

Folate Intake and the Risk of Incident Hypertension Among US Women

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HYPERTENSION AFFECTS AN ESTIMATED 65 million individuals in the United States and many more worldwide.^{1,2} Because the risk of hypertension increases with age, the prevalence is growing along with the aging population. Hypertension is a potent independent risk factor for cardiovascular disease³⁻⁶ and renal failure.⁷⁻⁹ Therefore, identifying risk factors for hypertension could lead to specific preventive interventions that may favorably affect public health.

Folate may have beneficial effects on blood pressure by increasing nitric oxide synthesis in endothelial cells,^{10,11} or by reducing plasma homocysteine, which itself can cause endothelial cell injury.¹²⁻¹⁶ Oral folic acid supplementation improves endothelial function in vivo.^{17,18} Although there are no published studies on the association between folate intake and risk of incident hypertension, 2 small randomized trials have demonstrated that high-dose folic acid supplementation may lower systolic and diastolic blood pressure.^{19,20} Taken together, these data suggest that a higher intake of folate may reduce an individual's risk of hypertension. We prospectively examined the association between folate intake and risk of incident hypertension in 2 large studies of younger and older women who were followed up for 8 years.

METHODS

Study Populations

The younger cohort (Nurses' Health Study II [NHS II]) was assembled in

Context Folate has important beneficial effects on endothelial function, but there is limited information about folate intake and risk of incident hypertension.

Objective To determine whether higher folate intake is associated with a lower risk of incident hypertension.

Design, Setting, and Participants Two prospective cohort studies of 93 803 younger women aged 27 to 44 years in the Nurses' Health Study II (1991-1999) and 62 260 older women aged 43 to 70 years in the Nurses' Health Study I (1990-1998), who did not have a history of hypertension. Baseline information on dietary folate and supplemental folic acid intake was derived from semiquantitative food frequency questionnaires and was updated every 4 years.

Main Outcome Measure Relative risk of incident self-reported hypertension during 8 years of follow-up.

Results We identified 7373 incident cases of hypertension in younger women and 12 347 cases in older women. After adjusting for multiple potential confounders, younger women who consumed at least 1000 µg/d of total folate (dietary plus supplemental) had a decreased risk of hypertension (relative risk [RR], 0.54; 95% confidence interval [CI], 0.45-0.66; *P* for trend <.001) compared with those who consumed less than 200 µg/d. Younger women's absolute risk reduction (ARR) was approximately 8 cases per 1000 person-years (6.7 vs 14.8 cases). The multivariable RR for the same comparison in older women was 0.82 (95% CI, 0.69-0.97; *P* for trend=.05). Older women's ARR was approximately 6 cases per 1000 person-years (34.7 vs 40.4 cases). When the analysis was restricted to women with low dietary folate intake (<200 µg/d), the multivariable RR for younger women with total folate intake at least 800 µg/d compared with less than 200 µg/d was 0.55 (95% CI, 0.32-0.94; *P* for trend=.03), and 0.61 (95% CI, 0.34-1.11; *P* for trend=.05) in the older cohort. Among women who did not take folic acid-containing supplements, dietary folate intake of 400 µg/d or more was not significantly associated with risk of hypertension.

Conclusion Higher total folate intake was associated with a decreased risk of incident hypertension, particularly in younger women.

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1989 when 116 671 female registered nurses aged 25 to 42 years returned an initial questionnaire.²¹ The older cohort (Nurses' Health Study I, [NHS I]) was assembled in 1976 when 121 700 female nurses aged 30 to 55 years returned a mailed questionnaire.²² Subsequent questionnaires have been mailed every 2 years to update information on health-related behavior and medical events. Detailed dietary information was collected every 4 years using a semiquantitative food frequency questionnaire.²³ The assembly of the 2

populations for the purpose of this study is outlined in FIGURE 1. Each cohort was followed up for 8 years (1991 to 1999 in NHS II and 1990 to 1998 in NHS I). The institutional review board at Brigham and Women's Hospital re-

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viewed and approved this study, including that participants provided implied consent by virtue of returning their questionnaires.

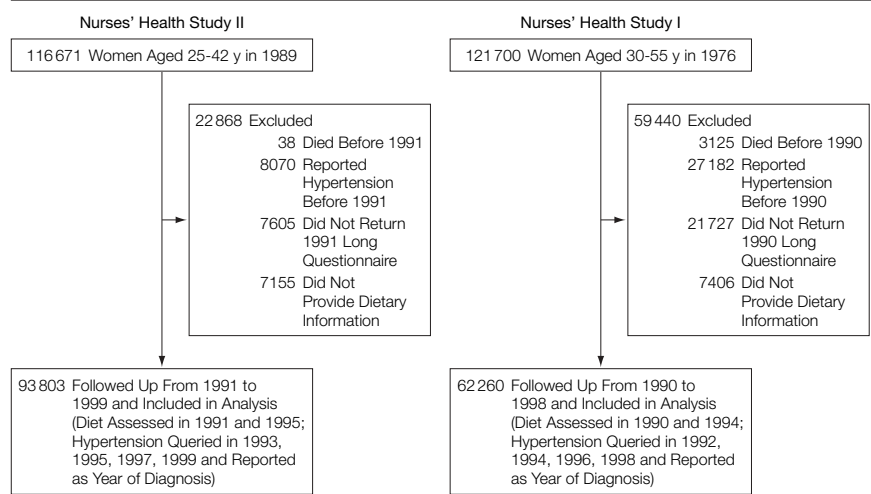
Assessment of Folate Intake

The semiquantitative food frequency questionnaire asks about commonly used portion sizes of various foods and prompts participants to record frequency of consumption during the previous year, with 9 possible response categories ranging from less than once per month to 6 or more times per day; this questionnaire has been validated in these as well as several other cohorts.²³ Nutrient intakes were calculated by multiplying the frequency of consumption by the nutrient content of the specified portion. Nutrient contents of food were obtained from the Harvard University food consumption database, which was derived from US Department of Agriculture sources, manufacturers, and published reports. Information on folate-containing supplements was also collected. The validity of the food frequency questionnaire for measurement of folate intake has been previously demonstrated; the deattenuated correlation between the questionnaire and 4 one-week dietary records was 0.77 for total folate intake,²⁴ and the correlation between the questionnaire and measured serum folate was 0.63.²³ Values for total folate intake (food source plus supplement source), food source folate, and supplemental folic acid were derived. Participants returned food frequency questionnaires every 4 years during the period of follow-up (1991 and 1995 in NHS II and 1990 and 1994 in NHS I), and total folate intake was updated after 4 years. Because dietary information in both cohorts was collected prior to 1998, data on the folate content of foods reflected values before mandated fortification of the nation's food supply.

