Non-Narcotic Analgesic Dose and Risk of Incident Hypertension in US Women

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John P. Forman, Meir J. Stampfer, Gary C. Curhan

Abstract—Acetaminophen, ibuprofen, and aspirin are the most commonly used drugs in the United States. Although the frequency of their use has been associated with hypertension, prospective data examining the dose of these drugs and risk of hypertension are lacking. Furthermore, whether certain indications for analgesic use, particularly headache, mediate the association is unclear. We conducted 2 prospective cohort studies among older women 51 to 77 years of age (n=1903) from the Nurses' Health Study I and younger women 34 to 53 years of age (n=3220) from the Nurses' Health Study II who completed detailed supplemental questionnaires pertaining to their analgesic use and who did not have hypertension at baseline. We analyzed incident hypertension according to categories of average daily dose of acetaminophen, nonsteroidal anti-inflammatory drugs, and aspirin. Information on indications for analgesic use as well as relevant confounders was also gathered prospectively. Compared with women who did not use acetaminophen, the multivariable adjusted relative risk for those who took >500 mg per day was 1.93 (1.30 to 2.88) among older women and 1.99 (1.39 to 2.85) among younger women. For nonsteroidal anti-inflammatory drugs, similar comparisons yielded multivariable relative risks of 1.78 (1.21 to 2.61) among older women and 1.60 (1.10 to 2.32) among younger women. These associations remained significant among women who did not report headache. Aspirin dose was not significantly associated with hypertension. Higher daily doses of acetaminophen and nonsteroidal anti-inflammatory drugs independently increase the risk of hypertension in women. Because acetaminophen and nonsteroidal anti-inflammatory drugs are commonly used, they may contribute to the high prevalence of hypertension in the United States. **(*Hypertension*. 2005;46:500-507.)**

Key Words: epidemiology ■ lifestyle ■ risk factors ■ human ■ women

Acetaminophen, ibuprofen, and aspirin are the 3 most frequently used drugs in the United States.[1] These drugs may lead to high blood pressure through various mechanisms, including inhibition of vasodilatory prostaglandins.[2–5] In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) increase renal sodium reabsorption,[6–8] and acetaminophen and NSAIDs may impair endothelial function.[9–17]

In 2 large prospective cohorts of women, we previously reported an association between the frequency of analgesic use (days per month) and the risk of developing hypertension.[18,19] The major criticisms of these previous analyses were the lack of information on drug doses used by participants and the indications for their use, in particular, the concern that headache as a result of higher blood pressure may lead to analgesic use (confounding by indication).

To address these concerns and to further examine this important public health issue, we studied the association between dose of nonnarcotic analgesic drug use, indication for use, and the risk of incident hypertension among subcohorts consisting of 1903 older female participants of Nurses' Health Study I (NHS I) and 3220 younger female participants of NHS II without a history of hypertension at baseline.

Methods

Nurses' Health Studies

The NHS I cohort was assembled in 1976, when 121 700 female nurses 30 to 55 years of age returned a mailed questionnaire. Subsequent questionnaires have been mailed every 2 years to update information on health-related behaviors and medical events. On the 1990, 1992, and 1998 questionnaires, we inquired about the frequency of use of acetaminophen, NSAIDs, and aspirin.

NHS II is an independent cohort of 116 671 female registered nurses who were 25 to 42 years of age when they returned an initial questionnaire in 1989. These women are also followed with similar biennial questionnaires. Beginning in 1995, we inquired about the frequency of use of nonnarcotic analgesics.

Study Populations

For this study, subcohorts were assembled within the older cohort (NHS I) and within the younger cohort (NHS II). The assembly of these subcohorts and the delineation of the populations for the analysis of incident hypertension is detailed in the Figure. These subcohorts were originally assembled to obtain detailed information on analgesic use and study associations between analgesics and renal function.[20] None of the participants of these analyses were cases from the previously published studies that examined frequency of analgesic use and hypertension in NHS I[18] and NHS II.[19] The

