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Diet and lifestyle risk factors associated with incident hypertension in women

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Abstract

Context—Hypertension is an important preventable risk factor for death among women. While several modifiable risk factors have been identified, their combined risk and distribution in the population has not been assessed.

Objective—To estimate the hypothetical fraction of hypertension associated with dietary and lifestyle factors in women.

Design, Setting, and Participants—Prospective cohort study of 83,882 adult women aged 27-44 years in the second Nurses' Health Study who were free from hypertension, cardiovascular disease, diabetes, and cancer in 1991, and who had normal reported blood pressures (defined as 120/80 or less), with follow-up for incident hypertension for 14 years through 2005. We identified 6 modifiable lifestyle and dietary factors for hypertension and defined 6 low risk categories: body mass index (BMI) <25 kg/m^2, a daily mean of 30 minutes of vigorous exercise, a DASH style diet, modest alcohol intake up to 10 g/day, non-narcotic analgesic use less than once per week, and intake of 400 μg/day or more of supplemental folic acid. We analyzed the association between combinations of three (normal body mass index, daily vigorous exercise, and DASH style diet), four (three low risk factors plus modest alcohol intake), five (four low risk factors plus avoidance of analgesics), and six (addition of folic acid supplements) low risk factors and the risk of developing hypertension.

Main Outcome Measures—Adjusted hazard ratios (HRs) for incident self-reported hypertension and population attributable risks.

Results—A total of 12,319 incident cases of hypertension were documented. All six modifiable factors were independently associated with the risk of developing hypertension during follow-up after also adjusting for age, race, family history of hypertension, smoking status, and use of oral

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contraceptives. For women who had all six low-risk factors (0.3% of the population), the hazard ratio for incident hypertension was 0.22 (95% CI, 0.10-0.51); the hypothetical population attributable risk (PAR) was 78% (95% CI, 49-90%) for women who lacked these low-risk factors. The corresponding hypothetical absolute incidence rate difference (ARD) was 8.37 cases per 1000 person-years. The PARs were 72% (95% CI, 57-82%; ARD=7.76) for 5 low risk factors (0.8% of the population), 58% (95% CI, 46-67%; ARD=6.28) for 4 low risk factors (1.6% of the population), and 53% (95% CI, 45-60%; ARD=6.02) for 3 low risk factors (3.1% of the population). BMI alone was the most powerful predictor, with BMI ≥25 kg/m^2 having an adjusted PAR of 40% (95%CI, 38%-41%) compared with BMI <25 kg/m^2.

Conclusion—Adherence to low-risk dietary and lifestyle factors was associated with a significantly lower incidence of self-reported hypertension. Adopting low risk dietary and lifestyle factors has the potential to prevent a large proportion of new onset hypertension occurring among young women.

Introduction

Hypertension contributes to more excess deaths in women than any other preventable factor.[1] Pharmacologic treatment of established hypertension has proven benefits, yet these efforts are costly, require medical intervention, and have adverse effects. Furthermore, just 37% of individuals with hypertension in the US have controlled blood pressure, a proportion that rises to 57% with pharmacologic intervention.[2] Primary prevention of hypertension, therefore, would have major positive public health ramifications.

Many modifiable risk factors for hypertension have been identified, including overweight and obesity,[3, 4] physical inactivity,[5-7] and poor diet.[8, 9] In recent years, excessive alcohol intake and alcohol abstinence,[10-12] non-narcotic analgesic use,[13-15] and low folate intake[16] have been identified as independent novel and modifiable risk factors for developing hypertension among women.

Although the effects of interventions to modify one or several of these factors have been documented,[17-19] the proportion of new onset hypertension that could conceivably be prevented by modification of a combination of lifestyle factors has not been evaluated. In this study, we examined the association between combinations of low-risk lifestyle factors and the risk of developing hypertension during 14 years of follow-up among 83,882 women in the Nurses' Health Study II.

Methods

Source Population

The Nurses' Health Study II (NHS II) is an ongoing prospective cohort study of 116,671 female registered nurses that began in 1989. Participants are followed via biennial questionnaires that gather information on health-related behaviors (including diet) and medical events. Follow-up of participants was >90% through 2005. The 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.

Study Population

Because diet was first assessed in NHS II in 1991, we defined 1991 as the baseline period. Of the 116,430 women in NHS II at the study start in 1989, we limited our analysis to 83,882 women for the following non-mutually exclusive reasons at baseline in 1991: did not return the 1991 questionnaire or did not provide dietary information (n=16,415); existing diagnosis of hypertension reported on 1989 or 1991 questionnaires (n=8,070); use of antihypertensive medications (n=2,962); median reported blood pressure greater than 120/80 mmHg

(n=10,776); existing diagnoses of diabetes mellitus (n=489), myocardial infarction (n=42), angina (n=238), stroke (n=100), elevated cholesterol (n=8,697), or cancer (n=624), except for non-melanoma skin cancer. We excluded women whose median reported blood pressure was higher than 120/80 mmHg because pre-hypertension is one of the strongest risk factors for incident hypertension,[20] and because many of the modifiable risk factors under study may be related to pre-hypertension. Excluding these women meant that the population under study had normal blood pressure at baseline. The remaining 83,882 women were included in the analysis.

Ascertainment of Diet

To assess dietary intake, we used a semiquantitative food-frequency questionnaire (FFQ) that asked about the usual intake of more than 130 foods and beverages during the previous year. Participants completed the baseline FFQ in 1991 and subsequent FFQs were completed every four years thereafter.

Intake of individual dietary factors was computed from the reported frequency of consumption of each specified unit of food and from United States Department of Agriculture data on the content of the relevant nutrient in specified portions. The intake of supplements (including folic acid) in multivitamins or in isolated form was determined by the brand, type, and frequency of reported use.