Assessment of Other Covariates

Age, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), smoking status, and physical activity (metabolic equivalent tasks) were ascertained on the 1991

Figure 1. Assembly of the Study Populations



The "long questionnaire" is the standard questionnaire sent biennially to participants that asks about personal and physical characteristics, reproductive history, family history, environmental and personal exposures, physical activity, screening and other examination history, medication use, use of supplements and certain dietary features, psychosocial history, and disease outcomes.

(NHS II) and 1990 (NHS I) questionnaires and updated after 4 years. Self-reported weight and physical activity have been validated in these cohorts by direct weight measurement (r , 0.97) and activity diaries (r , 0.79). Intakes of alcohol, caffeine, sodium, potassium, magnesium, calcium, protein, fiber, methionine, vitamin B₆, vitamin B₁₂, and vitamin D were ascertained and updated from the food frequency questionnaires. For these dietary covariates, prior validation studies have shown correlations with dietary records ranging from 0.56 for vitamin B₁₂ to 0.90 for alcohol intake. Detailed information on analgesic use was available in NHS II from the 1995 questionnaire and in NHS I from the 1990 questionnaire. Information on the use of oral contraceptives was obtained in NHS II from questionnaires in 1991 and 1995. Information on family history of hypertension was available on the 1989 (NHS II) and 1992 (NHS I) questionnaires. Participants reported their blood pressure in 1989 (NHS II) and 1990 (NHS I) in 1 of 9 systolic categories (<105 mm Hg, 105-114 mm Hg, 115-124 mm Hg, 125-134 mm Hg, 135-144 mm Hg, 145-154 mm Hg, 155-164 mm Hg, 165-174 mm Hg, and \geq 175 mm Hg) and in 1 of 7 diastolic categories

(<65 mm Hg, 65-74 mm Hg, 75-84 mm Hg, 85-89 mm Hg, 90-94 mm Hg, 95-104 mm Hg, and \geq 105 mm Hg). A participant's blood pressure was defined as the middle systolic and middle diastolic values of the reported categories. Participants self-classified their race; classification options were defined by the investigators.

Assessment of Hypertension

The baseline and follow-up biennial questionnaires asked participants to report whether a clinician had made a new diagnosis of hypertension during the preceding 2 years, and were also asked whether they had undergone a physical examination or screening examination. Self-reported hypertension was shown to be highly reliable in the NHS I cohort. In a subset of women who reported hypertension, medical record review confirmed a documented systolic and diastolic blood pressure higher than 140 and 90 mm Hg, respectively, in 100% and higher than 160 mm Hg and 95 mm Hg in 77%; additionally, self-reported hypertension was predictive of subsequent cardiovascular events.²⁵ A participant was considered to have prevalent hypertension if she reported this diagnosis on any questionnaire up to and in-

cluding the 1991 (NHS II) or 1990 (NHS I) questionnaires. Women with prevalent hypertension were excluded. Cases included individuals who first reported hypertension on subsequent questionnaires and whose year of diagnosis was after the return of the 1991 or 1990 questionnaires.

Statistical Analysis

Total folate intake was categorized as less than 200 µg/d, 200 to 399 µg/d, 400 to 599 µg/d, 600 to 799 µg/d, 800 to 999 µg/d, and 1000 µg/d or more. Supplemental folic acid use was analyzed by categorizing total folate intake as less than 200 µg/d, 200 to 399 µg/d, 400 to 599 µg/d, 600 to 799 µg/d, and 800 µg/d or more among those participants with very low dietary folate intake (<200 µg/d). Dietary folate intake among those who did not take folic acid-containing supplements was divided into categories of less than 200 µg/d, 200 to 399 µg/d, and 400 µg/d or more. In all analyses, the reference group was the lowest intake category. Folate intake, as well as other dietary variables, was adjusted for total energy intake.

For each participant, person-months of follow-up were counted from the date of return of the first questionnaire to the date of return of the last questionnaire and allocated according to exposure status. Person-time was truncated when an event occurred. Women were censored at the date of death; or, if they did not return a subsequent questionnaire, they were censored at the date the subsequent questionnaire was mailed. Women who did not provide dietary information at baseline (1991 or 1990) were analyzed during the last 4-year period if they provided dietary information in 1995 or 1994. Incidence rates were computed by dividing the number of new cases of hypertension by the number of person-years in the particular category of folate intake.

Multivariable relative risks (RRs) were calculated using Cox proportional hazards regression and folate intake and other covariates were updated after 4 years. To adjust for potential confounding factors, multivariable models were

adjusted for variables that have been previously associated with incident hypertension or that may affect the plasma homocysteine level (age [continuous], BMI [6 categories], smoking status [past, current, never], physical activity [quintiles], alcohol intake [6 categories], family history of hypertension [yes/no], oral contraceptive use [NHS II only, yes/no], and intakes of sodium, potassium, magnesium, calcium, protein, caffeine, fiber, methionine, vitamin B₆, vitamin B₁₂, and vitamin D [quintiles]). We also controlled for baseline systolic and diastolic blood pressure. Secondary analyses additionally considered adjustment for race (5 categories); frequency of use of aspirin, other nonsteroidal anti-inflammatory drugs, and acetaminophen (days per month); and intakes of cholesterol, saturated fat, polyunsaturated fat, vitamin C, beta carotene, and vegetable and animal protein separately (quintiles).²⁶⁻²⁸ To address the possibility of residual confounding, we analyzed models with BMI and physical activity as continuous variables. Multivariable tests for linear trend were assessed using the median of each exposure category.