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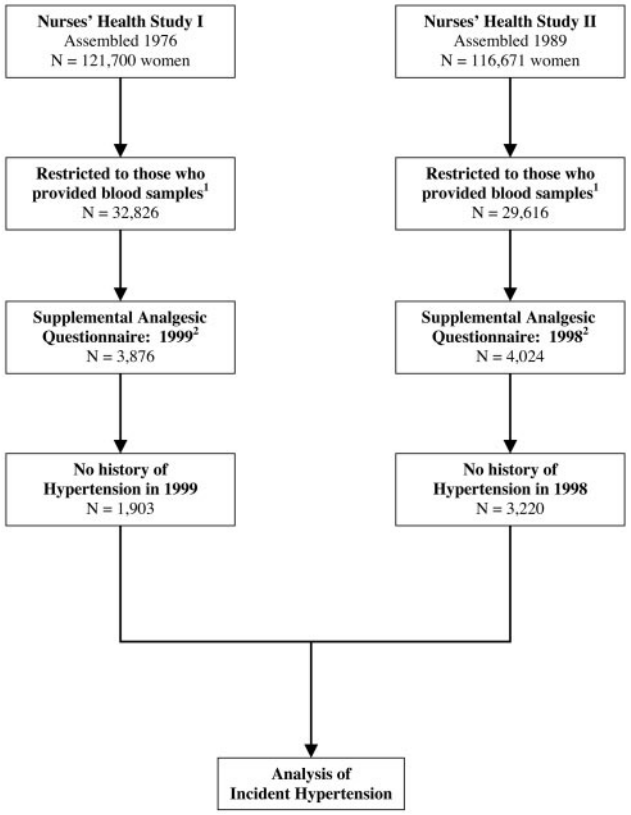

Assembly of the subcohorts for analysis of incident hypertension. 1. The purpose of restricting the study population to those who had blood samples available was to examine the association between analgesic use and renal function.[20] 2. To enrich the subcohorts with participants likely to have either high or low analgesic intake, recipients of the supplemental analgesic questionnaires reported using either no analgesics or a high frequency of analgesics (≥15 days per month) on the main biennial questionnaires that are sent to all participants of NHS I and NHS II. The supplemental questionnaire was sent to 4238 women in NHS I and 4454 women in NHS II. The figure shows the numbers of women who responded to the supplemental questionnaires (91% and 90%, respectively). Participants in these subcohorts also received the main biennial questionnaire that is sent to all participants of NHS I and NHS II.

institutional review board at Brigham and Women's Hospital reviewed and approved this study, including that participants provided implied consent by virtue of returning their questionnaires.

Assessment of Analgesic Use and Indications

Each supplementary questionnaire collected detailed information specifically about the participant's current use of acetaminophen, NSAIDs, and aspirin, including frequency of current use (in days per month), number of tablets per day when used, dosage per tablet, brand used, and the indications for use. From this information, we first calculated an estimated average monthly dose of each analgesic class by multiplying together the days/month, tablets/day, and dose/tablet; we then computed the average daily dose by dividing by 30 days/month. We classified participants into 1 of 4 categories of current use for each analgesic: acetaminophen (0 mg per day, 1 to 100 mg per day, 101 to 500 mg per day, and >500 mg per day); aspirin (0 mg per day, 1 to 100 mg per day, 101 to 400 mg per day, and >400 mg per day); and NSAIDs (0 mg per day, 1 to 100 mg per day, 101 to 400 mg per day, and >400 mg per day). Because ibuprofen was by far the most commonly used NSAID (accounting for 67% of NSAID users in NHS I and 80% of NSAID users in NHS II), the doses of nonibuprofen NSAIDs were converted into roughly equivalent doses of ibuprofen using the following scheme: naproxen, 2-fold higher potency per mg; celecoxib, 4-fold higher potency per mg; other NSAIDs including ketoprofen, diclofenac, indomethacin, and others, 10-fold higher potency per mg.[21] The combination of ibuprofen and naproxen accounted for 81% of NSAIDs used in NHS I and 92% of NSAIDs used in NHS II. When information regarding type of NSAID used was missing (3% in NHS I and 2% in NHS II), ibuprofen was assumed.

The supplementary questionnaires also asked participants to report the indication for use of each class of analgesic. For acetaminophen and NSAIDs, possible response categories were "headache," "backache," "muscle or joint pain," "menstrual cramps," and "other." For aspirin, "prevent heart disease" was added to these categories. Participants were allowed to report >1 indication. Our analysis examined the potential role of headache as an indication for use.

