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Effects of Dietary Sodium and the DASH Diet on the Occurrence of Headaches: Results from DASH-Sodium Trial

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Abstract

Objectives: Headaches are a common medical problem, yet few studies, particularly trials, have evaluated therapies that might prevent or control headaches. We, thus, investigated the effects on the occurrence of headaches of three levels of dietary sodium intake and two diet patterns [the **D**ietary **A**pproaches to **S**top **H**ypertension (DASH) diet (rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat) and a control diet (typical of Western consumption patterns).

Design: Randomized clinical trial.

Setting: Post-hoc analyses of the DASH-Sodium trial in the USA.

Participants: In a multicenter feeding study with three 30 day periods, 390 participants were randomized to the DASH or control diet. On their assigned diet, participants ate food with high sodium during one period, intermediate sodium during another period, and low sodium during another period, in random order.

Outcome measures: Occurrence and severity of headache were ascertained from self-administered questionnaires, completed at the end of each feeding period.

Results: The occurrence of headaches was similar in DASH vs. Control, at high [odds ratio (95% confidence interval) = 0.65 (0.37-1.12); p=0.12)], intermediate [0.57 (0.29-1.12); p =0.10], and low [0.64 (0.36-1.13); p=0.12] sodium levels. By contrast, there was a lower risk of headache on the low, compared to high, sodium level, both on the control [0.69 (0.49 - 0.99); p = 0.05] and DASH [0.69 (0.49-0.98); p=0.04] diets.

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Conclusions: A reduced sodium intake was associated with a significantly lower risk of headache, whilst dietary patterns had no effect on the risk of headaches in adults. Reduced dietary sodium intake offers a novel approach to prevent headaches.

Key words: Headache; Sodium; Dietary Approaches to Stop Hypertension; DASH-Sodium trial

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Strengths and limitations of this study

- Post-hoc analysis of a multicenter randomized clinical trial comparing effects of the two diet patterns using parallel design together with a three-period crossover of three levels of dietary sodium [high (150 mmol), intermediate (100 mmol), low (50 mmol)] on headaches in healthy adults with stage 1 hypertension.
- Three screening and two run-in feeding periods prior to randomization to assess participant's eligibility, compliance with dietary requirements and to estimate caloric requirements to maintain weight during study.
- Vigorous efforts made to promote adherence with assigned diets during feeding periods.
- Lack of information on the prevalence of headaches at baseline as well as type of self-reported headaches experienced by participants at the end of feeding periods.

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Introduction

Worldwide, headache is a common medical problem and amongst the most frequently reported disorders of the nervous system [1-3]. Globally, 46% of adults are estimated to have an active headache disorder (42% for tension-type headaches; 11% for migraines) [2, 4-6]. Headaches affect all age groups, with a higher prevalence in women compared to men [4-6]. The direct cost of health care services, and medications for the management of headache,s is likewise substantial [7-11], as are indirect costs. Patients with frequent headaches have a poor quality of life and a higher number of days absent from work, compared with others [12-15]. Hence, successful strategies to prevent and treat headache would confer substantial benefits to afflicted individuals, as well as to society in general.

Available data support a direct association between blood pressure and the occurrence of headache [16-19]. Therefore, it is reasonable to speculate that dietary factors that lower blood pressure (e.g. reduced sodium intake and the DASH diet [20, 21]) might also reduce the occurrence of headache. However, evidence on the relationship of headaches with sodium intake and other dietary factors is sparse, with most attention focusing on the potential role of monosodium glutamate intake [22-24]. In the primary results paper of the DASH-Sodium trial, which focused on the blood pressure effects of the dietary interventions, the authors briefly comment on the occurrence of headaches in the broad context of side effects. They reported that the side effect of headache occurred in 47% of participants during the high, compared to 39 percent during the low, sodium feeding period [21]. In this paper, we expand on these preliminary observations.