We also investigated whether age, BMI, or alcohol consumption modified the relationship between folate intake and risk of hypertension. These analyses were performed by creating interaction terms based on total folate intake and age (≤35 years, 36-40 years, and >40 years in NHS II and <50 years, 50-60 years, and >60 years in NHS I), BMI (≥25 or <25), or alcohol consumption (no alcohol vs any alcohol). The *P* value for interaction was computed from the log likelihood ratio test comparing models with and without the interaction terms.

For all RRs, we calculated 95% confidence intervals (CIs). All *P* values are 2-tailed. Statistical tests were performed using SAS statistical software (version 8.2, SAS Institute Inc, Cary, NC).

RESULTS

Participant Characteristics and Folate Intake

During 646 167 person-years of follow-up, 7373 participants in the younger co-

hort (NHS II) reported having hypertension (11.4 cases per 1000 person-years). At baseline, the cohort mean age was 36.0 years (median, 36.0 years; interquartile range [IQR], 33.0-40.0 years) and the mean BMI was 24.3 (median, 23.0; IQR, 21.0-26.2). TABLE 1 shows baseline characteristics of women stratified by category of total folate intake who were in the NHS II cohort in 1991. With increasing folate intake, we observed lower BMIs and less cigarette, alcohol, and caffeine use. Higher folate intake was also coupled with increased physical activity and higher consumption of vitamin B₆, vitamin B₁₂, vitamin D, potassium, calcium, magnesium, and fiber.

During 321822 person-years of follow-up in NHS I, 12347 participants reported incident hypertension (38.4 cases/1000 person-years). At baseline, the mean age of the cohort was 55.4 years (median, 55.0 years; IQR, 49.0-62.0 years) and the mean BMI was 24.9 (median, 24.0; IQR, 21.9-26.8). Baseline characteristics of the cohort by category of total folate intake in 1990 appear in TABLE 2. Similar relationships between folate category and the covariates were noted as in the younger cohort.

Analysis of Total Folate Intake

In the younger NHS II cohort, total folate intake was associated with a decreased risk of hypertension (TABLE 3). Women who consumed 1000 µg/d or more of total folate had a significant 46% reduction in the risk of incident hypertension after adjusting for multiple confounders (multivariable RR, 0.54 [95% CI, 0.45-0.66]; *P* for trend <.001) compared with women who consumed less than 200 µg/d. Younger women's absolute risk reduction was approximately 8 per 1000 person-years (6.7 vs 14.8 cases). In the cohort of older women (NHS I), higher total folate consumption was also associated with a decreased risk of incident hypertension (Table 3). Compared with women who consumed less than 200 µg/d of folate, those whose average daily intake was 1000 µg or more had a multivariable RR of 0.82 (95% CI, 0.69-0.97; *P* for trend=.05). Older wom-

en's absolute risk reduction was approximately 6 cases per 1000 person-years (34.7 vs 40.4 cases). We also adjusted for baseline systolic and diastolic blood pressure reported by participants in 1989 (NHS II) and 1990 (NHS I), and the results were not substantially altered. For example, comparing women whose intake was 1000 µg/d or more with those whose intake was less than 200 µg/d, the multivariable RR was 0.58 (95% CI, 0.47-0.70) in younger women and 0.84 (95% CI, 0.70-1.00) in older women. After we controlled for BMI and physical activity as continuous variables, the results did not materially change. Furthermore, when analgesic use and race were included in the multivariable models (<4% of the NHS II cohort and <2% of the

NHS I cohort indicated they were either black, Hispanic, or Asian), the results were not substantially altered. When we additionally controlled for cholesterol, saturated fat, polyunsaturated fat, vitamin C, beta carotene, and separate variables for vegetable and animal protein, the results were essentially unchanged (results available on request).

Because the US recommended daily allowance for folate is 400 µg, we examined whether higher folate intake was still associated with a decreased risk of hypertension when the upper limit of the reference category was changed to the recommended daily allowance. Compared with younger women whose total daily folate intake was less than 400 µg, those who consumed 1000 µg/d

or more of folate had a significant 40% reduction in the risk of incident hypertension (multivariable RR, 0.60; 95% CI, 0.51-0.71). In the older cohort, those who consumed 1000 µg/d or more had a multivariable RR of hypertension of 0.87 (95% CI, 0.75-1.01) compared with participants whose intake was less than 400 µg/d.

Finally, because a clinician's diagnosis of hypertension would require an office visit during the 8-year period of follow-up, the analyses were repeated after limiting the populations to those who had at least 1 physical or screening examination during the study period (88 795 women in NHS II and 59 465 women in NHS I). Women who had at least 1 examination during fol-

