Analgesic Use and Risk of Subsequent Hypertension in Apparently Healthy Men

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Background: Prospective studies have suggested that women who self-select for use of analgesics have an increased risk of hypertension, but data in men are sparse. We tested whether apparently healthy male physicians who reported analgesic use had an increased risk of subsequent hypertension.

Methods: Prospective cohort study of 8229 participants in the Physicians' Health Study who were free of hypertension and completed detailed analgesic questionnaires. Hypertension was defined as self-reported blood pressure of 140/90 mm Hg or higher or use of antihypertensive medication.

Results: After a mean of 5.8 years' follow-up, 2234 men (27.2%) reported subsequent hypertension. We categorized the cumulative analgesic use in quintiles. After adjusting for potential confounders, men in the highest quintile had no statistically significant increased risk of hypertension (hazard ratio, 1.12; 95% confidence interval, 0.97-1.31) when compared with those in the lowest quintile. In subgroup analyses, we evaluated the cumulative use of nonsteroidal anti-inflammatory drugs, acetaminophen, and aspirin. Compared with never users, men who reported consuming at least 2500 pills had hazard ratios of 1.05 (95% confidence interval, 0.89-1.24) for nonsteroidal anti-inflammatory drugs, 1.08 (95% confidence interval, 0.87-1.34) for acetaminophen, and 1.16 (95% confidence interval, 0.92-1.48) for aspirin. The results were similar for analgesic use in the year preceding the analgesic questionnaire.

Conclusion: In this large cohort, apparently healthy male physicians who self-selected for analgesic use had no significantly increased risk of subsequent hypertension, although a small to moderately increased risk cannot be excluded in observational studies.

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Hypertension is a major independent risk factor for cardiovascular disease, including stroke and myocardial infarction, as well as for heart failure and renal disease.1 In the United States, obesity is perhaps the major contributor to increasing rates of hypertension.2 Nonetheless, other potentially modifiable determinants merit consideration. The role of prostaglandins (PGs) in blood pressure regulation has been well studied.3 The imbalances between vasodilator and vasoconstrictor PGs may affect blood pressure.4 On the partial basis of their ability to inhibit PG production, nonsteroidal anti-inflammatory drugs (NSAIDs) have been postulated to increase blood pressure.5

Two meta-analyses6,7 of randomized trials of small sample size and short duration indicate that NSAIDs but not aspirin increase blood pressure. In both analyses, the overall effect sizes were small and reached statistical significance only among the subgroups of patients with hypertension or who took antihypertensive drugs. One case-control study8 showed that individuals prescribed NSAIDs were more likely to initiate antihypertensive drug therapy when compared with those not prescribed these drugs. Two large prospective cohort studies9,10 in women evaluated whether self-selection for analgesic use was associated with an increased risk of hypertension. One study9 showed increased risks of hypertension among users of NSAIDs and acetaminophen but not aspirin, and the other10 showed increased risks for users of NSAIDs, acetaminophen, and aspirin.

To our knowledge, no large-scale prospective cohort studies have tested this hypothesis in men. We analyzed prospective data among more than 8000 apparently healthy male physicians with no history of hypertension.

Methods

Study Population

The study population was a subgroup from the Physicians’ Health Study (PHS), a randomized trial designed to test the benefits and risks of aspirin (325 mg every other day) or beta carotene (30 mg every other day) in the primary

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prevention of cardiovascular disease and cancer among 22,071 apparently healthy men aged 40 to 84 years at baseline in 1982. Participants had no indication or contraindication to the use of aspirin or other NSAIDs at entry. The design, methods, and results of the PHS have been described previously.\textsuperscript{11,12} Post-trial follow-up has continued,\textsuperscript{13} and this analysis includes data through March 31, 2004.

Baseline information was collected by mailed questionnaires that included anthropometric, demographic, clinical, and lifestyle variables. Twice in the first year and yearly thereafter, follow-up questionnaires were sent out asking about compliance with trial medications; development of adverse effects; new-onset clinical cardiovascular disease, cancer, or other diseases; and changes in risk factors.