Assessment of Hypertension

Hypertension was self-reported in these cohorts of health professionals on biennial questionnaires, and self-reported hypertension has been shown to be highly reliable. In a subset of women who reported hypertension, medical record review confirmed a documented blood pressure >140/90 in 100%; additionally, self-reported hypertension was predictive of subsequent cardiovascular events.[22]

Women were considered to have prevalent hypertension at the time they returned the first supplementary questionnaire if they reported a diagnosis of hypertension on any previous main biennial questionnaire (sent to all NHS I and NHS II members) or reported hypertension on the supplementary questionnaire (which only members of these subcohorts received). For the analysis of incident hypertension, women with prevalent hypertension were excluded. In those without prevalent hypertension at baseline, women were considered to have incident hypertension if they reported an initial diagnosis of hypertension after the return of the supplementary questionnaire.

Assessment of Other Factors

Age, body mass index (BMI; kg/m^2), smoking status, physical activity (metabolic equivalent task scores), and oral contraceptive use (in NHS II) were ascertained from the main biennial questionnaires returned just before the supplemental analgesic questionnaire. Intakes of alcohol, caffeine, folate, sodium, potassium, magnesium, and calcium were ascertained from semiquantitative food frequency questionnaires that were mailed to participants of NHS I and II every 4 years. The food frequency questionnaire returned just before the analgesic supplementary questionnaire was used to obtain this information. Information on family history of hypertension was available on the 1992 (NHS I) and 1989 (NHS II) questionnaires. We obtained self-reported blood pressure from the supplementary questionnaire. Systolic blood pressure was reported in 9 categories (<105, 105 to 114, 115 to 124, 125 to 134, 135 to 144, 145 to 154, 155 to 164, 165 to 174, and ≥175 mm Hg), and diastolic blood pressure was reported in 7 categories (<65, 65 to 74, 75 to 84, 85 to 89, 90 to 94, 95 to 104, and ≥105 mm Hg). A participant's blood pressure was defined as the middle systolic and middle diastolic value of the reported category. Clinician visits (during which blood pressure measurement is likely to occur) were reported in 2000 (NHS I) and 2001 (NHS II).

Statistical Analysis

For each participant, person months of follow-up were counted from the date of return of the supplementary questionnaire to the date of return of the last biennial questionnaire and allocated according to exposure status. Incidence rates were computed by dividing the number of new cases of hypertension by the number of person years in the particular category of analgesic use. The association between the previously defined categories of analgesic use and incident hypertension were analyzed using Cox proportional hazards regression. We computed hazard ratios (reported as relative risks [RRs]) for age-adjusted models, as well as multivariable-adjusted models that included age (continuous), BMI (continuous), physical activity

(quintiles), smoking (never, past, current), family history of hypertension (yes/no), and intakes of alcohol, caffeine, and other nutrients (quintiles). We also included oral contraceptive use (yes/no) in multivariable models when examining the younger NHS II cohort. In all models, we simultaneously adjusted for each of the 3 classes of analgesics. In each class of analgesic, the reference category consisted of those with no use of that class. Age-adjusted and multivariable tests for linear trend were assessed using the median daily analgesic dose within each exposure category.

Because it has been suggested that the presence of headache may be the focus of an indirect link between analgesic use and hypertension,[23] we performed secondary analyses restricting the study populations to those women who did not report headache as an indication for analgesic use. To reduce ascertainment bias, we performed other secondary analyses limited to women who reported having ≥1 clinician examination during follow-up.

For all RRs, we calculated 95% confidence intervals (CIs). All *P* values are 2-tailed. Statistical tests were performed using SAS statistical software, version 9 (SAS Institute Inc).

Results

Participant Characteristics

The baseline characteristics of those included in the primary analysis, according to categories of average daily analgesic dose, are given in Table 1. Among the older cohort (NHS I; Table 1A), individuals who did not take analgesics had lower BMI and lower systolic and diastolic blood pressure, whereas physical activity was higher among nonusers of acetaminophen. In the younger cohort (NHS II; Table 1B), systolic and diastolic blood pressures were lower in those who did not use analgesics, whereas BMI was lower among nonusers of acetaminophen and NSAIDs.

During 5268 person years of follow-up in NHS I, we identified 211 incident cases of hypertension. During 13 405 person years of follow-up in NHS II, we identified 299 incident cases of hypertension.