Table 1. Baseline Characteristics of the Nurses' Health Study II Cohort in 1991*

	Entire Cohort (N = 88 999)	Total Folate Intake, µg/d					
		<200 (n = 4637)	200-399 (n = 44 191)	400-599 (n = 17 109)	600-799 (n = 11 742)	800-999 (n = 5588)	≥1000 (n = 5732)
No. (%) of Participants							
Smoking history							
Past	19 744 (22.2)	772 (16.6)	9657 (21.8)	3993 (23.3)	2693 (22.9)	1309 (23.4)	1320 (23.0)
Current	10 962 (12.3)	1088 (23.5)	5903 (13.4)	1787 (10.4)	1189 (10.1)	579 (10.4)	416 (7.3)
Family history of hypertension	44 373 (50.1)	2372 (51.1)	22 194 (50.2)	8551 (50.0)	5930 (50.5)	2745 (49.1)	2834 (49.4)
Oral contraceptive use†	74 656 (84.5)	3925 (85.2)	37 337 (85.1)	14 190 (83.6)	9774 (83.8)	4655 (83.8)	4775 (83.8)
Mean (SD)							
Folate, µg/d	480 (293)	173 (22.5)	297 (52.6)	489 (58.7)	693 (56.7)	883 (55.7)	1279 (259)
Age, y	36.0 (4.7)	35.8 (4.7)	36.2 (4.6)	36.2 (4.6)	35.9 (4.7)	35.7 (4.8)	34.2 (4.6)
Body mass index	24.3 (5.0)	24.9 (6.0)	24.5 (5.1)	24.0 (4.7)	24.0 (4.7)	23.8 (4.5)	24.3 (4.5)
Physical activity, METs/wk	21.0 (27.4)	14.7 (23.7)	19.2 (24.9)	23.2 (28.7)	24.2 (30.8)	25.3 (32.8)	23.0 (30.0)
Alcohol intake, g/d	3.1 (6.0)	2.7 (6.7)	3.3 (6.3)	3.3 (6.1)	3.2 (5.8)	2.6 (5.4)	1.9 (4.0)
Caffeine intake, mg/d	244 (223)	284 (255)	260 (227)	237 (213)	227 (213)	217 (220)	164 (193)
Vitamin intake							
B ₆ , mg/d	8.2 (25.3)	3.2 (14.5)	5.0 (19.2)	8.4 (24.0)	12.8 (30.4)	15.4 (35.3)	20.4 (42.0)
B ₁₂ , µg/d	9.8 (12.6)	5.2 (3.8)	6.7 (5.2)	9.9 (9.4)	14.2 (14.5)	16.9 (18.8)	21.6 (30.2)
D, IU/d	389 (262)	180 (127)	251 (128)	391 (167)	604 (197)	728 (234)	845 (339)
Mineral intake, mg/d							
Sodium	2153 (369)	1945 (436)	2165 (360)	2172 (362)	2157 (356)	2165 (371)	2153 (369)
Potassium	2934 (539)	2306 (467)	2865 (460)	3079 (553)	3062 (539)	3155 (593)	3073 (578)
Calcium	886 (305)	674 (283)	857 (291)	907 (288)	939 (303)	974 (320)	1025 (341)
Magnesium	316 (74.8)	229 (46.4)	292 (51.3)	334 (65.0)	353 (78.0)	376 (92.1)	373 (102)
Total protein intake, g/d	86.4 (15.3)	78.3 (17.5)	86.4 (14.8)	86.6 (15.2)	87.6 (15.2)	88.0 (15.8)	87.6 (15.5)
Fiber intake, g/d	4.9 (1.6)	3.1 (0.8)	4.6 (1.2)	5.4 (1.8)	5.2 (1.7)	5.4 (1.8)	5.3 (1.8)
Methionine intake, g/d	2.0 (0.4)	1.9 (0.4)	2.0 (0.4)	2.0 (0.4)	2.0 (0.4)	2.1 (0.4)	2.0 (0.4)
Baseline blood pressure, mm Hg‡							
Systolic	113 (9.2)	113 (10.0)	113 (9.3)	112 (9.1)	112 (9.1)	112 (9.0)	112 (8.9)
Diastolic	71 (7.7)	72 (8.2)	71 (7.8)	71 (7.7)	70 (7.6)	70 (7.6)	70 (7.5)

Abbreviation: METs, metabolic equivalent tasks.

*Women were aged 27 to 44 years. Nutrient intakes are adjusted for total energy intake.

†Total number of participants in the entire cohort for oral contraceptive use was 88 373; and by total folate category, less than 200 µg/d: 4605; 200-399 µg/d: 43 876; 400-599 µg/d: 16 983; 600-799 µg/d: 11 667; 800-999 µg/d: 5551; 1000 µg/d or more: 5697.

‡Blood pressure was reported in 1989.

low-up had slightly higher mean total folate intakes (483 vs 439 µg/d in younger women and 430 vs 411 µg/d in older women; $P < .001$ for both comparisons). In these restricted populations, the multivariable RR for incident hypertension comparing women who consumed 1000 µg/d or more compared with less than 200 µg/d was 0.53 (95% CI, 0.43-0.65) in the younger cohort and 0.82 (95% CI, 0.69-0.97) in the older cohort.

Analysis of Supplemental Folic Acid Intake

We examined the association between supplemental folic acid and the risk of incident hypertension by restricting the populations to those women whose dietary folate consumption was less than 200 µg/d. In this limited population,

women in the highest total folate categories derived most of their folate from vitamin supplements.

Among younger women whose dietary folate intake was less than 200 µg/d (n=14249), a total folate intake of 800 µg/d or more compared with less than 200 µg/d was associated with a multivariable RR for hypertension of 0.55 (95% CI, 0.32-0.94; P for trend = .03; TABLE 4). In older women whose dietary folate intake was less than 200 µg/d (n=9007), the same comparison resulted in a nonsignificant 39% decrease in risk of hypertension (multivariable RR, 0.61 [95% CI, 0.34-1.11]; P for trend = .05; Table 4).

Finally, we did not find an independent association between multivitamin use and risk of hypertension in NHS II (multivariable RR, 1.02; 95% CI,

0.98-1.07) or in NHS I (multivariable RR, 1.03; 95% CI, 0.99-1.07) compared with women who did not take multivitamins.