The reproducibility and validity of this FFQ has been documented in similar cohorts of health professionals, including nurses.[21, 22] Correlations between the intakes of individual food items as measured by the FFQ and intakes as assessed by dietary records were high. For example, correlations were 0.88 for skim milk, 0.86 for yogurt, 0.95 for bananas, 0.76 for oranges, 0.59 for green peppers, 0.71 for tomatoes, 0.77 for bacon, 0.63 for hamburger, and 0.84 for sugar-sweetened cola.[23] The correlation for folic acid intake was 0.77,[21] and for alcohol intake was 0.90.[24]

Based on the diet prescribed in the Dietary Approaches to Stop Hypertension (DASH) trial, [17] we constructed a DASH score based on food and nutrients emphasized or minimized in the DASH diet, focusing on 8 components: high intake of fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains and low intake of sodium, sweetened beverages, and red and processed meats.25 The first four components were directly targeted in the DASH diet, which also included lower consumption of red and processed meats and greater consumption of whole grains.25

We calculated each participant's DASH score at baseline in 1991 using the FFQ, and then updated the DASH score every four years (1995, 1999, and 2003) during the period of follow-up as participants completed subsequent FFQs. For each of the components, we classified participants into quintiles according to their intake. The component score for fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains was the participant's quintile ranking (i.e., quintile 1 was assigned 1 point and quintile 5 was assigned 5 points). For sodium, red and processed meats, and sweetened beverages, low intake was desired: the lowest quintile was given a score of 5 points and the highest quintile a score of 1 point. We then summed up the component scores to obtain an overall DASH score ranging from 8 to 40.

Ascertainment of Non-dietary Factors

In 1991 and every 2 years thereafter, we ascertained body mass index (BMI, weight in kilograms divided by height in meters squared); self-reported weight was highly reliable (r=0.97) among a subset of regionally-residing participants who underwent direct measurement of their weight.[26] Women also reported the amount of time they spent doing vigorous physical activity (either as days per week, or minutes per week, depending on the questionnaire cycle),

including jogging, running, swimming, racquet sports, bicycling, or other aerobic activity; questionnaire-derived information about these activities has been validated in comparison to physical activity diaries (r=0.79).27 Walking was not included because walking speed was not specified and reported walking did not correlate with vigorous exercise. Use of non-narcotic analgesics, including non-steroidal anti-inflammatory drugs, acetaminophen, and aspirin, was reported on biennial questionnaires in two basic formats. Until 1995, women were asked whether they regularly used any of these medications, with regular use defined as 2 or more days per week. From 1995 onwards, women were asked to report the frequency with which they used these medications in greater detail, allowing for categorization into none, 1 day/week, 2-3 days/week, 4-5 days/week, and 6-7 days/week.13

In addition to these factors, age, smoking status, and use of oral contraceptive (OC) pills were updated with each questionnaire cycle. Family history of hypertension was ascertained from the 1989 questionnaire. Race was included in the analysis because it is a risk factor for hypertension. Participants self-classified their race in 1989; classification options included: Southern European/Mediterranean, Scandinavian, Other Caucasian, African-American, Hispanic, Asian, Other, and participants were permitted to select more than one.

Definition of Low-risk Groups

A BMI of <25 kg/m^2, which is the current WHO defined cut-point separating normal weight from overweight and obesity, was selected as the low-risk category for weight. Higher BMI is a strong risk factor for developing hypertension, and weight loss may reduce blood pressure.[3, 4, 18, 19]

Low-risk physical activity was defined as a mean of 30 minutes per day spent in vigorous exercise, in keeping with published guidelines.[28, 29] Physical activity, lowers blood pressure and decreases hypertension risk.[7, 18]

The DASH diet has been shown in randomized trials to lower blood pressure,17 and long-term observational data have shown that a DASH style diet is associated with smaller 5-year increments in blood pressure.[8] In keeping with these studies, we classified women whose DASH scores were in the top quintile (20%) as having a low-risk diet.

Previous observational studies have demonstrated a J-shaped relation between alcohol use and risk of hypertension; specifically, modest alcohol use is associated with a lower risk of hypertension.10-12 We defined low-risk alcohol intake as greater than zero but not exceeding 10 g/day (approximately one alcoholic beverage per day).

Because previous studies documented increases in the risk of incident hypertension with even a low frequency of analgesic use,13-15 we defined use less frequent than once per week as the low-risk category. In terms of supplemental folic acid use, our previous data indicated that, among women with very low dietary intake of folate, higher intake of folate (principally from supplements) was inversely related to risk of incident hypertension, with a significant reduction in risk observed first in women whose intake exceeded 400 μg/day.[16] Although, in that prior analysis, total folate intake (from both diet and supplements) was also inversely associated with hypertension, we considered only supplemental folic acid for the present analysis because the DASH score served as our assessment of diet. Therefore, we defined women who took ≥400 μg/day of supplemental folic acid as being in the low-risk group.

At two year intervals during the course of follow-up, we updated information regarding BMI, diet, exercise, and other covariates to reflect participants' responses to the most recent questionnaire.

Ascertainment 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 two years. We previously validated self-reported hypertension in this cohort.[30] Among a randomly selected subset (n=147) of women who reported a new diagnosis of hypertension, 94% had the diagnosis confirmed by medical record review. Cases included individuals who first reported hypertension on questionnaires after 1991; new cases of hypertension were recorded as month and year of diagnosis.

Statistical Analyses

The person-time for each participant was calculated from the date of the return of the 1991 questionnaire to the date at which hypertension was first diagnosed, death, or June 2005, whichever came first.

We initially analyzed the association between each of the six modifiable risk factors and the risk of developing incident hypertension. We used Cox-proportional hazards regression to compute the hazard ratio (HR) and 95% confidence intervals (95% CI) for categories of each factor. This analysis adjusted simultaneously for all six of these modifiable factors, as well as for the following *a priori* potential confounders: age (continuous), smoking status (current, past, never), OC use (current user, non-user), race, and family history of hypertension. As with the six low risk factors, age, smoking status, and OC use were updated as time-dependent variables with each questionnaire cycle to reflect the most recent information.