Incident Hypertension

Nurses' Health Study I

In the older women, a higher average daily dose of acetaminophen and NSAIDs was associated with an increased risk of incident hypertension (Table 2A). Older women whose daily dose of acetaminophen exceeded 500 mg had a 93% increased risk of developing hypertension after controlling for potential confounders compared with acetaminophen nonusers (multivariable RR, 1.93; 95% CI, 1.30 to 2.88; *P* trend <0.001). Compared with nonusers of NSAIDs, those who consumed >400 mg per day of NSAIDs had a 78% increased risk of hypertension (multivariable RR, 1.78; 95% CI, 1.21 to 2.61; *P* trend=0.01). We also examined whether NSAID doses exceeding 800 mg per day conferred even higher risk by splitting the highest category of NSAID dose into 401 to 800 mg per day and >800 mg per day groups; compared with those who did not use NSAIDs, women whose usual dose was >800 mg per day had a 2.2-fold higher risk of incident hypertension compared with nonusers (multivariable RR, 2.17; 95% CI, 1.38 to 3.42). Aspirin dose was not associated with incident hypertension.

Because women who take analgesics may be more likely to visit their clinicians (and thus more likely to be diagnosed with hypertension), we analyzed the subset of women (n=1804 with 204 cases) who reported ≥1 examination during the period of follow-up, in which blood pressure was likely to be measured. The RR comparing the highest to lowest category of use remained significantly elevated for acetaminophen (RR, 1.96; 95% CI, 1.30 to 2.96) and NSAIDs (RR, 1.66; 95% CI, 1.12 to 2.46). After adjusting for baseline systolic and diastolic blood pressure, acetaminophen (RR, 1.68; 95% CI, 1.11 to 2.56; *P* trend=0.009) and NSAIDs (RR, 1.74; 95% CI, 1.16 to 2.61; *P* trend=0.02) remained associated with incident hypertension. Further adjustment for sodium, potassium, magnesium, and calcium did not materially alter the results.

Nurses' Health Study II

Among the younger women, a higher average daily dose of acetaminophen and NSAIDs was also associated with an increased risk of incident hypertension (Table 2B). Younger women whose average daily acetaminophen intake was >500 mg had a 2-fold higher risk of developing hypertension compared with those who did not use acetaminophen (multivariable RR, 1.99; 95% CI, 1.39 to 2.85; *P* trend <0.001). Compared with nonusers of NSAIDs, women whose intake exceeded 400 mg per day had a 60% increased risk of hypertension (multivariable RR, 1.60; 95% CI, 1.10 to 2.32; *P* trend=0.04). The risk among women whose usual NSAID dose exceeded 800 mg per day was similar (multivariable RR, 1.61; 95% CI, 1.06 to 2.44). Aspirin dose was marginally associated with an increased risk of incident hypertension in younger women (*P* trend=0.06).

In younger women who reported ≥1 examination during the follow-up (n=3030; 289 cases), results for acetaminophen (RR, 1.96; 95% CI, 1.36 to 2.85) and NSAIDs (RR, 1.58; 95% CI, 1.09 to 2.30) were not materially different from the entire sample. After additionally controlling for baseline blood pressure, acetaminophen remained significantly associated with hypertension (RR, 1.64; 95% CI, 1.10 to 2.45; *P* trend=0.02), but the association between NSAIDs and hypertension was no longer significant (RR, 1.45; 95% CI, 0.97 to 2.16; *P* trend=0.21). Controlling for intake of sodium, potassium, magnesium, and calcium did not substantially change the results.

Analgesic Use and Incident Hypertension in Those Without Headache

To address the possibility that the association between analgesic use and hypertension may be mediated by headache, we repeated our analyses among women without headache. Among women who did not report headache as an indication for analgesic use (n=1239 with 123 cases in NHS I; n=822 with 82 cases in NHS II), intakes of acetaminophen and NSAIDs were associated with incident hypertension in the older and younger cohorts (Table 3). Compared with nonusers of acetaminophen, older women who consumed >500 mg per day had a 2.4-fold increased risk of hypertension; in younger women, the same comparison yielded a 4.7-fold increased risk. Among the older women without headache, those whose NSAID consumption exceeded 400 mg per day had a 1.75-fold higher risk of incident hypertension compared with NSAID nonusers; in younger women, the same compar-

TABLE 1. A. Baseline Characteristics of NHS I Participants According to Category of Analgesic Use