Analysis of Dietary Folate Intake

We investigated the association of dietary folate intake with risk of incident hypertension by restricting our cohorts to those who did not report taking any folic acid-containing supplements (60441 women in NHS II and 38387 women in NHS I). Because the number of women who consumed at least 600 µg/d of dietary folate was too small to obtain stable estimates, we analyzed dietary folate in 3 categories with intake of at least 400 µg/d as the highest category. In NHS II, the multivariable RR for women who did not take folic acid-containing supplements and who con-

Table 2. Baseline Characteristics of the Nurses' Health Study I Cohort in 1990*

	Entire Cohort (N = 53 739)	Total Folate Intake, µg/d					
		<200 (n = 3606)	200-399 (n = 28 422)	400-599 (n = 9910)	600-799 (n = 8147)	800-999 (n = 2535)	≥1000 (n = 1119)
No. (%) of Participants							
Smoking history							
Past	20 726 (38.6)	1 138 (31.6)	10 848 (38.2)	3 846 (38.8)	3 327 (40.8)	1 086 (42.8)	481 (43.0)
Current	9 388 (17.5)	1 109 (30.8)	5 072 (17.8)	1 508 (15.2)	1 184 (14.5)	368 (14.5)	147 (13.1)
Family history of hypertension	22 281 (41.5)	1 477 (41.0)	11 931 (42.0)	4 126 (41.6)	3 285 (40.3)	1 025 (40.4)	437 (39.0)
Mean (SD)							
Folate, µg/d	428 (224)	171 (23.2)	295 (52.8)	489 (59.6)	690 (55.1)	875 (55.4)	1 198 (198)
Age, y	55.4 (7.1)	53.8 (7.0)	55.0 (7.1)	55.8 (7.1)	56.6 (7.1)	56.9 (6.9)	56.3 (7.1)
Body mass index	24.9 (4.3)	25.3 (4.9)	25.1 (4.3)	24.6 (4.2)	24.4 (4.0)	24.4 (3.9)	24.4 (4.0)
Physical activity, METs/wk	16.1 (21.9)	11.3 (19.5)	15.1 (20.7)	17.5 (22.4)	18.0 (24.4)	19.8 (24.3)	18.6 (23.2)
Alcohol intake, g/d	5.1 (9.1)	5.6 (11.0)	5.2 (9.1)	5.0 (9.1)	5.1 (9.1)	4.0 (7.1)	3.7 (7.4)
Caffeine intake, mg/d	270 (229)	355 (279)	277 (227)	250 (212)	241 (216)	251 (233)	240 (249)
Vitamin intake							
B ₆ , mg/d	7.4 (23.4)	3.4 (16.4)	4.6 (17.1)	7.5 (20.8)	11.8 (27.2)	17.4 (38.5)	35.5 (63.5)
B ₁₂ , µg/d	9.9 (15.1)	5.4 (3.1)	7.2 (6.6)	10.5 (10.2)	14.9 (13.5)	18.0 (19.2)	31.2 (75.9)
D, IU/d	338 (252)	159 (119)	219 (130)	364 (174)	589 (194)	720 (240)	1 002 (445)
Mineral intake, mg/d							
Sodium	1 840 (339)	1 744 (376)	1 845 (322)	1 845 (330)	1 837 (329)	1 859 (382)	1 940 (553)
Potassium	2 860 (520)	2 320 (424)	2 804 (428)	2 994 (544)	2 968 (485)	3 189 (589)	3 320 (957)
Calcium	731 (270)	591 (243)	716 (250)	755 (258)	773 (276)	810 (303)	883 (496)
Magnesium	303 (78.3)	229 (45.4)	283 (51.0)	322 (66.5)	342 (80.8)	377 (102)	425 (204)
Total protein intake, g/d	75.7 (13.4)	70.4 (14.9)	75.5 (12.7)	76.2 (13.5)	77.0 (13.2)	77.6 (14.8)	79.9 (17.9)
Fiber intake, g/d	5.0 (1.5)	3.5 (1.0)	4.9 (1.3)	5.4 (1.7)	5.3 (1.5)	5.9 (1.8)	6.0 (2.3)
Methionine intake, g/d	1.8 (0.4)	1.7 (0.4)	1.8 (0.4)	1.8 (0.4)	1.8 (0.4)	1.8 (0.4)	1.8 (0.5)
Baseline blood pressure, mm Hg†							
Systolic	121 (12)	121 (12)	121 (12)	121 (12)	121 (12)	120 (12)	120 (12)
Diastolic	75 (8)	76 (8)	75 (8)	75 (8)	75 (8)	75 (8)	75 (8)

Abbreviation: METs, metabolic equivalent tasks.

*Women were aged 43 to 70 years. Nutrient intakes are adjusted for total energy intake.

†Blood pressure was reported in 1990.

sumed at least 400 µg/d of dietary folate compared with women whose dietary folate intake was less than 200 µg/d was 0.87 (95% CI, 0.74-1.03; *P* for trend=.15; TABLE 5). In the cohort of older women, the same comparison was also not significant (multivariable RR, 0.96 [95% CI, 0.85-1.10]; *P* for trend=.60; Table 5).

Period Analyses

Although the federal mandate for fortification of the US food supply with folic acid took effect in 1998, many manufacturers began fortification in 1996 and 1997 in anticipation of this mandate.¹² In our analyses, we classified par-

ticipants' dietary folate intake in 1991 and 1995 (NHS II), and in 1990 and 1994 (NHS I). We suspected that participants' actual dietary folate intake likely increased in 1996 or 1997 due to fortification. We therefore repeated our analyses for each 4-year period. In younger women, the RR of hypertension in the highest compared with lowest category of total folate intake was 0.48 (95% CI, 0.36-0.64; *P* for trend <.001) from 1991 to 1995 and 0.65 (95% CI, 0.50-0.85; *P* for trend=.02) from 1995 to 1999. This same comparison in older women yielded RRs of 0.68 (95% CI, 0.52-0.89; *P* for

trend=.01) from 1990 to 1994 and 0.93 (95% CI, 0.74-1.16; *P* for trend=.52) from 1994 to 1998.