**ASSESSMENT OF ANALGESIC USE**

In 1996, participants completed detailed questionnaires about analgesic use from baseline to the 14-year follow-up. Details regarding the questionnaire and the results of a validation study\textsuperscript{14} have been published previously. Participants were asked if they had taken analgesics 12 or more times since enrolling in the PHS. Those answering yes were asked how many days per month and how many pills per day these medications were taken on average in the preceding year. The participants were also asked if this pattern had been constant since enrollment. Those answering no were asked to record the number of years for which this had been the pattern of use and to describe their earlier use pattern. Aspirin use was determined from the compliance data reported on each participant’s annual questionnaire.

The number of pills per year was recorded, and the cumulative number of pills during the 14-year period was calculated. We categorized cumulative analgesic use in quintiles. For use of NSAIDs, acetaminophen, and aspirin, we used the following 4 categories to be consistent with previous studies\textsuperscript{14,15}: never use (<12 pills), 12 to 1499 pills, 1500 to 2499 pills, and 2500 pills or more pills during the 14-year period.

To evaluate more current use and risk of subsequent hypertension, we categorized the total number of pills used in the last 12 months preceding the analgesic questionnaire in quintiles. We further categorized the number of pills of specific analgesics as 0, 1 to 14, 15 to 60, and 61 pills or more.

**ASSESSMENT OF HYPERTENSION**

On the baseline, 24-month, 84-month, 180-month, and 216-month questionnaires, participants reported their systolic and diastolic blood pressures. On the baseline questionnaire, the 84-month questionnaire, and yearly thereafter, participants were asked whether they had initiated antihypertensive medications. We defined hypertension during follow-up according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines\textsuperscript{56}: a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or any use of antihypertensive medications.

**STATISTICAL ANALYSIS**

In 1996, 19,390 participants returned the analgesic questionnaire. Of those, we excluded 11,161 participants, of whom 11,134 had missing information on hypertension or developed cardiovascular events and 27 reported renal disease before completion of the questionnaire, leaving 8229 participants without hypertension at the beginning of follow-up. To estimate the relationships of cumulative analgesic use and use in the year preceding the 1996 analgesic assessment with risk of subsequent hypertension, we used the Cox proportional hazards model.\textsuperscript{17} We tested the proportional hazards assumption and found no violation. We censored participants if they reported cardiovascular events before reporting hypertension because such an event might have differentially affected blood pressure and analgesic use. We calculated age- and multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs). We included missing information for each of the analgesic classes as a separate category in the models. We used the most recent information for any of the covariates before the time point of the analgesic questionnaire and 3 multivariable models. Model 1 controlled for age (as an exponential term), body mass index (in quintiles), and other analgesic categories (except for the model including cumulative analgesic use). Model 2 controlled for all variables in model 1 plus indicators of chronic pain, including any report of arthritis, headache, or migraine, as well as headache and migraine frequency (≥6 vs <6 times).

Model 3 controlled for all variables in model 2 plus potential risk factors for hypertension, including alcohol consumption (≤1 drink/wk; 2-6 drinks/wk; ≥1 drink/d), exercise (<1/wk; 1-4/wk; ≥5/wk), smoking (never, past, current), history of diabetes mellitus, history of high cholesterol or lipid-lowering treatment, parental history of premature myocardial infarction, and systolic and diastolic blood pressures. We calculated P values for trend across cumulative analgesic use categories, excluding the missing information category.

We evaluated whether there was effect modification by age by performing stratified analyses among participants 59 years or younger, 60 to 69 years, or 70 years or older. The use of body mass index as a continuous variable and different classifications for alcohol consumption, exercise, and headache frequency yielded similar results.

**RESULTS**

The age range of the 8229 apparently healthy men was 53 to 97 years (mean±SD age, 63.9±7.7 years). After a mean of 5.8 years’ follow-up (47,794 person-years), 2234 men (27.2%) reported subsequent hypertension. In Table 1, we summarize age-adjusted characteristics of participants according to cumulative analgesic use categories. Men who consumed 2500 pills or more of any of the analgesics were heavier and reported more headaches or migraine headaches compared with participants who reported use of fewer than 12 pills. Participants in the highest intake category of NSAIDs or acetaminophen were more likely to report arthritis, whereas participants in the highest intake category of NSAIDs and aspirin were more likely to report a parental history of premature myocardial infarction.