Next, we dichotomized each of these factors into low-risk vs. non-low-risk categories, according to our description in the section above; specifically: BMI (<25 vs. ≥ 25 kg/m^2); vigorous physical activity (daily vs. non-daily); DASH score (highest quintile vs. lower four quintiles); alcohol intake (0.1 to 10 g/day vs. other levels of intake); analgesic use (< once/week vs. once or more/week); supplemental folic acid use (≥ 400 μg/day vs. <400 μg/day). We then analyzed the association between combinations of low-risk factors with incident hypertension using Cox-proportional hazards regression.

Because weight control, healthy eating, and exercise are the three lifestyle modifications with the strongest evidence base for blood pressure control (and are the three strongest lifestyle recommendations by the JNC),[31] we first compared women with a combination of these 3 low-risk factors with all other women, and adjusted for alcohol intake, analgesic use, and supplemental folic acid use, as well as for age, smoking, OC use, race, and family history of hypertension. We then analyzed women with a combination of the 4 low-risk factors of BMI, physical activity, diet, and alcohol intake because limiting alcohol intake is also supported by interventional studies and is recommended by the JNC.31 Finally, we analyzed women with the 5 low-risk factors of BMI, physical activity, diet, alcohol intake, and analgesic use, and all 6 low-risk factors of BMI, physical activity, diet, alcohol intake, analgesic use, supplemental folic acid use compared with all other women. Analgesic use and folate intake were also pre-specified low risk factors based upon our prior research,[15, 16, 32] but were added last because they are not present in current guidelines for control of blood pressure.

For each of these analyses, we calculated the hypothetical population attributable risk,[33] an estimate of the percentage of new hypertension cases occurring in this population that could hypothetically have been prevented if all women had been in the low-risk group (assuming a causal and independent relation between the risk factor and hypertension). The standard equation was used to compute this hypothesized attributable fraction, where P_e is the exposed proportion:

$$PAR = \{(HR-1) \times P_e\} \div \{([HR-1] \times P_e + 1\}$$

Finally, we performed stratified analyses by family history of hypertension (yes vs. no), OC use (yes vs. no, as a time-varying variable), and by BMI group (<25, 25-29.9, and ≥30 kg/m^2, as a time-varying variable). For stratification by BMI, we divided our low-risk combinations into the 4 low-risk factors of physical activity, diet, alcohol intake, and analgesic use, and the 5 low-risk factors of physical activity, diet, alcohol intake, analgesic use, and supplemental folic acid use. We tested effect modification by family history, OC use, and BMI. We used multiplicative interactions terms and P-values for interaction were generated using the -2 log likelihood ratio test comparing multivariable models with and without inclusion of the interaction term..

To estimate hypothetical absolute reductions in hypertension incidence rates associated with constellations of low risk factors, we first computed adjusted incidence rates for women with low risk constellations by multiplying the incidence rate among the group lacking the low risk factors by the multivariable HR among women with the low risk constellation. Second, these incidence rates were subtracted to get the hypothesized absolute incidence rate difference (ARD), expressed as number of cases per 1,000 person-years (py). Third, we divided 100 by the ARD to compute the hypothesized "number needed to treat" (NNT) per 10 years. The meaning of the NNT in the context of this observational study assumes causal associations between the low-risk factors and hypertension, and represents the number of women who were not following the low risk constellation who would have to adopt the low risk constellation over a period of 10 years to hypothetically prevent the development of 1 hypertension case.

All statistical tests were performed using SAS statistical software (version 9.1, SAS Institute Inc, Cary, NC). All p-values were two-tailed; a p-value <0.05 was considered statistically significant.

Results

At baseline in 1991, the mean age of the population was 36 years (standard deviation, 4.6 years), and the mean BMI was 23.7 kg/m^2 (standard deviation, 4.3 kg/m^2). During 14 years of follow-up, 12,319 women reported a new diagnosis of hypertension (approximately 15% of the population).

The multivariable-adjusted associations between the 6 individual modifiable risk factors and incident hypertension are shown in Table 1. The strongest risk factor was a higher BMI, with obese women having a HR for incident hypertension of 4.70 (95% CI, 4.45-4.96) compared with women whose BMI was <23.0 kg/m^2. In this population, 40% of new hypertension cases (95% CI, 38-41%) could hypothetically be attributed to overweight or obesity (defined as a BMI ≥25 kg/m^2), and 50% of new cases could hypothetically be attributed to a BMI ≥23.0 (95% CI, 49-52%). The other 5 modifiable risk factors were also associated with incident hypertension after multivariable adjustment (Table 1). The other modifiable risk factors were associated with individual hypothetical PARs much lower than overweight and obesity: 17% (95% CI, 15-19%) for routine analgesic use, 14% (95% CI, 10-17%) for not following a DASH style diet, 14% (95% CI, 9-19%) for not engaging in daily vigorous exercise, 10% (95% CI, 8-12%) for no or excessive alcohol consumption, and 4% (95% CI, 1-7%) for folic acid supplement use <400 μg/d.

