creatinine levels. Patients with chronic renal failure whose cause was prerenal (e.g., severe heart failure) or postrenal (i.e., obstruction of the urinary tract) and patients who had received kidney transplants were excluded. A second creatinine measurement, three months after the first, was obtained when the chronic nature of the renal failure was uncertain. To allow for day-to-day variation, the thresholds for eligibility with this second measurement were lower (2.8 mg per deciliter for men and 2.3 mg per deciliter [200  $\mu$ mol per liter] for women); patients with lower values were excluded from the study. The diagnosis of underlying disease was based on the results of routine clinical evaluation.

The controls were randomly selected throughout the ascertainment period from the Swedish Population Register<sup>13</sup> and were frequency-matched to the patients with renal failure according to age (in 10-year age groups) and sex. The ethics committees of the participating centers and the Swedish Data Inspection Board approved the study protocol. All study subjects provided oral informed consent before being enrolled.

**Collection of Data**

Subjects received a mailed, self-administered questionnaire and later underwent a face-to-face, computer-assisted interview. The

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interviewers, from Statistics Sweden (a government agency), were unaware of the study hypotheses and were trained to interview subjects in a standardized manner. The interviewers also ensured that the answers to the mailed questionnaire were complete. Interviews with patients with renal failure lasted an average of 80 minutes, and interviews with control subjects lasted an average of 70 minutes.

### Lifetime Exposure to Analgesics

Each subject reviewed a booklet that included color pictures of the packaging of all analgesics containing acetaminophen or phenacetin as well as most other frequently sold nonnarcotic analgesics (78 major brands of the 174 that were on the Swedish market between 1960 and 1996). Subjects reported their lifetime consumption of the brands of drugs that appeared in the booklet as well as their lifetime consumption of aspirin and any other analgesics. Information about the consumption of brand-name drugs was converted to amounts of generic drug ingredients.

Regular use of an analgesic was defined as use at least twice a week for two months. All subjects were asked to report their age during each period of regular use, the duration of regular use, and the dose used during that period. Subjects whose cumulative lifetime dose exceeded 20 tablets of an analgesic but who did not use it regularly were classified as sporadic users. Nonusers were defined as those who reported taking a total of fewer than 20 tablets during their lifetime. Subjects also answered questions about changes in their pattern of use and in the patterns of aches and pains prompting the use of analgesics.

### Statistical Analysis

We used unconditional logistic regression to model odds ratios and 95 percent confidence intervals as measures of the association between analgesic use and chronic renal failure while controlling for potential confounders. Nonusers of a given analgesic served as the reference category for all comparisons related to that analgesic. We initially considered marital status; body-mass index (the weight in kilograms divided by the square of the height in meters); consumption of caffeine, alcohol, and illicit drugs; and the presence of hypertension, angina, claudication, kidney stones, or gout as potential confounders. The final model was based on the scientific literature and the statistical significance of explanatory variables in the model, as assessed by the likelihood-ratio test.<sup>14</sup> The model contained terms for sex, age (in 10-year age groups), smoking status (lifetime use of <100 or ≥100 cigarettes), level of education (≤9 years, 10 to 12 years, or ≥13 years), regular use of other analgesics, and when applicable, a term for the interaction between acetaminophen use and aspirin use. We excluded from the model 23 patients with renal failure (2.5 percent) and 29 control subjects (2.9 percent) because of missing information for one or more covariates.

To assess the dose-response relation, we performed tests for trend on groups of ordinal variables by assigning each group a score equal to the mean value, fitting the resulting scores into the model,<sup>15</sup> and assessing statistical significance by the likelihood-ratio test.

We examined the associations between analgesic use and overall chronic renal failure and between analgesic use and disease-specific types of chronic renal failure. Results for both sexes are combined, since associations for men did not differ materially from those for women. To exclude the possibility that analgesic use was prompted by conditions that were precursors to renal failure, we performed analyses in which reported use during the 5 to 10 years before the interview was disregarded.