Effect Modification

We investigated whether the association between folate intake and the risk of incident hypertension varied by age, BMI, or alcohol intake. The magnitude of the inverse association was greater among participants in NHS II who were 35 years or younger and aged 36 to 40 years than in participants who were older than 40 years (*P* for interaction=.01; FIGURE 2A). The interaction between folate intake and age in NHS I (in which

Table 3. Total Folate Intake and Risk of Incident Hypertension

	Total Folate Intake, µg/d						<i>P</i> Value for Trend
	<200	200-399	400-599	600-799	800-999	≥1000	
Nurses' Health Study II (1991-1999; Aged 27-44 y at Baseline)							
Person-years	43 970	311 468	125 508	88 139	39 631	37 451	
No. of cases	652	3653	1304	1076	437	251	
RR (95% CI)							
Age-adjusted	1.00	0.81 (0.74-0.88)	0.72 (0.65-0.79)	0.84 (0.76-0.92)	0.78 (0.69-0.88)	0.57 (0.50-0.66)	<.001
Multivariable*	1.00	0.91 (0.83-1.00)	0.81 (0.72-0.92)	0.88 (0.75-1.02)	0.80 (0.68-0.95)	0.54 (0.45-0.66)	<.001
Nurses' Health Study I (1990-1998; Aged 43-70 y at Baseline)							
Person-years	21 886	163 305	60 934	52 778	16 000	6 919	
No. of cases	885	6065	2406	2134	617	240	
RR (95% CI)							
Age-adjusted	1.00	0.92 (0.85-0.98)	0.91 (0.84-0.98)	0.89 (0.82-0.96)	0.84 (0.76-0.94)	0.79 (0.68-0.91)	<.001
Multivariable†	1.00	0.94 (0.87-1.02)	0.94 (0.85-1.04)	0.91 (0.81-1.01)	0.89 (0.78-1.02)	0.82 (0.69-0.97)	.05

Abbreviations: CI, confidence interval; RR, relative risk.

*Adjusted for age, body mass index, smoking, physical activity, intakes of alcohol and caffeine, family history of hypertension, use of oral contraceptives, and intakes of sodium, potassium, calcium, magnesium, protein, fiber, methionine, vitamin B₆, vitamin B₁₂, and vitamin D at baseline and 4-year follow-up.

†Adjusted for everything in the asterisk footnote except for oral contraceptive use.

Table 4. Total Folate Intake and Risk of Incident Hypertension Among Women Whose Dietary Folate Intake Was Less Than 200 µg/d

	Total Folate Intake, µg/d					<i>P</i> Value for Trend
	<200	200-399	400-599	600-799	≥800	
Nurses' Health Study II (1991-1999; Aged 27-44 y at Baseline)						
Person-years	39 766	10 080	7 857	3 920	2 784	
Cases	600	164	104	66	31	
RR (95% CI)						
Age-adjusted	1.00	1.04 (0.87-1.24)	0.86 (0.70-1.06)	1.11 (0.86-1.44)	0.85 (0.59-1.23)	.49
Multivariable*	1.00	0.95 (0.78-1.18)	0.66 (0.47-0.91)	0.83 (0.54-1.26)	0.55 (0.32-0.94)	.03
Nurses' Health Study I (1990-1998; Aged 43-70 y at Baseline)						
Person-years	19 516	4 924	4 573	2 099	4 72	
Cases	777	220	199	86	16	
RR (95% CI)						
Age-adjusted	1.00	1.06 (0.91-1.24)	0.96 (0.82-1.14)	0.98 (0.78-1.24)	0.74 (0.44-1.22)	.39
Multivariable†	1.00	0.93 (0.78-1.12)	0.82 (0.62-1.07)	0.76 (0.53-1.10)	0.61 (0.34-1.11)	.05

Abbreviations: CI, confidence interval; RR, relative risk.

*Adjusted for age, body mass index, smoking, physical activity, intakes of alcohol and caffeine, family history of hypertension, use of oral contraceptives, and intakes of vitamin B₆, vitamin B₁₂, and vitamin D at baseline and 4-year follow-up.

†Adjusted for everything in the asterisk footnote except for oral contraceptive use.

Table 5. Dietary Folate Intake and Risk of Incident Hypertension Among Women Who Did Not Take Folic Acid–Containing Supplements

	Total Folate Intake, $\mu\text{g}/\text{d}$			P Value for Trend
	<200	200-399	≥ 400	
Nurses' Health Study II (1991-1999; Aged 27-44 y at Baseline)				
Person-years	39 558	254 658	45 784	
Cases	601	2950	432	
RR (95% CI)				
Age-adjusted	1.00	0.78 (0.71-0.85)	0.63 (0.55-0.71)	<.001
Multivariable*	1.00	0.89 (0.80-1.00)	0.87 (0.74-1.03)	.15
Nurses' Health Study I (1990-1998; Aged 43-70 y at Baseline)				
Person-years	19 614	133 808	22 496	
Cases	762	4797	756	
RR (95% CI)				
Age-adjusted	1.00	0.92 (0.85-1.00)	0.85 (0.76-0.94)	.002
Multivariable†	1.00	0.98 (0.90-1.07)	0.96 (0.85-1.10)	.60

Abbreviations: CI, confidence interval; RR, relative risk.

*Adjusted for age, body mass index, smoking, physical activity, intakes of alcohol and caffeine, family history of hypertension, use of oral contraceptives, and intakes of sodium, potassium, calcium, magnesium, protein, fiber, methionine, vitamin B₆, vitamin B₁₂, and vitamin D at baseline and 4-year follow-up.

†Adjusted for everything in the asterisk footnote except for oral contraceptive use.

approximately 75% of the cohort were ≥ 50 y) was not significant (P for interaction = .49; Figure 2B). When we stratified the younger cohort into those with normal BMI (< 25) and those with elevated BMI (≥ 25), the inverse association between folate intake and incident hypertension was greater in women with normal BMI compared with women with elevated BMI (P for interaction $< .001$; Figure 2C). We found no interaction between folate intake and BMI among older women (P for interaction = .51; Figure 2D). The relationship between folate and hypertension was not significantly modified by alcohol consumption (P for interaction = .09 in NHS II and P for interaction = .11 in NHS I).