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Methods

A detailed description of the rationale, design, and methods of the DASH-Sodium trial has been published [25]. Briefly, DASH-Sodium was a multicenter, randomized clinical trial, conducted between September 1997 and November 1999, designed to compare the effects on blood pressure of three levels of dietary sodium and two diet patterns. The study design incorporated a parallel, two-group, comparison of diet (DASH diet vs. control diet) together with a three-period crossover of the three levels of dietary sodium intake, with a primary outcome of mean systolic blood pressure (Figure 1). The three sodium levels were 1) "high" (150 mmol, at 2100 Kcal caloric intake), reflecting average consumption in the USA, 2) "intermediate" (100 mmol) reflecting the upper limit of current recommendations for adults [26], and 3) "low" (50 mmol). The DASH diet is rich in fruits, vegetables, and low-fat dairy products, high in dietary fiber, potassium, calcium and magnesium, moderately high in protein, and low in saturated fat, cholesterol, and total fat. The control diet is typical of what many in the Western world eat.

Study participants were 412 adults (age ≥ 22 years) with systolic blood pressure between 120 and 159 mm Hg and diastolic blood pressure between 80 and 95 mm Hg (i.e., pre-hypertension or stage 1 hypertension). Major exclusion criteria were diabetes mellitus, evidence of active malignancy, history of cardiovascular event (angina, myocardial infarction, angioplasty, or stroke), renal insufficiency (serum creatinine > 1.2 mg/dL for females or 1.5 mg/dL for males), anemia (hematocrit at least 5 percent below normal range), pregnancy, inflammatory bowel disease, body mass index > 40 kg/m^2, use of antihypertensive drugs and corticosteroids, and consumption of more than 14 alcoholic beverages per week.

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Three screening visits (each separated by at least seven days) were conducted to assess general eligibility and to collect baseline data. Following the screening visits, eligible participants started a two-week run-in feeding period during which they ate the control diet at the high sodium level. The run-in feeding period was designed to exclude participants who were unlikely to comply with the dietary requirements and to estimate caloric requirements needed to maintain weight. Participants were then randomly assigned to one of the two diets using a parallel-group design, and ate each of three sodium levels (feeding periods) for 30 days each, in a randomized crossover design. Participants were not notified of their assigned dietary pattern or sodium sequence.

During feeding periods (run-in and intervention), participants were required to eat at least one meal per day on site at the clinical center, five days per week, and to take food home for other meals. Participants were expected to eat all of their food and were instructed to record the type and amount of any uneaten study food. Caffeinated beverages and alcohol were limited and monitored. Individual energy intake (calorie content) was adjusted so that each participant's weight during each feeding period remained stable.

Data collection staff were masked to randomized sodium and diet sequence. Measurements were obtained during screening and at the end of each feeding period. Blood pressure was measured in a seated position, using the right arm of participants. Twenty-four hour urine (for analysis of sodium, potassium, urea nitrogen, and creatinine) and body weight were also collected. Compliance with the feeding protocol was assessed by urinary excretion of sodium, potassium, phosphorus, urea nitrogen, and creatinine, estimated from 24 hour urine collections.

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Symptoms (side effects) including headache, bloating, dry mouth, excessive thirst, fatigue or low energy, lightheadedness, nausea, and change in taste, were collected via self-administered questionnaires (see Supplement) completed during the last seven days of each sodium feeding period. For each symptom, potential responses were (1) "none" for not experiencing any symptom, (2) "mild" if symptom occurred but did not interfere with usual activities, (3) "moderate" if symptom occurred and somewhat interfered with usual activities, and (4) "severe" if participants were unable to perform usual activities due to the symptom.

This analysis of the DASH-Sodium trial included 390 (95%) of the 412 randomized participants. Excluded participants were those with missing information on headaches in any of the 3 feeding periods. For the primary analysis in this study, headache was defined as "any headache" (mild, moderate or severe) during the last seven days of each feeding period. Subsequently, we report frequency of headache by severity.