## RESULTS

We identified 1189 eligible patients of whom 69 (6 percent) died shortly after they were determined to be eligible for the study. The remaining 1120 patients were approached, and 926 participated. A total of 918 patients provided information on exposure to analgesics (77 percent of the 1189 eligible

patients). A total of 111 patients declined to participate, and 83 had severe diseases that precluded participation. Of 1330 eligible control subjects, 998 participated. A total of 980 controls provided information on exposure to analgesics (74 percent of the eligible controls); 221 declined to participate, 56 could not be reached, and 55 had diseases that precluded participation. Half of the patients with chronic renal failure were interviewed within 1 month of inclusion, and 95 percent were interviewed within 12 months.

### Characteristics of the Study Subjects

Sixty-five percent of the subjects were men. Among both patients and control subjects, the mean age of the men at the time of the interview was 58 years, and the mean age of the women was 57 years. The patients with chronic renal failure lived alone more often than the control subjects did, had fewer years of education, were somewhat more likely to smoke, and were less likely to drink alcohol.

The distribution of patients with chronic renal failure according to underlying disease is shown in Table 1. The median serum creatinine levels were 3.8 mg per deciliter (336 μmol per liter) among men and 3.2 mg per deciliter (281 μmol per liter) among women. The estimated glomerular filtration rate<sup>16</sup> ranged from 2 to 53 ml per minute. The median values for men and women were 22 and 19 ml per minute, respectively.

Overall, 86 percent of the patients and 75 percent of the control subjects reported the use of nonnarcotic analgesics. Fifty-one percent of the patients and 29 percent of the control subjects had used at least one analgesic regularly. Among regular users, the mean and median cumulative lifetime doses differed only slightly between the patients and the control subjects (Table 2). Aspirin and acetaminophen were used regularly by 37 percent and 25 percent, respectively, of the patients with renal failure and by 19 percent and 12 percent, respectively, of the controls. A total of 22 percent of male patients and 10 percent of male controls reported regular acetaminophen use, and 38 percent of male patients and 20 percent of male controls reported regular aspirin use. Thirty-two percent of female patients and 16 percent of female controls reported regular acetaminophen use, and 36 percent of female patients and 17 percent of female controls reported regular aspirin use.

### Risk of Chronic Renal Failure

#### *Acetaminophen Use in the Absence of Regular Aspirin Use*

Among subjects who did not use aspirin regularly, the regular use of acetaminophen was associated with a risk of chronic renal failure that was 2.5 times as high as that for nonusers of acetaminophen. The risk increased with an increasing cumulative lifetime dose (P for trend <0.001) (Table 3). The average dose

**TABLE 1.** DIAGNOSES AMONG 926 PATIENTS WITH CHRONIC RENAL FAILURE.

DIAGNOSIS	No. OF PATIENTS (%)*
Diabetic nephropathy	286 (30.9)
Glomerulonephritis	222 (24.0)
IgA nephropathy	63 (28.4)
No renal biopsy	54 (24.3)
Unclassified on biopsy	42 (18.9)
Proliferative	26 (11.7)
Focal segmental sclerosis	16 (7.2)
Crescentic glomerulonephritis	12 (5.4)
Other	9 (4.1)
Nephrosclerosis	139 (15.0)
Benign hypertension	125 (89.9)
Malignant hypertension	8 (5.8)
Other	6 (4.3)
Hereditary disease	98 (10.6)
Polycystic kidney disease	83 (84.7)
Other	10 (10.2)
Agensis or dysgenesis	5 (5.1)
Systemic disease or vasculitis	82 (8.9)
Amyloidosis	20 (24.4)
Wegener's granulomatosis	12 (14.6)
Rheumatoid arthritis	11 (13.4)
Multiple myeloma	11 (13.4)
Systemic lupus erythematosus	9 (11.0)
Hemolytic-uremic syndrome	8 (9.8)
Other vasculitis	6 (7.3)
Other systemic disease	5 (6.1)
Other renal disease	99 (10.7)
Unknown renal disease	44 (44.4)
Interstitial nephritis	27 (27.3)
Chronic pyelonephritis	21 (21.2)
Other	6 (6.1)
Phenacetin nephropathy	1 (1.0)

\*Percentages of patients with subcategories of each general diagnosis are calculated on the basis of the number of patients with that general diagnosis.