Table 2 gives the age- and multivariable-adjusted HRs and their 95% CIs for new-onset hypertension according to cumulative analgesic use categories. After adjustment for age, cumulative analgesic use was statistically significantly associated with risk of subsequent hypertension. Men in the highest quintile of cumulative analgesic use had an age-adjusted HR of 1.27 (95% CI, 1.10-1.47) when compared with those in the lowest quintile (P for trend = .008). The HRs of the specific analgesics ranged from 1.18 (95% CI, 1.00-1.39) for NSAIDs to 1.23 (95% CI, 0.98-1.56) for aspirin.

The age-adjusted association between cumulative analgesic use and subsequent hypertension was reduced to
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonsteroidal Anti-inflammatory Drug Use</th>
<th>Acetaminophen Use</th>
<th>Aspirin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12-1499</td>
<td>1500-2499</td>
<td>≥2500</td>
</tr>
<tr>
<td>No. of physicians</td>
<td>4188</td>
<td>2631</td>
<td>347</td>
</tr>
<tr>
<td>Age, mean ± SE, y</td>
<td>64.0 ± 0.02</td>
<td>63.9 ± 0.03</td>
<td>63.9 ± 0.08</td>
</tr>
<tr>
<td>Body mass index, mean ± SE*</td>
<td>25.0 ± 0.05</td>
<td>25.3 ± 0.06</td>
<td>25.3 ± 0.16</td>
</tr>
<tr>
<td>Body mass index ≥30†</td>
<td>5.4</td>
<td>6.6</td>
<td>7.8</td>
</tr>
<tr>
<td>Physical activity sessions per week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>18.8</td>
<td>17.3</td>
<td>15.6</td>
</tr>
<tr>
<td>1-4</td>
<td>62.3</td>
<td>66.5</td>
<td>69.5</td>
</tr>
<tr>
<td>≥5</td>
<td>18.9</td>
<td>16.2</td>
<td>14.9</td>
</tr>
<tr>
<td>Alcoholic drinks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1/wk</td>
<td>37.7</td>
<td>32.5</td>
<td>30.5</td>
</tr>
<tr>
<td>2-6/wk</td>
<td>48.7</td>
<td>51.7</td>
<td>53.7</td>
</tr>
<tr>
<td>≥1/d</td>
<td>13.6</td>
<td>15.8</td>
<td>15.8</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>54.4</td>
<td>52.8</td>
<td>53.1</td>
</tr>
<tr>
<td>Past</td>
<td>41.6</td>
<td>43.7</td>
<td>44.1</td>
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<tr>
<td>Current</td>
<td>4.0</td>
<td>3.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.9</td>
<td>1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>21.4</td>
<td>21.1</td>
<td>25.4</td>
</tr>
<tr>
<td>Parental history of premature myocardial infarction</td>
<td>14.8</td>
<td>23.3</td>
<td>30.7</td>
</tr>
<tr>
<td>Arthritis</td>
<td>46.2</td>
<td>57.7</td>
<td>58.0</td>
</tr>
<tr>
<td>Migraine</td>
<td>11.3</td>
<td>13.5</td>
<td>12.5</td>
</tr>
</tbody>
</table>

*Data are given as percentages unless otherwise indicated and are adjusted for age in 5-year increments.
†Calculated as weight in kilograms divided by the square of height in meters.
In this cohort of 8229 apparently healthy men free of hypertension at the start of follow-up, those who self-selected for cumulative analgesic use of NSAIDs, acetaminophen, or aspirin had no significantly increased risk of subsequent hypertension after adjustments for all potential confounding variables. Our data also showed a lack of association between apparently healthy men who self-selected for recent analgesic use in the preceding year of the assessment and risk of subsequent hypertension. For specific analgesic use, the finding appeared to be null for NSAIDs and aspirin but raised the possibility of a small to moderate increase for acetaminophen.