	Category of Acetaminophen Use (mg/day)			
	0	1–100	101–500	>500
No. of participants	1202	200	234	267
Age, years	64.0	63.9	63.6	64.0
BMI, kg/m^2	24.7	25.1	25.6	26.3
Smoking history, %				
Past	41.8	48.5	43.2	53.2
Current	9.3	6.0	4.7	10.1
Physical activity, METs/week	22.5	20.9	19.4	16.8
Family history of HTN, %	38.4	39.5	44.4	37.1
Alcohol intake, g/day	5.6	5.1	5.3	4.5
Caffeine intake, mg/day	191	209	205	189
Folate intake, μg/day	633	660	712	669
Baseline SBP (mm Hg)	124	124	126	126
Baseline DBP (mm Hg)	75	75	76	76
	Category of NSAID Use (mg/day)			
	0	1–100	101–400	>400
No. of participants	1146	223	155	379
Age, years	64.6	62.9	62.3	63.2
BMI, kg/m^2	24.6	24.8	25.6	26.6
Smoking history, %				
Past	42.2	48.0	45.2	48.2
Current	9.2	7.6	7.1	7.6
Physical activity, METs/week	21.8	23.7	17.1	19.4
Family history of HTN, %	37.7	45.7	36.8	40.4
Alcohol intake, g/day	5.1	5.6	5.1	6.0
Caffeine intake, mg/day	184	200	225	210
Folate intake, μg/day	648	634	683	654
Baseline SBP (mm Hg)	124	124	125	126
Baseline DBP (mm Hg)	75	75	75	76
	Category of Aspirin Use (mg/day)			
	0	1–100	101–400	>400
No. of participants	1122	304	292	185
Age, years	63.9	64.3	64.2	63.5
BMI, kg/m^2	24.8	25.5	25.6	25.5
Smoking history, %				
Past	42.8	47.0	46.9	44.9
Current	8.9	4.9	6.5	15.1
Physical activity, METs/week	21.5	19.1	23.5	18.6
Family history of HTN, %	38.7	43.8	36.0	38.9
Alcohol intake, g/day	5.2	5.3	5.7	5.6
Caffeine intake, mg/day	185	195	219	215
Folate intake, μg/day	627	686	684	682
Baseline SBP (mm Hg)	123	126	126	124
Baseline DBP (mm Hg)	75	75	76	75

METs indicates metabolic equivalent task scores; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE 1. B. Baseline Characteristics of NHS II Participants According to Category of Analgesic Use

	Category of Acetaminophen Use (mg/day)			
	0	1–100	101–500	>500
No. of participants	1437	606	845	332
Age, years	45.4	44.9	45.0	45.5
BMI, kg/m^2	25.7	25.8	26.1	27.3
Smoking history, %				
Past	27.7	25.4	28.6	28.0
Current	7.7	7.2	7.5	8.0
Oral contraceptive use, %	3.1	4.7	3.1	3.5
Physical activity, METs/week	20.2	18.9	18.5	17.5
Family history of HTN, %	51.1	45.2	48.4	52.9
Alcohol intake, g/day	4.8	4.2	4.4	2.8
Caffeine intake, mg/day	238	223	252	236
Folate intake, μg/day	651	647	634	637
Baseline SBP (mm Hg)	116	116	117	119
Baseline DBP (mm Hg)	72	72	73	74
	Category of NSAID Use (mg/day)			
	0	1–100	101–400	>400
No. of participants	756	790	708	966
Age, years	45.6	44.7	45.0	45.4
BMI, kg/m^2	25.0	24.8	26.3	27.4
Smoking history, %				
Past	24.4	24.9	30.6	30.0
Current	8.2	6.6	7.2	8.2
Oral contraceptive use, %	3.3	4.0	4.4	2.4
Physical activity, METs/week	20.7	19.2	18.1	19.0
Family history of HTN, %	47.0	47.6	52.4	50.8
Alcohol intake, g/day	3.8	4.3	4.3	5.0
Caffeine intake, mg/day	229	224	242	255
Folate intake, μg/day	647	650	617	657
Baseline SBP (mm Hg)	115	115	117	118
Baseline DBP (mm Hg)	71	72	73	73
	Category of Aspirin Use (mg/day)			
	0	1–100	101–400	>400
No. of participants	1996	559	451	214
Age, years	44.7	45.8	46.0	46.3
BMI, kg/m^2	26.0	26.0	25.8	26.4
Smoking history, %				
Past	25.9	29.8	30.2	31.2
Current	6.2	7.1	9.8	17.3
Oral contraceptive use, %	3.9	2.4	2.8	3.0
Physical activity, METs/week	18.8	18.9	23.4	15.6
Family history of HTN, %	49.2	48.0	50.5	54.0
Alcohol intake, g/day	4.2	4.8	5.0	4.0
Caffeine intake, mg/day	230	259	247	248
Folate intake, μg/day	628	680	677	629
Baseline SBP (mm Hg)	116	117	117	118
Baseline DBP (mm Hg)	72	72	73	73