used during periods of regular acetaminophen use also correlated with risk ( $P$  for trend  $<0.001$ ) so that those who took 500 g or more per year ( $\geq 1.4$  g per day) during periods of regular use had an odds ratio for chronic renal failure of 5.3 (95 percent confidence interval, 1.8 to 15.1). The duration of use was unrelated to risk (data not shown). The odds ratios associated with regular use were greater than 1.0 for all types of renal failure (Table 4), but they were significant only for renal failure classified as diabetic nephropathy and that associated with systemic disease or vasculitis. Dose-related trends in risk were significant for all diagnoses except glomerulonephritis and nephrosclerosis (data not shown).

#### **Aspirin Use in the Absence of Regular Acetaminophen Use**

Among subjects who did not use acetaminophen regularly, the regular use of aspirin was associated with a risk of chronic renal failure that was 2.5 times as high as that for nonusers of aspirin (Table 3). This risk increased significantly with an increasing cumu-

lative lifetime dose of aspirin ( $P$  for trend = 0.01) and with an increasing average dose during periods of regular use ( $P$  for trend = 0.004), but not with an increasing duration of use. Among those with an average intake of 500 g or more of aspirin per year during periods of regular use, the odds ratio for chronic renal failure was 3.3 (95 percent confidence interval, 1.4 to 8.0). The strongest association was found between aspirin use and chronic renal failure classified as associated with "other renal disease," but the odds ratio was greater than 2.0 for all types of chronic renal failure except that linked to systemic disease or vasculitis (Table 4). The dose-related trends in risk, however, were nonsignificant for all types except glomerulonephritis ( $P=0.008$ ) (data not shown).

#### **Acetaminophen Use in Addition to Aspirin Use**

The odds ratio for chronic renal failure among regular users of both acetaminophen and aspirin was 2.2 (95 percent confidence interval, 1.4 to 3.5) when regular aspirin users served as the reference group. The trend toward greater risk with an increasing cumulative lifetime dose of acetaminophen was statistically significant ( $P=0.03$ ), with a risk that was 2.4 times as high (95 percent confidence interval, 1.4 to 4.4) for subjects who had consumed a total of more than 500 g of acetaminophen than for those who had used aspirin only. The types of chronic renal failure most strongly associated with regular use of acetaminophen in addition to aspirin were renal failure linked to diabetes (odds ratio, 2.8; 95 percent confidence interval, 1.5 to 5.4) and renal failure linked to systemic disease or vasculitis (odds ratio, 5.1; 95 percent confidence interval, 1.5 to 17.6), but estimates of relative risks of approximately 2.0 were found for all types of chronic renal failure (data not shown).

#### **Aspirin Use in Addition to Acetaminophen Use**

The odds ratio for chronic renal failure was 1.6 (95 percent confidence interval, 0.9 to 2.7) among regular users of both aspirin and acetaminophen as compared with users of acetaminophen only. The trend toward greater risk with an increasing cumulative lifetime dose of aspirin was significant ( $P=0.02$ ). The pattern of associations between aspirin use and specific types of chronic renal failure among users of acetaminophen was similar to that found among aspirin users without regular acetaminophen use, but there were lower point estimates for the risk associated with diabetic nephropathy (odds ratio, 1.7; 95 percent confidence interval, 0.8 to 3.4) and that associated with chronic renal failure classified as other renal disease (odds ratio, 1.4; 95 percent confidence interval, 0.5 to 3.7).

#### **Use of Other Analgesics**

More patients than control subjects used other nonnarcotic analgesics as well as aspirin and aceta-