Table 2. Hazard Ratios for Subsequent Hypertension According to Cumulative Analgesic Use*

<table>
<thead>
<tr>
<th>Cumulative Analgesic Use, No. of Pills</th>
<th>No. of Physicians (No. With Hypertension)</th>
<th>Age-Adjusted†</th>
<th>Model 1‡</th>
<th>Model 2§</th>
<th>Model 3ǁ</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1401</td>
<td>1309 (326)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1402-2139</td>
<td>1313 (370)</td>
<td>1.14 (0.98-1.32)</td>
<td>1.13 (0.97-1.31)</td>
<td>1.13 (0.97-1.31)</td>
<td>1.10 (0.95-1.28)</td>
</tr>
<tr>
<td>2140-2793</td>
<td>1311 (335)</td>
<td>1.00 (0.85-1.16)</td>
<td>1.00 (0.86-1.17)</td>
<td>1.00 (0.86-1.16)</td>
<td>0.99 (0.85-1.15)</td>
</tr>
<tr>
<td>2794-4511</td>
<td>1312 (352)</td>
<td>1.09 (0.94-1.27)</td>
<td>1.10 (0.94-1.28)</td>
<td>1.08 (0.93-1.26)</td>
<td>1.03 (0.88-1.20)</td>
</tr>
<tr>
<td>≥4512</td>
<td>1311 (394)</td>
<td>1.27 (1.10-1.47)</td>
<td>1.21 (1.05-1.41)</td>
<td>1.19 (1.03-1.38)</td>
<td>1.12 (0.97-1.31)</td>
</tr>
<tr>
<td>Missing information</td>
<td>1673 (457)</td>
<td>1.09 (0.95-1.26)</td>
<td>1.07 (0.92-1.23)</td>
<td>1.05 (0.91-1.21)</td>
<td>1.05 (0.90-1.21)</td>
</tr>
<tr>
<td><strong>Nonsteroidal Anti-inflammatory Drug Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>4188 (1128)</td>
<td>1.12 (0.95-1.31)</td>
<td>1.10 (0.94-1.29)</td>
<td>1.09 (0.89-1.29)</td>
<td>1.05 (0.90-1.21)</td>
</tr>
<tr>
<td>12-1499</td>
<td>2631 (712)</td>
<td>1.05 (0.96-1.16)</td>
<td>1.05 (0.95-1.16)</td>
<td>1.04 (0.95-1.15)</td>
<td>1.04 (0.94-1.15)</td>
</tr>
<tr>
<td>1500-2499</td>
<td>347 (83)</td>
<td>0.94 (0.75-1.17)</td>
<td>0.98 (0.71-1.11)</td>
<td>0.88 (0.70-1.10)</td>
<td>0.87 (0.69-1.10)</td>
</tr>
<tr>
<td>≥2500</td>
<td>357 (170)</td>
<td>1.18 (1.00-1.39)</td>
<td>1.10 (0.94-1.30)</td>
<td>1.09 (0.93-1.29)</td>
<td>1.05 (0.89-1.24)</td>
</tr>
<tr>
<td>Missing information</td>
<td>488 (141)</td>
<td>1.08 (0.91-1.29)</td>
<td>1.05 (0.87-1.26)</td>
<td>1.04 (0.87-1.24)</td>
<td>1.05 (0.85-1.23)</td>
</tr>
<tr>
<td><strong>Acetaminophen Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;12</td>
<td>4290 (1204)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>12-1499</td>
<td>2517 (607)</td>
<td>0.87 (0.79-0.96)</td>
<td>0.87 (0.79-0.96)</td>
<td>0.86 (0.78-0.95)</td>
<td>0.84 (0.77-0.95)</td>
</tr>
<tr>
<td>1500-2499</td>
<td>264 (87)</td>
<td>1.22 (0.98-1.52)</td>
<td>1.19 (0.96-1.49)</td>
<td>1.17 (0.94-1.64)</td>
<td>1.17 (0.93-1.46)</td>
</tr>
<tr>
<td>≥2500</td>
<td>310 (97)</td>
<td>1.20 (0.98-1.58)</td>
<td>1.16 (0.94-1.43)</td>
<td>1.13 (0.91-1.40)</td>
<td>1.08 (0.87-1.34)</td>
</tr>
<tr>
<td>Missing information</td>
<td>848 (239)</td>
<td>1.01 (0.88-1.16)</td>
<td>1.04 (0.86-1.25)</td>
<td>1.03 (0.86-1.25)</td>
<td>1.02 (0.85-1.23)</td>
</tr>
<tr>
<td><strong>Aspirin Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>333 (83)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>12-1499</td>
<td>2800 (737)</td>
<td>1.06 (0.84-1.33)</td>
<td>1.05 (0.84-1.33)</td>
<td>1.05 (0.83-1.32)</td>
<td>1.05 (0.83-1.32)</td>
</tr>
<tr>
<td>1500-2499</td>
<td>2723 (726)</td>
<td>1.07 (0.85-1.34)</td>
<td>1.07 (0.85-1.34)</td>
<td>1.06 (0.84-1.34)</td>
<td>1.06 (0.84-1.34)</td>
</tr>
<tr>
<td>≥2500</td>
<td>1552 (453)</td>
<td>1.23 (0.98-1.56)</td>
<td>1.20 (0.95-1.53)</td>
<td>1.19 (0.94-1.51)</td>
<td>1.16 (0.92-1.48)</td>
</tr>
<tr>
<td>Missing information</td>
<td>821 (225)</td>
<td>1.08 (0.84-1.39)</td>
<td>1.01 (0.76-1.34)</td>
<td>1.00 (0.75-1.33)</td>
<td>1.02 (0.76-1.36)</td>
</tr>
</tbody>
</table>