COMMENT

Higher total folate intake was significantly associated with a reduced risk of incident hypertension even after controlling for a large number of covariates including dietary intake, physical activity, BMI, and family history. The magnitude of the association was greater in younger women. Although plausible biological mechanisms exist that would predict an inverse association between folate and hypertension, to our knowledge this is the first prospective study to report an association

between folate intake and the risk of incident hypertension.

Many clinical studies have demonstrated that supplemental folic acid improves endothelial function in vivo.^{17,18,29-31} In addition, 2 small randomized trials have shown reductions in blood pressure with folic acid supplementation. In the first study, 130 participants were randomized to high-dose folic acid (5 mg/d) and pyridoxine (250 mg/d) or placebo and followed up for 2 years or less.¹⁹ Significant decrements in systolic blood pressure (by 3.7 mm Hg) and diastolic blood pressure (by 1.9 mm Hg) were noted with supplementation but not with placebo.¹⁹ The participants in this trial were relatively young (mean age, 45 years) and only 12% had a history of hypertension at baseline. Because vitamin B₆ was coadministered to the treatment group, the effect seen could not be completely ascribed to folate intake, and the authors concluded that a reduction in homocysteine accounted for the decrease in blood pressure. However, a recent prospective cohort study did not find an association between baseline level of homocysteine and subsequent risk of hypertension.³² Other data indicate that folic acid improves endothelial function in the acute setting before any change in plasma homocysteine.^{17,18} In

the second small randomized trial, 24 long-term smokers with endothelial dysfunction were randomized to 5 mg/d of folic acid or placebo for 4 weeks. Not only did endothelial function improve after treatment with folic acid but the mean systolic and diastolic blood pressure decreased significantly from 121 mm Hg and 71 mm Hg, respectively, to 113 mm Hg and 67 mm Hg; no change in blood pressure was noted in the placebo group.²⁰ As in the other trial, the participants were young (mean age, 38 years) and none had a history of hypertension at baseline.

Although there are no previous reports that higher folate intake is associated with reduced risk of incident hypertension, diets that are high in folate are associated with improvements in blood pressure. Margetts et al³³ showed that a vegetarian diet reduced systolic blood pressure by 5 mm Hg in participants with mild hypertension. Higher intakes of calcium, magnesium, potassium, and fiber have been associated with decreased risk of hypertension in observational studies,^{34,35} and both observational and randomized trials suggest that a diet high in fruits and vegetables lowers blood pressure.^{36,37} These foods are also high in folate. Notably, trials in which individual supplements of calcium, magnesium, potassium, or fiber were administered have not uniformly supported these associations, suggesting that some other active ingredient in food or a combination of nutrients may be necessary to reduce blood pressure.³⁸⁻⁴³

In our cohorts of 93 803 younger women and 62 260 older women followed up for 8 years, total folate intake remained significantly associated with a decreased risk of hypertension after controlling for dietary factors such as intakes of calcium, magnesium, potassium, and fiber, as well as other covariates. This inverse association was robust even after changing the upper limit of the reference group from 200 $\mu\text{g}/\text{d}$ to 400 $\mu\text{g}/\text{d}$, which is the target fortification level.⁴⁴

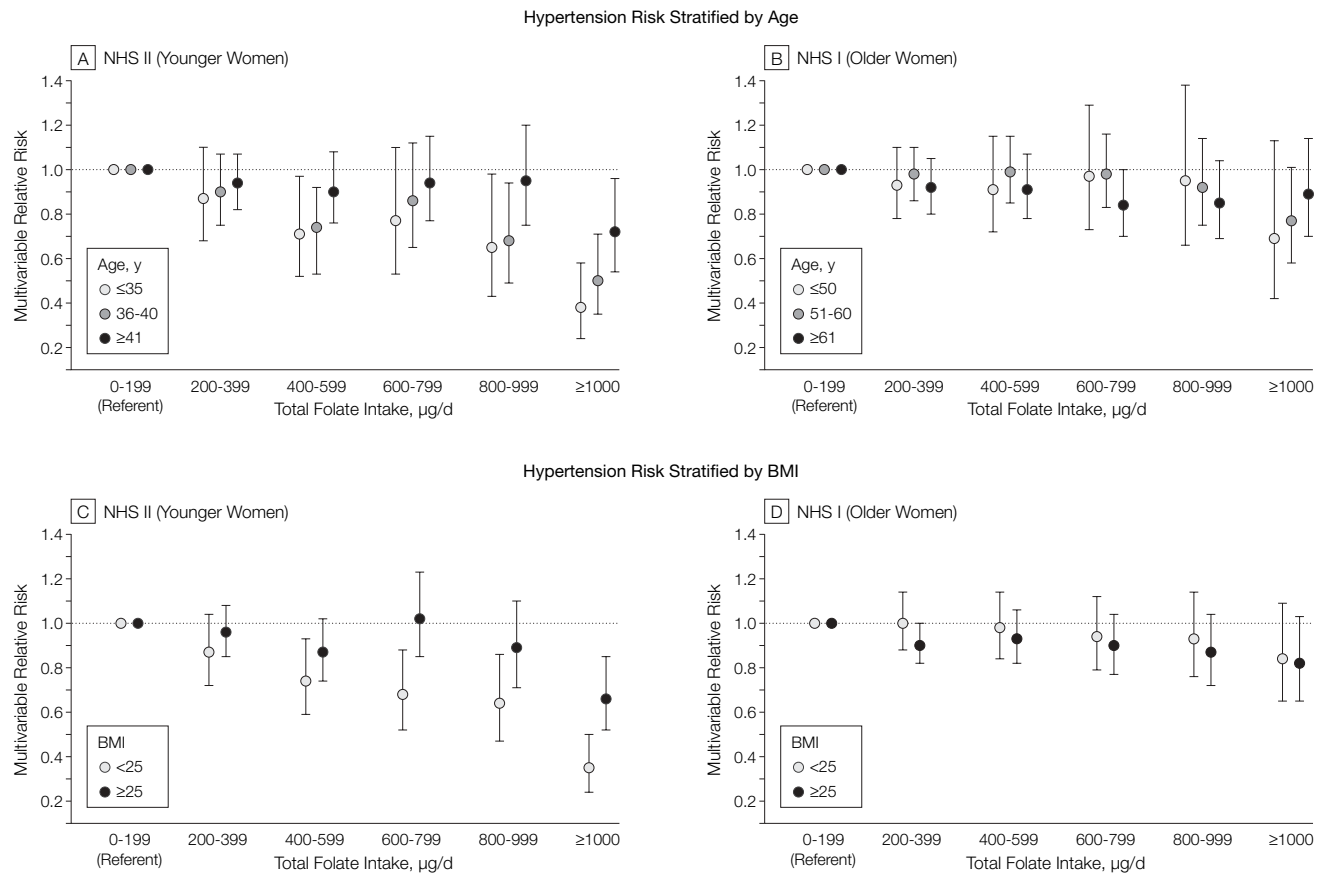
Total folate intake is a combination of both food source (dietary) folate and