**TABLE 2. LIFETIME CONSUMPTION OF ANALGESICS.\***

VARIABLE	PATIENTS WITH CHRONIC RENAL FAILURE (N=926)	CONTROL SUBJECTS (N=998)	P VALUE†
<b>Acetaminophen use</b>			
Subjects without regular aspirin use			
Never used — no. (%)	230 (24.8)	376 (37.7)	
Ever used — no. (%)	345 (37.3)	413 (41.4)	0.005
Use or used regularly — no. (%)	105 (11.3)	71 (7.1)	<0.001
Cumulative dose — g			
Mean	2142	1575	0.08
Median	525	275	
Range	6–34,969	9–35,416	
Subjects with any regular aspirin use			
Never used — no. (%)	101 (10.9)	83 (8.3)	
Ever used — no. (%)	242 (26.1)	108 (10.8)	0.001
Use or used regularly — no. (%)	130 (14.0)	50 (5.0)	<0.001
Cumulative dose — g			
Mean	3223	2899	0.42
Median	722	496	
Range	9–35,676	34–42,224	
<b>Aspirin use</b>			
Subjects without regular acetaminophen use			
Never used — no. (%)	224 (24.2)	363 (36.4)	
Ever used — no. (%)	459 (49.6)	496 (49.7)	<0.001
Use or used regularly — no. (%)	213 (23.0)	141 (14.1)	<0.001
Cumulative dose — g			
Mean	1649	1805	0.68
Median	191	215	
Range	6–42,927	5–26,567	
Subjects with any regular acetaminophen use			
Never used — no. (%)	59 (6.4)	35 (3.5)	
Ever used — no. (%)	176 (19.0)	86 (8.6)	0.44
Use or used regularly — no. (%)	130 (14.0)	50 (5.0)	0.11
Cumulative dose — g			
Mean	3544	1846	0.12
Median	684	277	
Range	4–38,220	9–25,714	
<b>Propoxyphene — no. (%)</b>			
Never used	695 (75.1)	812 (81.4)	
Ever used	223 (24.1)	168 (16.8)	<0.001
Use or used regularly	122 (13.2)	64 (6.4)	<0.001
<b>Nonaspirin NSAIDs — no. (%)</b>			
Never used	724 (78.2)	793 (79.5)	
Ever used	194 (21.0)	187 (18.7)	0.27
Use or used regularly	106 (11.4)	77 (7.7)	0.01
<b>Codeine — no. (%)</b>			
Never used	730 (78.8)	844 (84.6)	
Ever used	188 (20.3)	136 (13.6)	<0.001
Use or used regularly	66 (7.1)	37 (3.7)	<0.001
<b>Pyrazolones — no. (%)</b>			
Never used	827 (89.3)	916 (91.8)	
Ever used	91 (9.8)	64 (6.4)	0.008
Use or used regularly	46 (5.0)	23 (2.3)	0.002
<b>Phenacetin — no. (%)</b>			
Never used	901 (97.3)	963 (96.5)	
Ever used	17 (1.8)	17 (1.7)	0.85
Use or used regularly	4 (0.4)	6 (0.6)	0.60

\*Data on consumption of analgesics were missing for 8 patients and 18 controls. NSAID denotes nonsteroidal antiinflammatory drug.

†P values for the comparisons between subjects who had ever used the drug and those who had never used it and for the comparisons between subjects who used or had used the drug regularly and those who had never used it were calculated by the chi-square test. P values for the comparisons of the mean cumulative doses used by regular users in the two groups were calculated by the Wilcoxon two-sample test.

**TABLE 3.** ODDS RATIOS FOR CHRONIC RENAL FAILURE ASSOCIATED WITH THE LIFETIME USE OF EITHER ACETAMINOPHEN OR ASPIRIN AMONG SUBJECTS WHO DID NOT USE THE OTHER ANALGESIC REGULARLY.\*

VARIABLE	ACETAMINOPHEN USE	ASPIRIN USE
	odds ratio (95% confidence interval)	
Never used	1.0	1.0
Ever used	1.3 (1.0–1.6)	1.5 (1.2–1.8)
Use or used regularly	2.5 (1.7–3.6)	2.5 (1.9–3.3)
Cumulative dose		
1–99 g	1.2 (0.9–1.5)	1.4 (1.1–1.7)
100–499 g	1.3 (0.9–1.8)	1.6 (1.2–2.1)
≥500 g	3.3 (2.0–5.5)	1.9 (1.3–2.9)