*Data are given as age-adjusted and multivariable-adjusted hazard ratio (95% confidence interval) unless otherwise indicated.
†Adjusted for age as exponential term. Using the test for trend across categories, excluding the missing information category, the age-adjusted, model 1, model 2, and model 3 values, respectively, are as follows: cumulative analgesic use: P = .008, P = .03, P = .08, and P = .30; nonsteroidal anti-inflammatory drug use: P = .088, P = .40, P = .52, and P = .80; acetaminophen use: P = .47, P = .60, P = .88, and P = .85; and aspirin use: P = .01, P = .93, P = .04, and P = .07.
‡Model 1 adjusted for age, body mass index, and other analgesic classes (with the exception of the model including total analgesic use).
§Model 2 adjusted for all variables in model 1 plus history of arthritis, history of headache or migraine, and headache and migraine frequency.
ǁModel 3 adjusted for all variables in model 2 plus smoking, exercise, alcohol consumption, diabetes, high cholesterol, parental history of premature myocardial infarction, and systolic and diastolic blood pressure.

COMMENT

In this cohort of 8229 apparently healthy men free of hypertension at the start of follow-up, those who self-selected for cumulative analgesic use of NSAIDs, acetaminophen, or aspirin for cumulative use or use in the last year and subsequent hypertension.
The second study suggested that women who self-selected for even infrequent use of NSAIDs, acetaminophen, or aspirin had an increased risk of hypertension. After adjusting for potential confounders, those in the highest intake categories (≥22 d/mo) had statistically significant HRs of 1.35 for NSAIDs, 1.20 for acetaminophen, and 1.21 for aspirin. This study suggested that a significantly increased risk of hypertension was apparent among women who self-selected for NSAIDs, acetaminophen, or aspirin 5 to 14 days per month. Although chance effect is unlikely in this large cohort, uncontrolled and uncontrolled confounding remains plausible because the observed effects are small to moderate.

A large case-control study compared recent NSAID users among patients with newly initiated antihypertensive drug therapy and NSAID nonusers. After adjusting for potential confounding factors, the odds ratio for recent NSAID users compared with nonusers was 1.66 for newly initiated antihypertensive drugs. The effect estimate increased with increasing daily NSAID dose. The available data, however, did not allow adjustments for confounding by risk factors for hypertension.

Two meta-analyses of randomized trials on NSAIDs and blood pressure have been published. The first meta-analysis did not report overall effects but provided subgroup analyses. The subgroup of normotensive participants had little if any increase in mean arterial pressure (mean, 1.1 mm Hg), whereas hypertensive participants had an increase of 3.3 mm Hg. In the second meta-analysis, individuals assigned to NSAIDs had a statistically significant increase in supine mean arterial blood pressure of 5.0 mm Hg. This significant increase in blood pressure was apparent among the subgroup of patients

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**Table 3. Hazard Ratios for Subsequent Hypertension According to Analgesic Use in the Year Preceding the 1996 Assessment**