Specific groups of 3, 4, 5, and 6 low-risk factors were associated with progressively lower HRs of developing hypertension in multivariable models (Table 2). Women with a combination of normal BMI (<25 kg/m^2), daily vigorous physical activity, and a DASH type diet (in the highest

quintile of DASH score) had a HR for incident hypertension of 0.46 (95% CI, 0.39-0.54). The hypothetical population attributable risk was 53% (95% CI, 45-60%), suggesting that 53% of new onset hypertension in this population might potentially have been prevented if all women had these 3 low-risk factors. The corresponding hypothesized ARD was 6.02 cases/1000 py, and the hypothesized NNT over 10 years was 16.6 women. The hypothetical PAR increased to 58% (95% CI, 46-67%; ARD=6.28 cases/1000 py, NNT over 10 years=15.9) if the low-risk group also included modest alcohol intake (in addition to normal BMI, daily exercise, and DASH type diet), and to 72% (95% CI, 57-82%; ARD=7.76 cases/1000 py, NNT over 10 years=12.9) if women also avoided routine analgesic use. Only 0.3% of the population had all 6 low-risk factors (including use of ≥400 μg/day of folic acid supplementation), but the analysis of hypothetical PAR suggested that if all women were low-risk for all 6 factors, then 78% (95% CI, 49-90%; ARD=8.37 cases/1000 py, NNT over 10 years=11.9) of new-onset hypertension might potentially have been avoided.

The association between a parental family history of hypertension and the development of hypertension in the child may represent the effect of both genetic and non-genetic factors.[34] To address whether a low-risk lifestyle would be similarly associated with lower hypertension risk among those with and without a familial predisposition to developing hypertension, we repeated our analyses after stratifying by family history of hypertension (Table 3). The hypothetical PARs associated with the constellation of 3 low-risk factors was 57% (95% CI, 43-67%; ARD=4.60 cases/1000 py, NNT over 10 years = 21.7) among women without a family history of hypertension, and 51% (95% CI, 40-60%; ARD=7.66 cases/1000 py, NNT over 10 years=13.1) among women with a positive family history of hypertension. Among women without a family history of hypertension, the hypothetical PAR was 90% (95% CI, 32-99%; ARD=6.82 cases/1000 py, NNT over 10 years=14.7) in women who lacked 6 low-risk factors; a similar analysis among women with a family history of hypertension yielded a hypothetical PAR of 69% (95% CI, 25-87%; ARD=9.87 cases/1000 py, NNT over 10 years=10.1). Tests for interaction were null regardless of which constellation of low-risk factors was considered.

Oral contraceptive use at some point during follow-up was common (85.7% of women) and was independently associated with an increased risk of incident hypertension; OC use may potentially have contributed to 15% of all new cases of incident hypertension (95% CI, 11-20%). We addressed whether the association of various constellations of low-risk factors differed among those women who did vs. did not use OC (Table 4), with OC use updated with each questionnaire cycle as a time-dependent variable. Among non-OC users, the hypothetical population attributable risks ranged from 59% (95% CI, 48-69%) for 3 low-risk factors to 83% (95% CI, 30-96%) for the 6 low-risk factors. Among OC users, the hypothetical population attributable risks ranged from 48% (95% CI, 35-57%) to 73% (95% CI, 28-90%). Again, we found no evidence for effect modification.

Because BMI was by far the strongest risk factor for incident hypertension, we examined whether a low-risk lifestyle had similar hypothetical PARs depending upon whether women were normal weight, overweight, or obese (Table 5). Overall, we found that constellations of low-risk factors were inversely associated with hypertension among normal weight and overweight women, but not among obese women (p-interaction = 0.02). Specifically, among normal weight individuals (BMI<25 kg/m^2), a constellation of 4 low-risk factors (DASH type diet, daily exercise, modest alcohol intake, and avoidance of analgesics) was associated with a HR for incident hypertension of 0.46 (95% CI, 0.30-0.71); the corresponding hypothetical PAR was 54% (95% CI, 29-70%; ARD=3.19 cases/1000 py, NNT over 10 years=31.3). This same constellation of low-risk factors among overweight women (BMI 25.0-29.9 kg/m^2) yielded a hypothetical PAR of 47% (95% CI, 4-71%; ARD=6.83 cases/1000 py, NNT over 10 years=14.6); however, among obese women, the hypothetical PAR was a non-significant 5% (95% CI, 0-51%). We also tested a constellation of 5 low-risk factors (DASH type diet, daily

exercise, modest alcohol intake, avoidance of analgesics, and use of ≥400 μg/day of supplemental folic acid) among normal, overweight, and obese women, and found that the hypothetical PAR if women lacked these low-risk factors was 62% (95% CI, 14-83%, ARD=3.65 cases/1000 py, NNT over 10 years=27.4) among normal weight women, and not statistically significant among overweight and obese women, albeit the sample sizes were very small (Table 5).

Baseline mean blood pressures and end-of-follow-up blood pressures and anti-hypertensive medication use among all women (including those who did and did not develop hypertension during follow-up) are shown in Table 6. In 2005, mean systolic and diastolic blood pressure was lower by 4/3 mmHg for those with 3 low-risk factors up to 6/4 mmHg for those with 6 low-risk factors ($p<0.001$ for both comparisons). Additionally, anti-hypertensive medication use was lower among those with low-risk factors. Of the women with 3 low-risk factors, anti-hypertensive medication use at the end of follow-up in 2005 was 5.8% compared to 11.7% among those who did not have these low-risk factors ($p<0.001$). For 6 low-risk factors, this comparison was 3.9% vs. 11.9% ($p<0.001$).