\*The odds ratios have been adjusted for age, sex, level of education, smoking status, use or nonuse of other analgesics, and the interaction between aspirin use and acetaminophen use.  $P < 0.001$  for the trend toward greater risk with increasing cumulative doses of acetaminophen;  $P = 0.01$  for the trend toward greater risk with increasing cumulative doses of aspirin. Regular use was defined as the use of at least two tablets per week for a period of two months or longer.

minophen (Table 2), but after adjustment for acetaminophen use and aspirin use, no associations between the use of these other drugs and the risk of chronic renal failure remained. The adjusted odds ratios associated with the regular use of propoxyphene, nonsteroidal antiinflammatory drugs other than aspirin, codeine, and pyrazolones were 1.0, 1.0, 0.9, and 1.3, respectively.

#### Self-Reported Pain

More patients than control subjects reported having headaches (12 percent vs. 7 percent), joint pain (8 percent vs. 5 percent), and toothaches (4 percent vs. 2 percent). Headaches occurred most often among patients with hereditary renal disease (20 percent), “other” renal disease (17 percent), diabetic nephropathy (12 percent), and systemic disease or vasculitis (15 percent). As expected, many patients in the last category (30 percent) also reported joint pain. No clear relation was found between the frequency of self-reported pain or any quantitative measure of analgesic use and the glomerular filtration rate in our patients (data not shown).

#### Analyses Based on Different Periods of Use

Symptoms associated with renal disease may prompt the use of analgesics. Indeed, a greater proportion of patients than of control subjects had begun to use analgesics regularly (35 percent vs. 25 percent for acetaminophen and 37 percent vs. 28 percent for aspirin) within five years before the interview. We therefore performed additional analyses in which we disregarded the most recent exposure. The odds ratios

**TABLE 4.** ODDS RATIOS FOR CHRONIC RENAL FAILURE ASSOCIATED WITH ISOLATED REGULAR USE OF ACETAMINOPHEN OR ASPIRIN ACCORDING TO THE TYPE OF UNDERLYING RENAL DISEASE.\*

UNDERLYING DISEASE	ACETAMINOPHEN USE	ASPIRIN USE
	ODDS RATIO (95% CI)†	ODDS RATIO (95% CI)‡
Diabetic nephropathy	3.6 (2.1–6.0)	2.9 (1.9–4.5)
Glomerulonephritis	1.6 (0.9–3.0)	2.6 (1.4–4.8)
Nephrosclerosis	1.7 (0.8–3.7)	2.1 (1.3–3.5)
Hereditary renal disease	2.2 (0.8–5.9)	3.1 (1.6–6.0)
Systemic disease or vasculitis	2.8 (1.2–6.5)	1.1 (0.4–2.8)
Other renal disease	2.1 (0.9–4.6)	3.7 (1.8–7.7)

\*The odds ratios have been adjusted for age, sex, level of education, smoking status, use or nonuse of other analgesics, and the interaction between aspirin use and acetaminophen use. Regular use was defined as the use of at least two tablets per week for a period of two months or longer. CI denotes confidence interval.

†The reference group was nonusers of acetaminophen without regular aspirin use.

‡The reference group was nonusers of aspirin without regular acetaminophen use.