The means and proportions between groups were explored using t-tests and chi-square tests, respectively. A non-parametric test was used for trends in the frequency of headache by sodium intake. Since multiple observations were obtained on each participant, we used generalized estimating equation models [27], with a logit link and binomial error and an exchangeable covariance structure, to model the odds of a headache. Models were adjusted for age, sex, race, clinical site, systolic blood pressure, body mass index, smoking status, and carryover effects from the previous period. To address the qualitative consistency and benefit-hazard profiles between participants, subgroup analysis by diet stratified by age, sex, race, obesity (BMI ≥ 30 kg/m^2 *v* not) and hypertension (blood pressure ≥ 140/90 mmHg *v* not)

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status at baseline were also performed. Interactions between subgroups were tested by the addition of an interaction term to the main effects model.

Institutional review boards at the participating centers and an external data and safety monitoring committee approved the trial protocol and consent procedures. Each participant provided written, informed consent.

A p-value of ≤ 0.05 was considered statistically significant. All analyses were performed using Stata version 12.1 (Stata Corp LP, College Station, Texas, USA).

Results

The 390 participants included in our analyses were those with completed symptoms questionnaires - 192 (94%) of the 204 participants assigned to the control diet and 198 (95%) of the 208 participants assigned to the DASH diet. Clinical and demographic characteristics of the two groups were similar (Table 1).

Figure 2 displays the distribution of headaches by sodium level and assigned diet. The highest occurrence of headache was reported by participants on the control diet with high sodium (47%) and the lowest by participants on the DASH diet with low sodium level (36%). On both diets, the number of headaches reported was greatest for the high sodium level and least on the low sodium level.

Among those assigned to the control diet, mean (SD) urinary sodium excretion was 141 (55), 106 (43) and 64 (37) mmol per 24 hours during the high, intermediate, and low sodium feeding periods,

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respectively. In the DASH diet group, mean (SD) urinary sodium levels were 144 (57), 107 (52) and 67 (46) mmol per 24 hour during the high, intermediate, and low sodium feeding periods, respectively. On each sodium level, mean urinary sodium excretion was similar in those assigned to the two diets (each p > 0.05). Mean urinary potassium and urea nitrogen were higher in the DASH diet group, reflecting the higher vegetable, dairy, and protein content of the DASH diet compared with the control diet, at each sodium level (Table 2).

Table 3 shows differences in the odds of headache by diet and sodium level. Compared to the high sodium level, we observed a lower odds of any headache during the low sodium period both on the control diet (adjusted OR: 0.69, 95% CI: 0.49-0.99) and the DASH diet (adjusted OR: 0.69, 95% CI: 0.49-0.98). Although the relationship appeared graded (Figure 2), there was no significant difference between the intermediate level of sodium and either the low or high sodium levels, on either diet. There was no significant association of diet pattern (DASH vs. Control) with headache on any sodium level. There was also no significant interaction between diet and sodium on the occurrence of headaches (p-interaction > 0.05). Compared to the control diet with high sodium, there was a reduced risk of a headache on the DASH diet with low sodium (adjusted OR = 0.64, 95% CI: 0.41 – 0.99, p = 0.05).

While on control diet, the number of persons who reported a severe headache was 4 (2.1%) during high, 1 (0.5%) during intermediate, and 1 (0.5%) during low sodium periods, respectively (p for trend = 0.13). On DASH diet, the corresponding number of persons who reported a severe headache was 8 (4%) during high, 2 (1%) during intermediate, and 3 (1.5%) during low sodium periods, respectively (p for

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trend= 0.08). The frequency of severe headache was similar (p = 0.3) by diet [DASH 8 (4%) and control 4 (2%)] during high sodium feeding period. (Table 4)

There was no evidence that the relationship between sodium levels and headache was modified by age, sex, race, baseline BMI or blood pressure (Figure 3).

Discussion

In this secondary analysis of the DASH-Sodium trial, which enrolled adults with pre- and stage 1 hypertension, a reduced dietary sodium intake was associated with a lower risk of headache, both on the control diet and the DASH diet. In contrast, the risk of headache was similar on the DASH and control diets.