<table>
<thead>
<tr>
<th>Analgesic Use in the Year Preceding the 1996 Assessment, No. of Pills (No. With Hypertension)</th>
<th>No. of Physicians</th>
<th>Age-Adjusted†</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cumulative Analgesic Use in Quintiles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-156</td>
<td>1962 (521)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>157-299</td>
<td>1319 (341)</td>
<td>1.01 (0.88-1.16)</td>
<td>1.00 (0.87-1.15)</td>
<td>0.99 (0.87-1.14)</td>
<td>1.01 (0.88-1.16)</td>
</tr>
<tr>
<td>205-299</td>
<td>1278 (336)</td>
<td>1.03 (0.90-1.19)</td>
<td>1.03 (0.90-1.18)</td>
<td>1.01 (0.88-1.17)</td>
<td>0.99 (0.86-1.14)</td>
</tr>
<tr>
<td>300-516</td>
<td>1333 (370)</td>
<td>1.08 (0.95-1.24)</td>
<td>1.07 (0.94-1.23)</td>
<td>1.06 (0.92-1.21)</td>
<td>1.02 (0.89-1.17)</td>
</tr>
<tr>
<td>≥517</td>
<td>1059 (316)</td>
<td>1.20 (1.04-1.38)</td>
<td>1.14 (0.99-1.32)</td>
<td>1.12 (0.97-1.29)</td>
<td>1.05 (0.91-1.21)</td>
</tr>
<tr>
<td>Missing information</td>
<td>1278 (350)</td>
<td>1.06 (0.93-1.22)</td>
<td>1.04 (0.90-1.19)</td>
<td>1.02 (0.89-1.17)</td>
<td>1.04 (0.90-1.19)</td>
</tr>
</tbody>
</table>

**Nonsteroidal Anti-inflammatory Drug Use**

| Aspirin Use | | | | | |
|---|---|---|---|---|
| 0 | 4375 (1177) | 1.00 | 1.00 | 1.00 | 1.00 |
| 1-14 | 286 (68) | 0.87 (0.68-1.11) | 0.87 (0.68-1.11) | 0.86 (0.67-1.10) | 0.89 (0.70-1.14) |
| 15-60 | 1402 (376) | 1.06 (0.95-1.20) | 1.06 (0.94-1.19) | 1.05 (0.93-1.18) | 1.03 (0.91-1.16) |
| ≥61 | 1924 (541) | 1.11 (0.99-1.21) | 1.04 (0.94-1.19) | 1.03 (0.93-1.15) | 1.01 (0.91-1.13) |
| Missing information | 242 (72) | 1.11 (0.87-1.40) | 1.08 (0.84-1.38) | 1.07 (0.83-1.37) | 1.09 (0.85-1.41) |

**Acetaminophen Use**

| Aspirin Use | | | | | |
|---|---|---|---|---|
| 0 | 7176 (1930) | 1.00 | 1.00 | 1.00 | 1.00 |
| 1-14 | 130 (32) | 0.96 (0.88-1.36) | 0.95 (0.66-1.35) | 0.93 (0.65-1.33) | 0.95 (0.67-1.36) |
| 15-60 | 207 (62) | 1.14 (0.88-1.46) | 1.07 (0.83-1.38) | 1.06 (0.82-1.36) | 1.08 (0.84-1.40) |
| ≥61 | 129 (47) | 1.48 (1.11-1.97) | 1.43 (1.07-1.91) | 1.39 (1.04-1.86) | 1.34 (1.00-1.80) |
| Missing information | 587 (163) | 1.03 (0.88-1.21) | 0.98 (0.77-1.25) | 0.98 (0.77-1.25) | 1.00 (0.78-1.28) |

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*Data are given as age-adjusted and multivariable-adjusted hazard ratio (95% confidence interval) unless otherwise indicated. For an explanation of the 3 models, see the footnotes to Table 2.

†Adjusted for age as exponential term. Using the test for trend across categories, excluding the missing information category, the age-adjusted, model 1, model 2, and model 3 values, respectively, are as follows: cumulative analgesic use: P = .01, P = .04, P = .11, and P = .54; nonsteroidal anti-inflammatory drug use: P = .06, P = .33, P = .46, and P = .75; acetaminophen use: P = .01, P = .03, P = .06, and P = .06; and aspirin use: P = .30, P = .29, P = .30, and P = .47.*
with controlled hypertension. As in the other meta-analysis, the subgroup of normotensive subjects had no statistically significant increase in mean blood pressure. Both meta-analyses showed no association between aspirin use and hypertension. In addition, the individual trials were of small sample size, and the duration of analgesic use was short (<7 weeks).

Two cross-sectional studies23,24 showing no overall associations between NSAID use and hypertension, but the subgroup of patients using NSAIDs and antihypertensive drugs had significantly higher blood pressures. The lack of a temporal relationship between exposure and outcome limits the interpretability of the results.