supplemental folic acid. We observed a statistically significant association between supplemental folic acid and a reduction in the risk of hypertension; however, the relationship between dietary folate and hypertension was not significant. Several explanations may account for these findings. First, the range of dietary folate intake was limited and relatively few participants consumed very high quantities of dietary folate. The larger variability when supplements were analyzed allowed us to examine higher consumption of folate (eg, ≥ 800 $\mu\text{g}/\text{d}$)—lower dietary folate intake limited the contrast between the highest and lowest categories. Furthermore, an association between folate and hypertension may not be linear, thus precluding any inferences from being drawn when the variability of in-

take is so limited. A second explanation may stem from the increased bioavailability of supplemental folic acid, which has twice the bioavailability as naturally occurring folate from foods.⁴⁵ Finally, ongoing supplementation of the food supply during 1996 and 1997 may have led to misclassification of dietary folate intake during the second half of the 8-year follow-up period. Some participants classified into the reference group of less than 200 $\mu\text{g}/\text{d}$ in 1995 or 1994 may well have changed groups during the latter part of the last 4 years of follow-up. This type of misclassification would tend to obscure any association. Indeed, the magnitude of the inverse association between total folate intake and incident hypertension was greater during the first than the second 4 years of follow-up.

The magnitude of the inverse association between folate intake and hypertension was more pronounced in younger compared with older women. Similar observations have been made in these cohorts when other exposures, such as the association between nonnarcotic analgesic use and hypertension, have been examined.^{46,47} Participant age significantly modified the association between folate intake and incident hypertension, with the greatest reduction in those younger than 35 years for whom consumption of at least 1000 $\mu\text{g}/\text{d}$ of total folate was associated with one third the risk of developing hypertension compared with those consuming less than 200 $\mu\text{g}/\text{d}$. We observed a similarly pronounced reduction in the risk of hypertension among younger women with a BMI of less than 25. Although the mecha-

Figure 2. Incident Hypertension by Category of Total Folate Intake Stratified by Age and BMI



A, *P* for interaction = .01; B, *P* for interaction = .49; C, *P* for interaction $< .001$; and D, *P* for interaction = .51. NHS indicates Nurses' Health Study and BMI indicates body mass index. Error bars indicate 95% confidence intervals.

nisms for these associations are unclear, we speculate that differences in the pathogenesis of hypertension in younger compared with older and leaner compared with heavier individuals may explain differences in folate sensitivity.

Our study has limitations and strengths that deserve mention. First, current figures from the Framingham Offspring Study estimate that after US fortification was completed in 1998, folic acid intake increased by an average of 190 µg/d.⁴⁸ Therefore, in the United States today, there are probably few persons whose total folate intake falls below 200 µg/d. Nevertheless, we still observed a decreased risk of hypertension among women with high total folate intake compared with those who consumed less than 400 µg/d. Second, we did not directly measure the participants' blood pressure, and the diagnosis of hypertension was self-reported. However, self-reported hypertension is highly reliable in these cohorts of health professionals.²⁵ Third, we do not have information on which women had blood pressure measurements during the follow-up period. Despite this, when we limited our analysis to women who reported having physical or screening examinations during the follow-up period, increasing the likelihood that their blood pressure was measured, our findings were not altered. In addition, the mean total folate intake was slightly higher among women who had physical or screening examinations (483 vs 439 µg/d in younger women and 430 vs 411 µg/d in older women; $P < .001$ for both comparisons). Thus, if women who visited their clinicians were more likely to be diagnosed as having hypertension, then this difference in folate intake would have attenuated our results. Fourth, we did not measure serum folate levels, raising the potential for misclassification. Nevertheless, ascertainment of folate consumption from our questionnaires has been validated in the past and correlates well with dietary records and serum folate levels.^{23,24} Finally, the possibility for residual confounding in any observational study cannot be fully eliminated; however, we were able to adjust for multiple known

and suspected risk factors for hypertension, and we observed little difference between the age-adjusted and multivariable models.

In conclusion, higher intake of folate is associated with a decreased risk of incident hypertension, especially in younger women. Supplemental folic acid appears to be independently associated with a reduction in risk, and future trials should examine folic acid supplementation as a means of lowering blood pressure and preventing hypertension in young women. These results may have important public health implications in the United States, given the ready availability and safety of folic acid supplementation and the clinical importance of hypertension.

Author Contributions: Dr Forman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Forman, Curhan.

Acquisition of data: Stampfer, Curhan.

Analysis and interpretation of data: Forman, Rimm, Stampfer, Curhan.

Drafting of the manuscript: Forman.

Critical revision of the manuscript for important intellectual content: Forman, Rimm, Stampfer, Curhan.

Statistical analysis: Forman, Stampfer, Curhan.

Obtained funding: Forman, Curhan.

Administrative, technical, or material support: Forman, Stampfer, Curhan.

Study supervision: Rimm, Curhan.

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