The epidemiological literature on headaches in adults is limited [1, 2, 6]. However, it is well-recognized that, compared to normotensive individuals, individuals with hypertension have a higher frequency of headaches [16-19, 28]. Of note, Cooper *et al* reported a direct relationship of headaches with both systolic and diastolic blood pressure [17]. As regards trials, in a pooled analysis that included seven double–blinded, randomized placebo controlled trials of Ibesartan therapy, Hansson *et al* found a direct relationship of diastolic blood pressure with incident headaches in 2673 patients with mild to moderate hypertension [29].

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The association between dietary sodium intake and blood pressure is also well recognized [30, 31]. The DASH diet alone and in combination with reduced sodium intake lowers blood pressure in patients with or without hypertension [20, 21]. It is noteworthy that there was no significant relationship between diet pattern and headache. This suggests that a process that is independent of a blood pressure may mediate the relationship between sodium and headaches.

Our results contrast with the popular belief that a diet rich in fruits, vegetables and potassium and low in saturated and total fat may ease the frequency, or even prevent, headache [32]. Several dietary factors, including fasting, alcoholic drinks, chocolate, coffee, and cheese, appear to trigger vascular headache (cluster or migraine) in adults [33- 36]. In some studies, an increased intake of monosodium glutamate is associated with the occurrence of headaches [22-24]. However, a recent review concluded that evidence on the relationship of sodium glutamate intake and headaches is inconsistent [37]. In one study of 200 adults (mean age 37.7 years, 81% females), monosodium glutamate was identified as a trigger for migraine headache in only 5 (2.5%) of study participants [36]. However, data on the relationship between sodium intake and any form of headaches are sparse.

The results of this study provide encouraging evidence in support of dietary recommendations to lower sodium intake: recommendations which are currently based on the relationship of sodium intake with blood pressure. The daily intake of sodium in adults living in the United States is already in excess of their physiological need and for many individuals, is much higher than the highest level tested in this study [38, 39]. Our results also support the recent World Health Organization guidelines for reducing sodium intake to less than 87 mmol/day [40] and American Heart Association guidelines for reducing sodium intake to 65 mmol/day [31].

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Strengths of our study include its randomized controlled design comparing two diets using a parallel design and a three-period crossover of three levels of dietary sodium (high, intermediate, and low). Dietary intake during the feeding periods was closely monitored and vigorous efforts were made to promote adherence with assigned diets. The participants of this study were healthy, non-institutionalized, racially diverse, middle- and older-aged men and women. Hence we believe that these results are applicable to a large fraction of adults.

Our study also has limitations. Information on the prevalence of headache at baseline from eligible participants was lacking. In addition, there was no information about the type of headache (tension, cluster or migraine) experienced by study participants. However, we suspect that most of the headaches were tension headaches. Whether a reduced sodium intake can prevent vascular headache is unknown. Second, the instrument was administered just once in each feeding period and does not allow calculation of an event rate, such as person-days of headaches. Third, these are secondary, post-hoc analyses from a trial that was not explicitly designed to test the effects of dietary factors on headaches. Nonetheless, a rigorously controlled feeding study designed to test the effects of dietary factors on occurrence of headaches would be extremely expensive and logistically challenging. Fourth, our results likely underestimate the relationship of sodium intake with headaches. The range of sodium intake was relatively narrow - the highest sodium group in our trial actually corresponds to the average in the USA and is much lower than the intake in many countries, particularly in Asia. Self-report of symptoms is inherently imprecise and could bias results to the null, given that a validated instrument was not used for patient-reported headache.

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In conclusion, a reduced sodium intake was associated with significantly lower risk of headache, while diet patterns had no effect on the risk of headaches. A reduced dietary sodium intake offers a novel approach to prevent headache in adults. Additional studies are needed to replicate these findings and to explore mechanisms that mediate the association between sodium intake and headache.