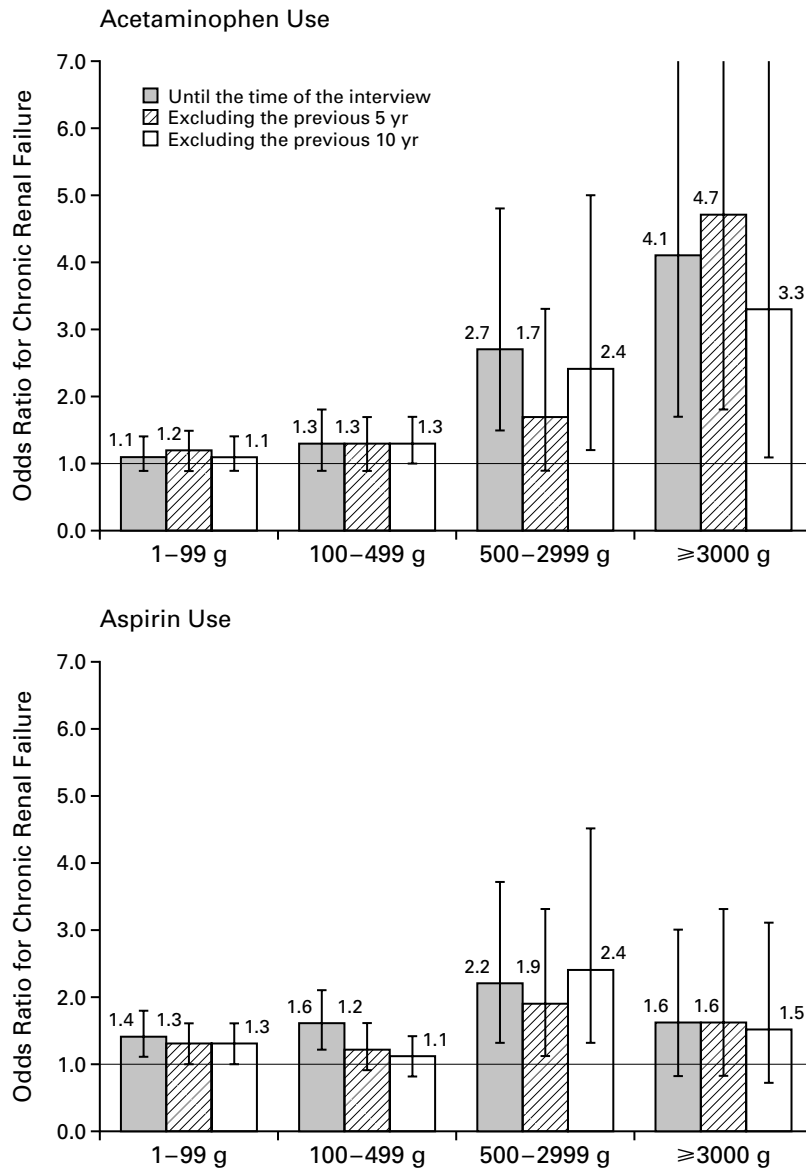
for chronic renal failure associated with either acetaminophen use or aspirin use were only slightly attenuated in these analyses (Fig. 1). The attenuation among subjects using both analgesics was moderate (20 percent) and was similar for acetaminophen and aspirin (data not shown).

#### Analyses Restricted to Subjects with Diabetes

To separate the effects of drugs from the effects of the underlying disease, we analyzed the association between analgesic use and the risk of renal failure among 67 control subjects with diabetes and 324 patients with chronic renal failure due to diabetes. The odds ratio associated with regular acetaminophen use in the absence of regular aspirin use was 4.0 (95 percent confidence interval, 1.0 to 16.1) and that in the presence of regular aspirin use was 2.4 (95 percent confidence interval, 0.7 to 8.1). The odds ratios associated with regular aspirin use in the absence and presence of regular acetaminophen use were 1.4 (95 percent confidence interval, 0.7 to 3.1) and 0.6 (95 percent confidence interval, 0.1 to 3.2), respectively.

## DISCUSSION

In this study, as in others,<sup>6,8</sup> regular use of either acetaminophen or aspirin or of both was associated in a dose-dependent manner with an increased risk of chronic renal failure. The odds ratios among reg-



**Figure 1.** Odds Ratios (and 95 Percent Confidence Intervals) for Chronic Renal Failure According to the Cumulative Lifetime Dose of Acetaminophen or Aspirin in Analyses Based on Different Periods of Exposure.

The odds ratios are for comparisons with nonusers of both classes of analgesics.

ular users exceeded 1.0 for all types of chronic renal failure, albeit not always significantly. The regular use of other nonnarcotic analgesics was not associated with an increased risk of chronic renal failure in general.