Comment

In this large-scale prospective study of women, low-risk combinations of modifiable lifestyle factors, such as maintenance of a normal BMI, eating a diet high in fruits, vegetables, low-fat dairy products and low in sodium, engaging in vigorous physical exercise on a daily basis, drinking a modest amount of alcohol, avoiding over-the-counter analgesics, and taking supplemental folic acid, were associated with dramatic reductions in the incidence of hypertension during follow-up. Although speculative, if these associations were causal and independent, then lifestyle modification could have the potential to prevent a large proportion of new onset hypertension occurring among young women. Each of these 6 modifiable lifestyle variables has been shown in various observational studies to be independently associated with risk for incident hypertension. Higher BMI or higher body weight has been well recognized for decades as a risk factor for developing hypertension among women.[4, 35] For example, the risk associated with a BMI≥31.0 kg/m^2 was 6-fold higher compared with a BMI<20 kg/m^2 in a large cohort of US women.[4] Higher physical activity level has also been shown in multiple studies to be associated with a lower risk of incident hypertension.[5-7] For example, the CARDIA study demonstrated a 15% reduction in the risk with higher physical activity levels, which is similar to our findings.6 Numerous prospective cohort studies have examined dietary factors and the risk of developing hypertension, with benefits generally observed for diets rich in fruits and vegetables but low in sweets, refined grains, and high-fat protein sources.[8, 9] In addition, 3 studies have documented J-shaped associations between alcohol intake and risk of hypertension in women, with modest alcohol intake (≤ 10 g/day) associated with the lowest risk.[10-12] In 2 independent prospective cohorts of women (the one currently under study plus the Nurses' Health Study I), individuals who used non-narcotic analgesics, specifically acetaminophen, NSAIDs, and aspirin, were at increased risk for development of hypertension compared with non-users after multivariable adjustment.[13-15] With respect to folate intake, 2 prospective cohort studies demonstrated a decreased risk of incident hypertension with higher intake of folate. The risk comparing women whose total daily intake was ≥1000 mcg/day to those whose intake was <200 mcg/day was 46% lower among younger women (NHS2) and 18% lower among older women (Nurses' Health Study I).16 When these analyses were restricted to women whose folate intake from food was negligible, higher daily intake from supplements was also associated with significantly lower risk of hypertension.16

Interventional trials have confirmed the findings of these observational studies. Reductions in blood pressure resulted from weight loss,[18, 19] physical activity,[18] DASH type diets,[17, 18, 36] alcohol reduction,[37] and folic acid supplementation,[38, 39] while increases in blood pressure

were noted with administration of acetaminophen, NSAIDs, and aspirin.[40-42] The PREMIER study randomized individuals to receive an intervention combining weight loss, physical activity, and a DASH diet or to receive advice only.[18] At 6 months, the change in systolic BP was 4.5 mmHg lower in the intervention group compared with the advice-only group, and at 18 months, the odds of developing incident hypertension were 23% lower.[18] These findings provide support for our assumptions that these associations might potentially be causal, and therefore that estimates of the PAR may be appropriate.

In our study, BMI was the most powerful predictor of incident hypertension and the largest single contributor to the hypothetical population attributable risk. We therefore tested whether individuals who were overweight, but otherwise followed a healthy lifestyle, had a lower likelihood of developing hypertension. Although we found that multiple low-risk factors were significantly associated with lower risk among normal weight and overweight women, there was no association among obese women; these findings imply that, in the context of hypertension risk, obese women might not benefit from other low-risk behaviors unless weight loss is also addressed. Because obesity is common (approximately one third of the US population), this finding has important consequences, particularly since, in the absence of calorie restriction and additional physical activity, adherence to the other five low risk factors may not reduce weight.

In contrast to the BMI-stratified models, our data indicate that adherence to a combination of low-risk lifestyle factors could have the potential to prevent the majority of new-onset hypertension in young women irrespective of family history of hypertension and irrespective of OC use. The former conclusion is particularly poignant given that some women may mistakenly believe that their parental history signifies that their own development of hypertension may be unavoidable; rather, these women may conceivably at least delay onset of hypertension through risk factor reduction.

Our study has limitations. First, we dichotomized lifestyle factors into low-risk vs. non-low-risk for the purposes of calculating population attributable risk; as can be seen in Table 1, the associations between these factors and hypertension risk are continuous, not dichotomous. However, increasing the number of categories for each of the 6 risk factors would have exponentially increased the number of possible low-risk constellations and thereby make calculation and presentation of the data overly complex and underpowered. Second, we did not include OC use in our analyses as a seventh modifiable factor even though it does contribute to risk. We did so because a woman's decision to use OCs is multidimensional, with both risks as well as proven benefits. Third, we did not have information in the whole cohort on other potentially important modifiable risk factors, such as plasma 25-hydroxyvitamin D levels, which have been recently demonstrated to be inversely related to hypertension risk,[30, 43] as well as waist circumference. Fourth, follow-up for hypertension incidence was 14 years; it is possible that low risk factors delay rather than entirely prevent hypertension at the rates calculated by the PAR. Fifth, it is possible that because of measurement error inherent in the questionnaires, some women may have had their BMI, level of physical activity, and analgesic use misclassified; however, the questionnaires have been demonstrated previously to reliably ascertain this information. Misclassification of diet is particularly relevant because, although most foods and nutrients are reliably measured, dietary sodium intake is not measured well with the FFQ. Nevertheless, this type of misclassification would likely be random, and therefore our calculations of risk may in fact be underestimates of true risk; indeed, others have estimated that a population-based program to lower dietary sodium could prevent 30% of hypertension.[44] Sixth, because hypertension was self-reported, some women may have had their hypertension status misclassified. Nonetheless, hypertension reporting in these nurses has been shown to be reliable. Similarly, we did not have information about whether hypertension was primary or secondary. Seventh, the findings in this population may not necessarily be

generalizable to the population as a whole; not only was our population most white, and entirely female, but all of the participants were nurses and thus presumably similar in socioeconomic status and health consciousness. On the other hand, the risk factors that we studied (BMI, diet, physical activity, alcohol intake, analgesic use, and folate intake) have all been associated with hypertension status in other cohort studies, including those with more broadly-based populations. Eighth, the proportion of women who followed all six low risk factors (0.3%) was very low, and it is unrealistic to believe that all of these low risk factors could be achieved in the other 99.7%. However, because of the staggering morbidity and mortality associated with hypertension, achieving risk factor modification in a fraction of these women could potentially have substantial positive health benefits. Finally, our study was not randomized; however, the impact of these modifiable factors on blood pressure has been documented in randomized trials, and a large-scale long-term randomized trial of six interventions may not be feasible.