Analgesics may affect blood pressure through several mechanisms, most of which are mediated through kidney or systemic cyclooxygenase-2–specific inhibition of PGs.3,25–28 The distortion of the balance between the vasodilators PGI2 and PGE2 and the vasoconstrictors PGF2α and thromboxane A2 may be particularly relevant. In the kidneys, the inhibition of PGs may lead to sodium and water retention.27–29 In addition, PGs inhibit vascular endothelial production of endothelin-1, which may lead to increased blood pressure through increased peripheral resistance.30 Nonsteroidal anti-inflammatory drugs,31 aspirin,32 and, to a lesser degree, acetaminophen33,34 have been associated with inhibition of PGs. It remains unclear whether the postulated biological effects of analgesics on PGs lead to a temporary increase in blood pressure or to sustained effects among normotensive subjects.

Among patients treated for hypertension, NSAIDs may interact with antihypertensive drug therapies, leading to an increase in blood pressure.6,27–29,35

Our study has several strengths, including its large sample size and number of reports of new-onset hypertension, high follow-up rates, detailed assessment of over-the-counter analgesics, and use of physicians as the study population, which reduces the potential for confounding due to variability in access to medical care, educational attainment, and socioeconomic status. In addition, we controlled for many potential confounding factors, including markers of chronic pain. Furthermore, participants in the PHS had no indication or contraindication for aspirin or NSAID use at enrollment into the PHS, which may reduce any residual confounding by indication.

Several limitations should be considered. Although we controlled for many risk factors for hypertension, residual and unmeasured confounding is possible because the study design is observational. We are not aware of any biologically plausible confounding factors that would yield substantially increased effect estimates of the association between analgesic use and hypertension. Despite the lack of association between analgesic use in the year preceding our assessment and risk of hypertension, cumulative analgesic use may not be a risk factor for the development of hypertension but rather short-term use or a different use pattern, as some studies7,9 suggested. Participants self-reported their analgesic use; thus, misclassification of exposure is possible. Furthermore, we had no information regarding specific dosage of these analgesics and no detailed information about the pattern of use. In a substudy,14 the correlation between a self-reported retrospective questionnaire and a structured telephone interview of analgesic use was moderate to good (correlation coefficient, 0.40–0.76), and most participants used standard over-the-counter doses. With regard to potential misclassification, it is unlikely that physicians who regularly used analgesics would report occasional use and vice versa. In addition, none of the subcategories of analgesics were associated with subsequent hypertension. It has been suggested that individual NSAIDs have different effects on blood pressure. Because we had information only on overall NSAID use, we cannot exclude the possibility that some NSAIDs are associated with an increased risk of hypertension. However, other observational studies6–10 found increased risk with overall NSAID use. We also had no information on cyclooxygenase-2 inhibitors. A recent meta-analysis56 of randomized trials found that use of cyclooxygenase-2 inhibitors was associated with a significant increase in blood pressure of 3.85 mm Hg compared with placebo and 2.83 mm Hg compared with NSAIDs. This meta-analysis further demonstrated an increased risk of developing hypertension when use of cyclooxygenase-2 inhibitors was compared with placebo (relative risk, 1.61; 95% CI, 0.91–2.84) or without selective NSAIDs (relative risk, 1.25; 95% CI, 0.87–1.78), although this was not statistically significant.

The information on hypertension in our study was self-reported, which may have led to misclassification. However, physicians are known to report medical conditions and treatment accurately, and we have no reason to believe that reports of hypertension were influenced by analgesic use. Although we found no effect modification by age, we cannot exclude the possibility that the lack of association is not generalizable to younger men because our study did not include men younger than 53 years. Furthermore, participants of the PHS were predominantly white. Nonetheless, differential biological effects of analgesic use on blood pressure in different populations seem unlikely. We believe the discrepancies between findings in men and women are more apparent than real and are likely to be explained by residual confounding.

Despite these and perhaps other limitations, we believe the most plausible interpretation of our data is that apparently healthy male physicians who self-select for analgesic use did not have a significantly increased risk of subsequent hypertension. These data suggest that in apparently healthy men, the use of analgesics is unlikely to produce large increases in hypertension, although a small to moderately increased risk cannot be excluded in any observational study.

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