The study base was well defined, and objective diagnostic criteria were used to identify renal failure. In contrast to previous case-control studies,<sup>7,8,17-20</sup> our study enrolled patients with chronic renal failure relatively early in the course of their disease, so the re-

ported extent of exposure to analgesics is more likely to pertain to a causally relevant period. Photographs of products and their packaging were used to improve the reliability of subjects' recall.<sup>21</sup>

A recent study conducted in the Physicians' Health Study cohort revealed no positive association between analgesic use and the risk of moderate renal dysfunction (serum creatinine concentration, >1.5 mg per deciliter [133 μmol per liter]); in fact, acetaminophen use appeared to be slightly protective.<sup>22</sup> That

study may have reduced the possibility of recall bias by ascertaining information about exposure to analgesics before renal dysfunction was diagnosed. Nonetheless, its results must be interpreted cautiously. The level of exposure to analgesics was ascertained retrospectively in that study, after a follow-up period of 14 years, and serum creatinine testing was performed no longer than 1 to 2 years after the assessment of exposure and involved only half of the initial cohort. We used considerably higher cutoff levels of serum creatinine to define renal disease. Preexisting renal or systemic disease was present in all our patients, suggesting that such disease has an important role in causing analgesic-associated chronic renal failure. Subjects with such conditions were unlikely to be recruited into the Physicians' Health Study or to remain in that study until the end of the follow-up period. Although the Physicians' Health Study may have had insufficient power to detect a true association between the heavy use of analgesics and the risk of clinically significant renal failure,<sup>23</sup> it supports the finding that persons without preexisting disease who use analgesics have only a small risk of end-stage renal disease.

We found no indications that the severity of the renal failure affects analgesic consumption. Symptoms of diseases that predispose patients to renal failure may, however, lead to an increased use of analgesics, thus possibly introducing a protopathic (reverse causality) bias<sup>24</sup> into our assessment of the effects of analgesics. Overall, however, the associations between the use of analgesics and the risk of chronic renal failure were not consistently stronger among subjects with underlying diseases causing frequent aches and pains. In addition, analyses restricted to subjects with diabetes produced risks associated with acetaminophen use that were similar in magnitude to those found in analyses of all patients and control subjects. Hence, although protopathic bias cannot be ruled out, its effect is likely to be small.

A strength of our study is the analyses based on different periods of exposure, in which we tried to separate analgesic use of causal importance from that possibly triggered by the renal disease or its prodromal symptoms. These analyses resulted in only minor reductions in the estimates of relative risk. Such analyses must, however, be interpreted cautiously,<sup>25-27</sup> particularly when any potential latency time between the exposure to analgesics and chronic renal failure is unknown.

Acetaminophen use and aspirin use had similar effects on the overall risk of chronic renal failure. This lack of specificity might suggest noncausal associations. However, in experiments in animals, both analgesics have induced irreversible renal injury.<sup>28,29</sup> In addition, increased risks were not observed with analgesics other than acetaminophen and aspirin.

The possibility of detection bias must be consid-

ered. Patients with diabetes or systemic disease, particularly those with substantial pain, would most likely undergo serum creatinine tests more often than healthy controls. We set the threshold for the serum creatinine concentration at a level at which renal failure is clinically significant and typically leads to referral to a nephrologist; this case definition helps to allay any concern about detection bias.

Blinding the interviewers to the case or control status of subjects was deemed impossible. This weakness constitutes a possible source of bias. However, the interview covered exposure to a multitude of substances, and interviewers were unaware of the study hypotheses. Moreover, they were trained to follow the questionnaire carefully in a standardized manner regardless of the subject's case or control status. The somewhat longer interview time for the patients with chronic renal failure than for the controls may be explained by their generally poorer condition, their more complicated medical history, and their greater use of drugs. Therefore, we do not believe that information bias has affected our results in any important way.

Although our study was not designed to confirm or refute the existence of a specific disease entity attributed exclusively to the use of analgesics, it should be noted that analgesic nephropathy, as defined by Elseviers,<sup>30</sup> was not observed in the population we studied. Misdiagnosed cases, if there were any, were likely to be assigned to the "other renal disease" category.<sup>31</sup> However, the associations with acetaminophen use and aspirin use did not stand out as exceptionally strong among the subjects in this category.

In conclusion, our results are consistent with exacerbating effects of acetaminophen and aspirin on chronic renal failure, practically regardless of accompanying disease. However, it is impossible to rule out bias caused by the consumption of these analgesics for symptoms of the conditions that predisposed patients to renal failure.

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