In conclusion, adherence to low-risk dietary and lifestyle factors was associated with significant reductions in the incidence of self-reported hypertension, and could have the potential to prevent a large proportion of new onset hypertension occurring among young women. Prevention of hypertension would, in turn, have major public health benefits.

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Table 1

Distribution of Modifiable Risk Factors and Multivariable Hazard Ratio of Hypertension among 83,882 Young Women in the Nurses' Health Study II, 1991-2005.

Risk factor	No. of cases	% of person-years	Multivariable HR (95% CI)
Quintile of DASH score (median)			
1 (17)	2,460	19.2	1.0 (reference)
2 (21)	2,697	21.2	0.96 (0.91-1.02)
3 (24)	2,193	19.4	0.94 (0.88-0.99)
4 (27)	2,317	20.4	0.91 (0.86-0.97)
5 (31)	1,853	19.8	0.82 (0.77-0.87)
Days/week vigorous exercise			
<1	5,472	43.4	1.0 (reference)
1	1,145	11.7	0.98 (0.92-1.05)
2-3	1,696	19.4	0.95 (0.90-1.01)
4-6	1,148	13.3	0.93 (0.87-0.99)
7	1,021	12.2	0.87 (0.81-0.93)
Body mass index (kg/m^2)			
<23.0	2,107	42.9	1.0 (reference)
23.0-24.9	1,768	19.2	1.66 (1.56-1.77)
25.0-29.9	3,779	24.5	2.56 (2.43-2.71)
≥30	4,076	13.4	4.70 (4.45-4.96)
Mean alcohol consumption (g/d)			
0	4,384	38.7	1.0 (reference)
0.1-5.0	3,399	37.1	0.88 (0.84-0.92)
5.1-10.0	955	11.9	0.84 (0.78-0.90)
10.1-15.0	650	6.5	0.98 (0.91-1.07)
15.0-29.9	484	4.2	1.11 (1.01-1.23)
≥30	280	1.6	1.61 (1.42-1.82)
Supplemental folic acid intake (μg/day)			
0	4,936	44.2	1.0 (reference)
1-399	3,758	31.6	0.98 (0.94-1.02)
400-799	2,403	19.3	0.94 (0.90-0.99)
≥800	423	4.9	0.88 (0.80-0.97)
Freq. of acetaminophen use (days/week)			
<1	8,499	76.6	1.0 (reference)
1	1,785	16.3	1.08 (1.02-1.14)
2-3	950	4.9	1.24 (1.16-1.33)
4-5	289	1.2	1.39 (1.23-1.57)
≥6	267	1.0	1.44 (1.27-1.63)
Freq. of NSAID use (days/week)			
<1	6,557	65.3	1.0 (reference)
1	2,146	18.3	1.18 (1.12-1.24)

Risk factor	No. of cases	% of person-years	Multivariable HR (95% CI)
2-3	2,018	11.1	1.24 (1.17-1.31)
4-5	587	2.8	1.30 (1.19-1.42)
≥6	673	2.5	1.48 (1.36-1.61)
Freq. of aspirin use (days/week)			
<1	9,545	86.4	1.0 (reference)
1	704	5.8	1.17 (1.08-1.27)
2-3	473	2.7	1.16 (1.05-1.27)
4-5	279	1.4	1.32 (1.17-1.49)
≥6	787	3.7	1.22 (1.13-1.31)

Multivariable models were adjusted for age, race, family history of hypertension, use of oral contraceptive pills, smoking status, and mutually for all of the factors that appear in the table. The number of cases for each individual factor may not add up to 12,319 due to missing data on the individual factor.

Table 2

Multivariable Relative and Hypothesized Population Attributable Risks of Incident Hypertension among 83,882 Young Women with Different Constellations of Low Risk Factors.

Constellation of factors	No. (%)	No. of cases	Multivariable HR (95% CI)	Hypothesized ARD	Hypothesized NNT over 10 years	Hypothesized PAR, % (95% CI)
Three low-risk factors*	2,600 (3.1)	145	0.46 (0.39-0.54)	6.02	16.6	53 (45-60)
Highest DASH quintile						
Daily vigorous exercise						
BMI < 25 kg/m^2						
Four low-risk factors†	1,342 (1.6)	64	0.42 (0.33-0.54)	6.28	15.9	58 (46-67)
Highest DASH quintile						
Daily vigorous exercise						
BMI < 25 kg/m^2						
Alcohol intake 0.1-10.0 g/d						
Five low-risk factors‡	671 (0.8)	21	0.28 (0.18-0.43)	7.76	12.9	72 (57-82)
Highest DASH quintile						
Daily vigorous exercise						
BMI < 25 kg/m^2						
Alcohol intake 0.1-10.0 g/d						
Analgesic use <1 d/w						
Six low-risk factors§	252 (0.3)	6	0.22 (0.10-0.51)	8.37	11.9	78 (49-90)
Highest DASH quintile						
Daily vigorous exercise						
BMI < 25 kg/m^2						
Alcohol intake 0.1-10.0 g/d						
Analgesic use <1 d/w						
Folic acid suppl ≥ 400 μg/d						

ARD, absolute rate difference, expressed as cases per 1000 person-years; NNT, number needed to treat; PAR, population attributable risk

The population attributable risk for a BMI < 25 kg/m^2 by itself was 40% (95% CI, 38-41%).

The hypothesized absolute rate difference is the adjusted difference in hypertension incidence rate among the higher risk group minus the incidence rate among the lower risk group.

The hypothesized number needed to treat is hypothesized number of higher-risk women that would have to “adopt” the low-risk constellation for a period of 10 years to prevent the occurrence of one hypertension case.

The hypothesized population attributable risk is the percentage of new hypertension cases in the population that would hypothetically not have occurred if all women had been in the low-risk group.

[*] Adjusted for age, race, family history of hypertension, use of oral contraceptive pills, smoking status, and for alcohol, analgesic, and supplemental folic acid intake.