METs indicates metabolic equivalent task scores; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE 2. Average Daily Dose of Non-Narcotic Analgesics and the Risk of Incident Hypertension

A. NHS I

	Average Daily Dose (mg/day)				
Acetaminophen	0	1–100	101–500	>500	*P* trend
Person years	3365	551	636	716	
Cases	107	20	34	50	
Age-adjusted RR (95% CI)	1.0 (reference)	0.78 (0.47, 1.31)	1.42 (0.92, 2.20)	2.02 (1.38, 2.97)	<0.001
Multivariable* RR (95% CI)	1.0 (reference)	0.82 (0.48, 1.39)	1.33 (0.84, 2.08)	1.93 (1.30, 2.88)	<0.001
NSAIDs	0	1–100	101–400	> 400	*P* trend
Person years	3212	611	422	1024	
Cases	99	30	22	60	
Age-adjusted RR (95% CI)	1.0 (reference)	1.74 (1.09, 2.76)	1.48 (0.86, 2.51)	1.89 (1.31, 2.72)	0.003
Multivariable* RR (95% CI)	1.0 (reference)	1.72 (1.07, 2.78)	1.53 (0.89, 2.66)	1.78 (1.21, 2.61)	0.01
Aspirin	0	1–100	101–400	>400	*P* trend
Person years	3127	827	808	506	
Cases	108	43	37	23	
Age-adjusted RR (95% CI)	1.0 (reference)	1.34 (0.91, 1.99)	1.11 (0.73, 1.70)	1.13 (0.68, 1.86)	0.71
Multivariable* RR (95% CI)	1.0 (reference)	1.28 (0.86, 1.92)	1.19 (0.77, 1.83)	1.12 (0.67, 1.86)	0.66

B. NHSII

	Average Daily Dose (mg/day)				
Acetaminophen	0	1–100	101–500	>500	*P* trend
Person years	6066	2531	3495	1313	
Cases	118	47	76	58	
Age-adjusted RR (95% CI)	1.0 (reference)	1.02 (0.72, 1.45)	1.10 (0.81, 1.50)	2.14 (1.53, 2.99)	<0.001
Multivariable† RR (95% CI)	1.0 (reference)	1.11 (0.76, 1.60)	1.09 (0.79, 1.50)	1.99 (1.39, 2.85)	<0.001
NSAIDs	0	1–100	101–400	>400	*P* trend
Person years	3206	3324	2930	3946	
Cases	51	57	74	117	
Age-adjusted RR (95% CI)	1.0 (reference)	1.33 (0.90, 1.98)	1.82 (1.25, 2.65)	2.06 (1.46, 2.91)	<0.001
Multivariable† RR (95% CI)	1.0 (reference)	1.22 (0.80, 1.85)	1.54 (1.04, 2.28)	1.60 (1.10, 2.32)	0.04
Aspirin	0	1–100	101–400	> 400	*P* trend
Person years	8332	2345	1854	874	
Cases	179	46	50	24	
Age-adjusted RR (95% CI)	1.0 (reference)	0.88 (0.62, 1.24)	1.36 (0.98, 1.90)	1.26 (0.80, 1.98)	0.09
Multivariable† RR (95% CI)	1.0 (reference)	0.89 (0.62, 1.27)	1.38 (0.96, 1.97)	1.35 (0.84, 2.18)	0.06

All models simultaneously adjust for intake of all 3 analgesics classes.