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FIGURE LEGEND:

Figure 1: DASH-Sodium Trial Flow Diagram

Figure 2: Frequency of headache by diet and sodium level.

Figure 3

(a): Odds of headache (low vs high sodium) by subgroup, in the DASH diet

(b): Odds of headache (low vs high sodium) by subgroup, in the Control diet

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Table 1: Baseline characteristics of participants in DASH-Sodium trial [Number (percentage) or mean (standard deviation)]

Characteristic	Control Diet (n=192)	DASH Diet (n=198)	Total (n=390)
Age (years)	49 (10)	47 (10)	48 (10)
Females, n (%)	104 (54)	118 (60)	222 (57)
Race, n (%)			
Caucasian	78 (41)	81 (41)	159 (41)
African American	109 (57)	114 (57)	223 (57)
Other	5 (3)	3 (2)	8 (2)
Body Mass Index, (kg/m^2)	30 (5)	29 (5)	29.2 (5)
Systolic Blood Pressure (mm Hg)	135 (9)	134 (9)	135 (9)
Diastolic Blood Pressure (mm Hg)	86 (4)	85 (5)	86 (4)
Hypertension, n (%) †	76 (40)	79 (40)	155 (40)
Current Smoker, n (%)	21 (11)	21 (11)	42 (11)

†Hypertension was defined as an average systolic blood pressure of 140 mm of Hg or an average diastolic blood pressure of 90 mmHg during the three screening visits.

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Table 2: Urinary excretion according to sodium level and diet [Mean (standard deviation)]

	Level of sodium					
	High		Intermediate		Low	
	DASH (n=198)	Control (n=192)	DASH (n=198)	Control (n=192)	DASH (n=198)	Control (n=192)
Sodium						
gram/day	3.3 (1.3)	3.2 (1.3)	2.5 (1.2)	2.4 (0.9)	1.5 (1.1)	1.5 (0.8)
mmol/day	144 (57)	141 (55)	107 (52)	106 (43)	67 (46)	64 (37)
Potassium						
gram/day	3.0 (1.1)	1.6 (0.5)	3.2 (1.2)	1.6 (0.5)	3.2 (1.1)	1.6 (0.5)
mmol/day	76 (27)	40 (14)	82 (31)	41 (14)	81 (29)	41 (14)
Urea Nitrogen gram/day	11.5 (4)	9.5 (3.2)	12.4 (4.5)	9.7 (3.4)	12 (4)	10 (3.3)
Creatinine gram/day	1.4 (0.5)	1.5 (0.5)	1.5 (0.6)	1.5 (0.6)	1.4 (0.5)	1.5 (0.6)

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Table 3: Odds ratio of headaches by diet and sodium sequence

	Odds ratio (95 %CI)	*p* value
Sodium effects on the DASH diet		
Intermediate *v* high sodium	0.72 (0.51-1.01)	0.06
Low *v* intermediate sodium	0.96 (0.68-1.37)	0.85
Low *v* high sodium	0.69 (0.49-0.98)	0.04
Sodium effects on the control diet		
Intermediate *v* high sodium	0.81 (0.57-1.15)	0.24
Low *v* intermediate sodium	0.86 (0.59-1.24)	0.42
Low *v* high sodium	0.69 (0.49-0.99)	0.05
Diet effects (DASH vs Control) at each sodium level		
On high sodium	0.65 (0.37-1.12)	0.12
On intermediate sodium	0.57 (0.29-1.12)	0.10
On low sodium	0.64 (0.36-1.13)	0.12
Low Sodium on DASH vs High Sodium on Control	0.64 (0.14-0.99)	0.05

Models adjusted for age, sex, race, site, systolic blood pressure, BMI, smoking status and carry over effects from the previous period. CI =confidence interval.