[†] Adjusted for age, race, family history of hypertension, use of oral contraceptive pills, smoking status, and for alcohol and supplemental folic acid intake.

[‡] Adjusted for age, race, family history of hypertension, use of oral contraceptive pills, smoking status, and supplemental folic acid intake.

[§] Adjusted for age, race, family history of hypertension, use of oral contraceptive pills, and smoking status

Table 3

Multivariable Relative and Hypothesized Population Attributable Risks of Incident Hypertension among 83,882 Young Women with Multiple Low Risk Factors and Stratified by Family History of Hypertension.

Constellation of factors	No. (%)[ξ]	No. of cases	Multivariable HR (95% CI)	Hypothesized ARD	Hypothesized NNT over 10 years	Hypothesized PAR, % (95% CI)
No family history of hypertension						
Three low-risk factors[*]	1,386 (3.2)	54	0.42 (0.32-0.56)	4.60	21.7	57 (43-67)
Highest DASH quintile						
Daily vigorous exercise						
BMI < 25 kg/m^2						
Four low-risk factors[†]	736 (1.7)	21	0.34 (0.23-0.53)	5.04	19.8	66 (47-77)
Highest DASH quintile						
Daily vigorous exercise						
BMI < 25 kg/m^2						
Alcohol intake 0.1-10.0 g/d						
Five low-risk factors[‡]	390 (0.9)	7	0.23 (0.11-0.48)	5.86	17.1	77 (52-89)
Highest DASH quintile						
Daily vigorous exercise						
BMI < 25 kg/m^2						
Alcohol intake 0.1-10.0 g/d						
Analgesic use <1 d/w						
Six low-risk factors[§]	123 (0.3)	1	0.10 (0.01-0.68)	6.82	14.7	90 (32-99)
Highest DASH quintile						
Daily vigorous exercise						
BMI < 25 kg/m^2						
Alcohol intake 0.1-10.0 g/d						
Analgesic use <1 d/w						
Folic acid suppl ≥ 400 μg/d						
Family history of hypertension						
Three low-risk factors[*]	1,217 (3.0)	91	0.48 (0.39-0.59)	7.66	13.1	51 (40-60)
Four low-risk factors[†]	649 (1.6)	43	0.46 (0.34-0.63)	7.75	12.9	53 (37-66)

Constellation of factors	No. (%)[ξ]	No. of cases	Multivariable HR (95% CI)	Hypothesized ARD	Hypothesized NNT over 10 years	Hypothesized PAR, % (95% CI)
Five low-risk factors[‡]	325 (0.8)	14	0.31 (0.19-0.53)	9.86	10.1	69 (47-81)
Six low-risk factors[§]	122 (0.3)	5	0.31 (0.13-0.75)	9.87	10.1	69 (25-87)

ARD, absolute rate difference, expressed as cases per 1000 person-years; NNT, number needed to treat; PAR, population attributable risk

The hypothesized absolute rate difference is the adjusted difference in hypertension incidence rate among the higher risk group minus the incidence rate among the lower risk group.

The hypothesized number needed to treat is hypothesized number of higher-risk women that would have to "adopt" the low-risk constellation for a period of 10 years to prevent the occurrence of one hypertension case. The hypothesized population attributable risk is the percentage of new hypertension cases in the population that would theoretically not have occurred if all women had been in the low-risk group.

[*] Adjusted for age, race, use of oral contraceptive pills, smoking status, and for alcohol, analgesic, and supplemental folic acid intake.

[†] Adjusted for age, race, use of oral contraceptive pills, smoking status, and for alcohol and supplemental folic acid intake.

[‡] Adjusted for age, race, use of oral contraceptive pills, smoking status, and for supplemental folic acid intake.

[§] Adjusted for age, race, use of oral contraceptive pills, smoking status

[ξ] The percent of women shown represents the percent of those within the given strata (i.e., among those with or without a family history of hypertension).

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Table 4

Multivariable Relative and Hypothesized Population Attributable Risks of Incident Hypertension among 83,882 Young Women with Multiple Low Risk Factors and Stratified by Oral Contraceptive Hormone Use.

Constellation of factors	No. (%)[ξ]	No. of cases	Multivariable HR (95% CI)	Hypothesized ARD	Hypothesized NNT over 10 years	Hypothesized PAR, % (95% CI)
No OC use						
Three low-risk factors[*]	588 (4.3)	58	0.40 (0.30-0.51)	6.84	14.6	59 (48-69)
Highest DASH quintile						
Daily vigorous exercise						
BMI < 25 kg/m^2						
Four low-risk factors[†]	273 (2.0)	20	0.33 (0.21-0.51)	7.40	13.5	67 (48-79)
Highest DASH quintile						
Daily vigorous exercise						
BMI < 25 kg/m^2						
Alcohol intake 0.1-10.0 g/d						
Five low-risk factors[‡]	150 (1.1)	6	0.20 (0.09-0.44)	8.78	11.4	80 (56-91)
Highest DASH quintile						
Daily vigorous exercise						
BMI < 25 kg/m^2						
Alcohol intake 0.1-10.0 g/d						
Analgesic use <1 d/w						
Six low-risk factors[§]	55 (0.4)	2	0.17 (0.04-0.70)	9.06	11.0	83 (30-96)
Highest DASH quintile						
Daily vigorous exercise						
BMI < 25 kg/m^2						
Alcohol intake 0.1-10.0 g/d						
Analgesic use <1 d/w						
Folic acid suppl ≥ 400 μg/d						
OC use						
Three low-risk factors[*]	1,755 (2.5)	87	0.51 (0.42-0.64)	5.4	18.5	48 (35-57)
Four low-risk factors[†]	983 (1.4)	44	0.48 (0.36-0.65)	5.57	18.0	52 (35-64)

Constellation of factors	No. (%)[ξ]	No. of cases	Multivariable HR (95% CI)	Hypothesized ARD	Hypothesized NNT over 10 years	Hypothesized PAR, % (95% CI)
Five low-risk factors[‡]	562 (0.8)	15	0.34 (0.20-0.56)	7.06	14.2	66 (44-80)
Six low-risk factors[§]	140 (0.2)	4	0.27 (0.10-0.72)	7.77	12.9	73 (28-90)

ARD, absolute rate difference, expressed as cases per 1000 person-years; NNT, number needed to treat; PAR, population attributable risk

The hypothesized absolute rate difference is the adjusted difference in hypertension incidence rate among the higher risk group minus the incidence rate among the lower risk group.