*Adjusted for age, BMI, physical activity, smoking, alcohol, caffeine, family history, and intake of folate; †adjusted for age, BMI, physical activity, oral contraceptive use, smoking, alcohol, caffeine, family history, and intake of folate.

ison yielded a 3.7-fold increased risk. Aspirin dose remained unassociated with risk of hypertension.

Discussion

We observed that NSAIDs as well as a higher average daily dose of acetaminophen were significantly and independently associated with a higher risk of incident hypertension. In those without headache, acetaminophen and NSAIDs remained independently associated with hypertension. Aspirin dose was not significantly associated with hypertension. We are unaware of other prospective studies that have examined a dose response between analgesic use and incident hypertension or addressed the possibility of headache as a mediator of the association between analgesic use and hypertension.

These results confirm and expand on our previous reports that frequency of acetaminophen and NSAID use increases the risk of incident hypertension in women.[18,19] The association between acetaminophen and hypertension may in part be mediated through a potential effect on endothelial function. Endothelial thiols such as glutathione (GSH) may

TABLE 3. Average Daily Dose of Non-Narcotic Analgesics and the Risk of Incident Hypertension Among Those Without Headache as an Indication

A. NHS I					
Among Those Women Without Headache					
	Average Daily Dose (mg/day)				
Acetaminophen	0	1–100	101–500	>500	*P* Trend
Person years	2593	199	274	389	
Cases	70	7	17	29	
Multivariable* RR (95% CI)	1.0 (reference)	1.03 (0.37, 2.89)	1.42 (0.68, 2.95)	2.38 (1.31, 4.35)	0.005
NSAIDs	0	1–100	101–400	>400	*P* trend
Person years	2322	305	171	656	
Cases	66	11	8	38	
Multivariable* RR (95% CI)	1.0 (reference)	1.99 (0.88, 4.51)	1.35 (0.54, 3.41)	1.75 (1.02, 3.00)	0.06
Aspirin	0	1–100	101–400	>400	*P* trend
Person years	2340	473	407	234	
Cases	77	21	16	9	
Multivariable* RR (95% CI)	1.0 (reference)	0.93 (0.50, 1.73)	1.09 (0.56, 2.11)	0.88 (0.36, 2.16)	0.89
B. NHSII					
Among Those Women Without Headache					
	Average Daily Dose (mg/day)				
Acetaminophen	0	1–100	101–500	>500	*P* trend
Person years	2590	201	374	270	
Cases	48	3	12	19	
Multivariable* RR (95% CI)	1.0 (reference)	0.73 (0.12, 4.43)	0.62 (0.21, 1.80)	4.68 (1.74, 12.6)	0.002
NSAIDs	0	1–100	101–400	>400	*P* trend
Person years	1328	495	519	1094	
Cases	20	10	10	42	
Multivariable* RR (95% CI)	1.0 (reference)	2.16 (0.67, 6.96)	1.01 (0.33, 3.10)	3.67 (1.53, 8.79)	0.002
Aspirin	0	1–100	101–400	>400	*P* trend
Person years	2529	339	377	191	
Cases	57	6	13	6	
Multivariable* RR (95% CI)	1.0 (reference)	0.42 (0.12, 1.40)	1.19 (0.41, 3.49)	1.70 (0.37, 7.70)	0.39

*All models simultaneously adjust for intake of all 3 analgesics classes, as well as age, BMI, physical activity, smoking, alcohol, caffeine, family history of hypertension, and intake of folate. Oral contraceptive use was included in the analysis of NHS II.

mediate some of the beneficial effects of NO.[9,10] Compounds similar to acetaminophen deplete GSH and can cause endothelial dysfunction in animal models, and infusion of GSH in humans enhances endothelial function.[11–14] Also, inhibition of vasodilatory prostaglandins may play a role.[2,4] In addition to the inhibition of vasodilatory prostaglandins[3,5] and increasing renal sodium and water reabsorption,[6–8] NSAIDS may also exert a deleterious effect on endothelial function. For example, indomethecin increases endothelin-1 production.[15,16] Although aspirin also inhibits prostaglandin synthesis,[5] it has not been associated with endothelial dysfunction. On the contrary, aspirin may improve endothelial function, as has been documented in patients with atherosclerosis.[24]

In the 2 previous studies from these cohorts, we found an association between frequency of aspirin use and incident hypertension among the older women and a marginally significant association among the younger women.[18,19] In the present study, we did not detect an association between aspirin dose and hypertension. However, the risk estimates for aspirin are consistent among the studies, and there may have been insufficient power in the subcohorts to detect a modest association.