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Table 4: Occurrence and severity of headache by sodium level and diet, n (%)

	Level of sodium					
	High		Intermediate		Low	
	DASH (n=198)	Control (n=192)	DASH (n=198)	Control (n=192)	DASH (n=198)	Control (n=192)
Mild	60 (30)	70 (36)	43 (22)	62 (32)	53 (27)	53 (28)
Moderate	17 (9)	17 (9)	31 (16)	16 (8)	16 (8)	21 (11)
Severe	8 (4)	4 (2)	2 (1)	1 (0.5)	3 (1)	1 (0.5)

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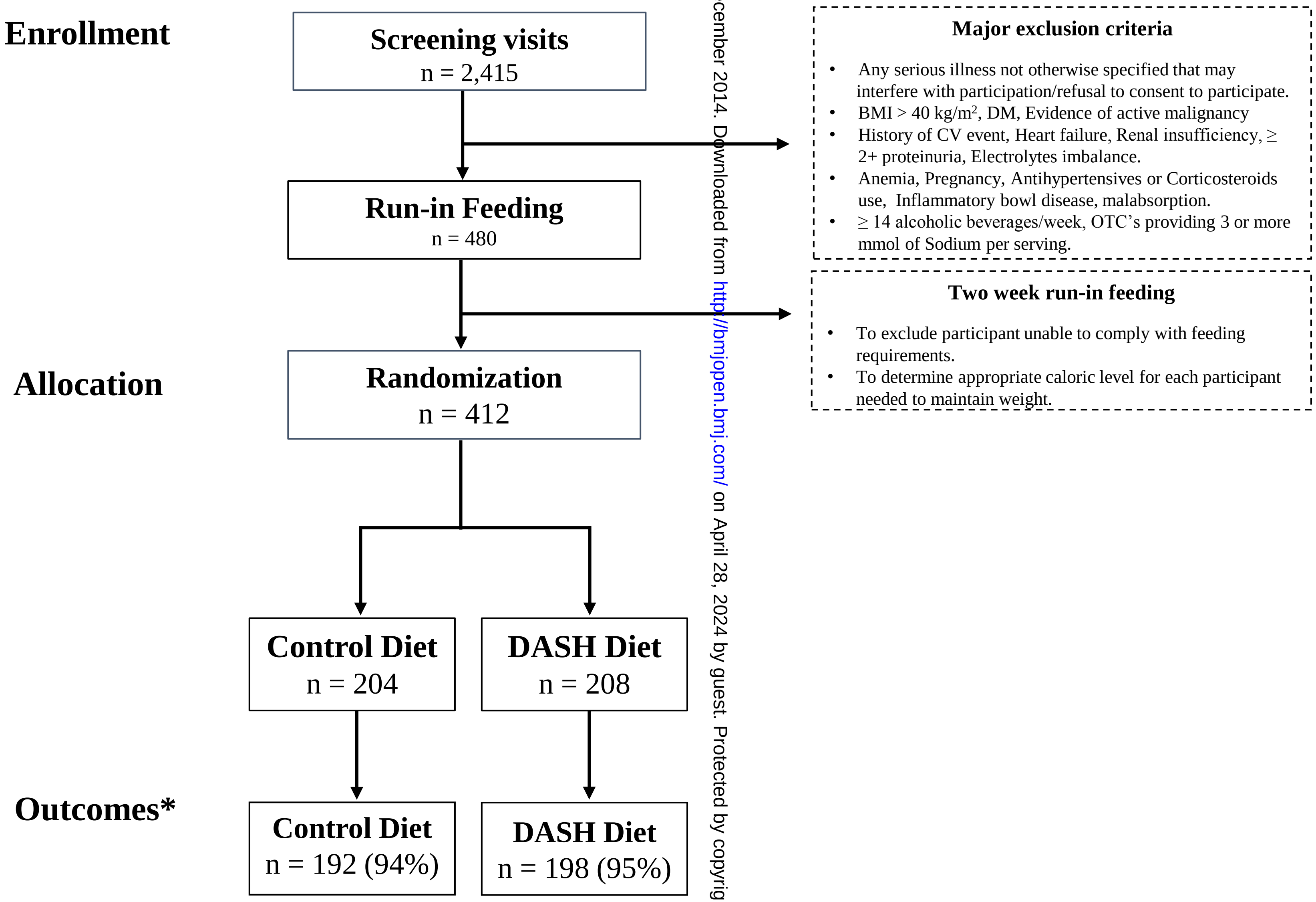
Figure 1: DASH-Sodium Trial Flow Diagram