The hypothesized number needed to treat is hypothesized number of higher-risk women that would have to “adopt” the low-risk constellation for a period of 10 years to prevent the occurrence of one hypertension case.

The hypothesized population attributable risk is the percentage of new hypertension cases in the population that would theoretically not have occurred if all women had been in the low-risk group.

OCP, oral contraceptive pill.

[*] Adjusted for age, race, use of oral contraceptive pills, smoking status, and for alcohol, analgesic, and supplemental folic acid intake.

[†] Adjusted for age, race, use of oral contraceptive pills, smoking status, and for alcohol and supplemental folic acid intake.

[‡] Adjusted for age, race, use of oral contraceptive pills, smoking status, and for supplemental folic acid intake.

[§] Adjusted for age, race, use of oral contraceptive pills, smoking status

[ξ] The percent of women shown represents the percent of those within the given strata (i.e., among those who do and do not use oral contraceptive hormones).

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Table 5

Multivariable Relative and Hypothesized Population Attributable Risks of Incident Hypertension among 83,882 Young Women with Multiple Low Risk Factors and Stratified by Body Mass Index.

Constellation of factors	No. (%)‡	No. of cases	Multivariable HR (95% CI)	Hypothesized ARD	Hypothesized NNT	Hypothesized PAR, % (95% CI)
Normal, BMI < 25.0 kg/m^2						
Four low-risk factors*	847 (1.4)	21	0.46 (0.30-0.71)	3.19	31.3	54 (29-70)
Highest DASH quintile						
Daily vigorous exercise						
Alcohol intake 0.1-10.0 g/d						
Analgesic use <1 d/w						
Five low-risk factors†	242 (0.4)	6	0.38 (0.17-0.86)	3.65	27.4	62 (14-83)
Highest DASH quintile						
Daily vigorous exercise						
Alcohol intake 0.1-10.0 g/d						
Analgesic use <1 d/w						
Folic acid suppl ≥ 400 μg/d						
Overweight, BMI, 25.0-29.9 kg/m^2						
Four low-risk factors	113 (0.7)	11	0.53 (0.29-0.96)	6.83	14.6	47 (4-71)
Five low-risk factors	32 (0.2)	3	0.43 (0.14-1.33)	NS	NS	57 (0-86)
Obese, BMI ≥ 30.0 kg/m^2						
Four low-risk factors	22 (0.3)	9	0.95 (0.49-1.84)	NS	NS	5 (0-51)
Five low-risk factors	7 (0.1)	2	0.57 (0.14-2.31)	NS	NS	43 (0-86)

ARD, absolute rate difference, expressed as cases per 1000 person-years; NNT, number needed to treat; PAR, population attributable risk; NS, not computed due to non-significant results

The hypothesized absolute rate difference is the adjusted difference in hypertension incidence rate among the higher risk group minus the incidence rate among the lower risk group.

The hypothesized number needed to treat is hypothesized number of higher-risk women that would have to "adopt" the low-risk constellation for a period of 10 years to prevent the occurrence of one hypertension case.

The hypothesized population attributable risk is the percentage of new hypertension cases in the population that would theoretically not have occurred if all women had been in the low-risk group.

*Adjusted for age, race, family history of hypertension, use of oral contraceptive pills, smoking status, and supplemental folic acid intake.

†Adjusted for age, race, family history of hypertension, use of oral contraceptive pills, and smoking status.

‡The percent of women shown represents the percent of those within the given strata of BMI.

Table 6

Blood Pressures and Anti-Hypertensive Medication Use at Baseline and End of Follow-up in all study participants, including those who developed hypertension.

	Baseline: mean (SD) systolic blood pressure (mmHg)		Baseline: mean (SD) diastolic blood pressure (mmHg)		End of follow-up: mean (SD) systolic blood pressure (mmHg)		End of follow-up: mean (SD) diastolic blood pressure (mmHg)		End of follow-up: Use of anti-hypertension medication	
Constellation of low-risk factors*	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent
3 low-risk factors	109 (7)	110 (7)	68 (7)	69 (7)	114 (10)	118 (11)	70 (8)	73 (8)	5.8%	11.7%
4 low-risk factors	109 (7)	110 (7)	68 (6)	69 (7)	114 (10)	118 (11)	70 (8)	73 (8)	5.3%	11.9%
5 low-risk factors	109 (7)	110 (7)	68 (7)	69 (7)	113 (10)	118 (11)	70 (7)	73 (8)	4.3%	11.9%
6 low-risk factors	109 (7)	110 (7)	67 (7)	69 (7)	112 (10)	118 (11)	69 (7)	73 (8)	3.9%	11.9%

P-values for all comparisons were <0.001.

No women were using anti-hypertensive medication at baseline.

3low-risk factors indicate: BMI<25 kg/m2, daily vigorous exercise, DASH score in the highest quintile

4low-risk factors indicate: 3 low-risk factors plus modest alcohol intake

5low-risk factors indicate: 4 low-risk factors plus non-narcotic analgesic use <1 day/week

6low-risk factors indicate: 5 low-risk factors plus use of folic acid supplements

These data include women who did and did not develop hypertension during follow-up; approximately 15% of women developed hypertension during 14 years of follow-up.

*For each outcome, “present” denotes women who met the constellation of low-risk factors, and “absent” denotes the women who did not