The relationship between NSAIDs and hypertension has been examined previously in epidemiologic and small interventional studies. Two community-based cross-sectional studies in elderly populations found significant associations between NSAID use (yes or no, rather than dose used) and hypertension, with odds ratios of 1.4 to 2.2, after adjusting for various potential confounders such as age and BMI.[25,26] A large case-control study of elderly Medicaid beneficiaries

reported a 1.6-fold increased odds of filling an initial prescription for antihypertensive medication if an NSAID prescription was filled during the previous 60 days after controlling for age, sex, race, nursing home status, and health care utilization.[27] Two meta-analyses of randomized trials reported that NSAIDs raised mean blood pressure.[28,29] One found that among 771 primarily white participants of various trials, NSAIDs increased mean blood pressure by 5 mm Hg overall (95% CI, 1.2 to 8.7).[28] However, the effect was largely limited to those participants receiving therapy for existing hypertension (5.4 mm Hg increase; 95% CI, 1.2 to 9.6); among the studies of normotensive individuals, blood pressure increases with NSAIDs were small and not statistically significant. Furthermore, in the trials in which antihypertensive medicines were administered, NSAIDs were found to antagonize the effect of these drugs.[28] The second meta-analysis found a 3 mm Hg increase in mean blood pressure with NSAIDs that was also limited to participants with pre-existing hypertension.[29] Additionally, only certain NSAIDs such as indomethecin and naproxen were associated with increased blood pressure, whereas others such as ibuprofen and sulindac were not.[29] Together, these meta-analyses suggest that NSAIDs may antagonize the efficacy of antihypertensive medication.

Less information has been published regarding the potential effect of acetaminophen on blood pressure and risk of hypertension. A short-term randomized crossover study of 20 patients with treated hypertension reported that 1000 mg given 4× per day of acetaminophen versus placebo for 4 weeks led to a statistically significant 4 mm Hg rise in systolic blood pressure.[30] Aspirin has also received less attention. A prospective cohort study of 1040 women found no association between baseline aspirin use (determined by urinary salicylates) and the odds of incident hypertension over a 20-year period.[31] In the 2 meta-analyses of NSAIDs mentioned above, aspirin use was also examined and had no significant effect on blood pressure.[28,29]

Our study has strengths and weaknesses that deserve mention. We determined analgesic use with detailed questionnaires before the diagnosis of hypertension, and we used reliable information on many known hypertension risk factors. In addition, we were able to examine average daily dose as the primary exposure rather than simply examining frequency of use. Finally, the information we gathered on indications for analgesic use allowed us to reanalyze these associations in those without headache. As a potential weakness, we did not directly examine participants during follow-up to confirm self-reported hypertension; however, all participants were registered nurses, and hypertension reporting has been shown previously to be reliable in our cohorts.[22] Also, it was possible that women taking analgesics were more likely to visit their clinicians and thus more likely to be diagnosed with hypertension. However, most women in this study (91% to 95%) had ≥1 clinician visit during follow up, and after limiting our analysis to this subset, the results were unchanged. Random misclassification of analgesic use may have occurred because of inaccuracy of reporting, but in this prospective study, such misclassification, if anything, would have led to an underestimation of the true association. Residual confounding is always a potential concern in observational studies, but we carefully adjusted for factors such as BMI, physical activity, and other known hypertension risk factors in our multivariable models; such adjustment had only a modest impact on the associations, and we are unaware of common medical conditions that are simultaneously indications for analgesic use and independently associated with hypertension. Finally, we had insufficient power to dissect the relationships between individual NSAID types, such as ibuprofen versus naproxen, and the risk of hypertension. However, ibuprofen was by far the most commonly used (67% to 80%) in this data set, as it is nationwide.[1]

Perspectives

Although clinicians may believe that NSAIDs have the potential for untoward renal and hemodynamic consequences, it is commonly held that acetaminophen is safe. These data add further support to the hypothesis that acetaminophen and NSAIDs may independently elevate the risk of hypertension. Given their common consumption and the high prevalence of hypertension, our results have substantial public health implications, and suggest that these agents be used with greater caution. The contribution of non-narcotic analgesics to the hypertension disease burden merits further study.

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