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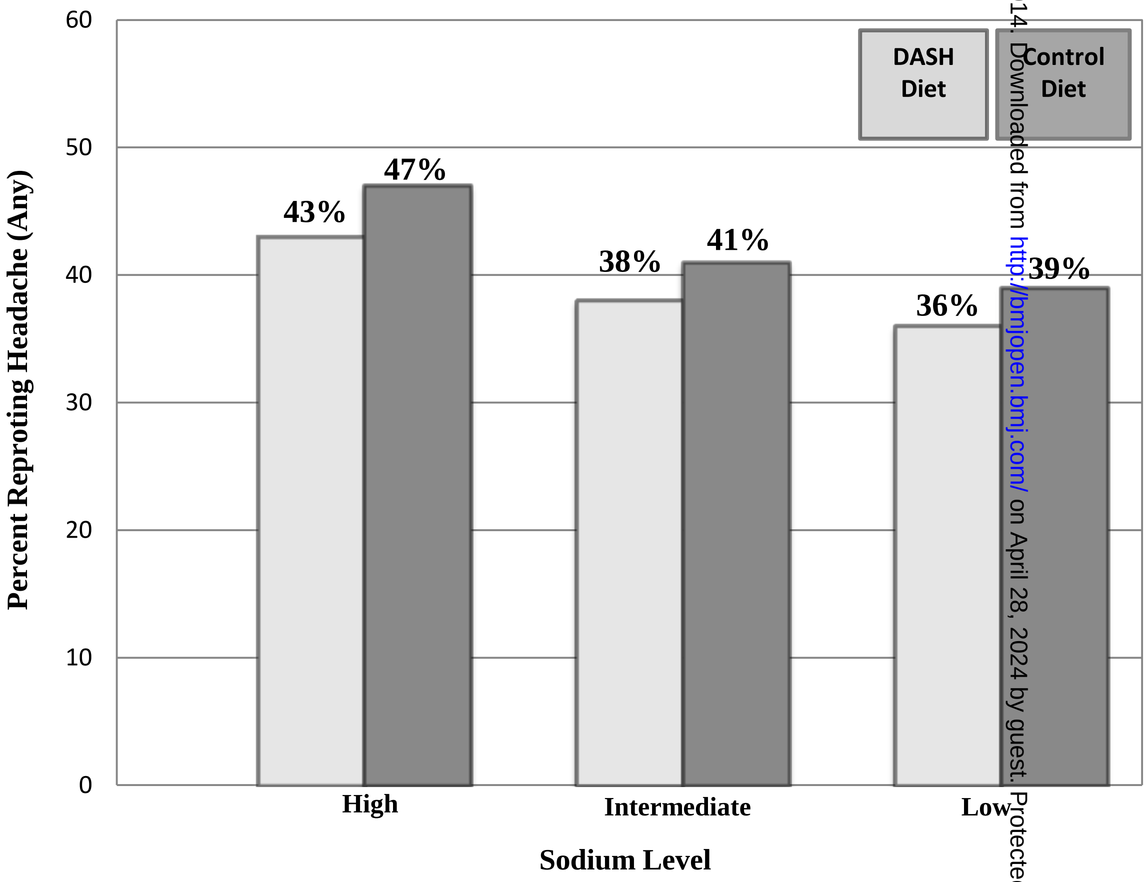
***Participants with complete questionnaire data on headaches in all 3 periods.**

Figure 2: Frequency of headache by diet and sodium level



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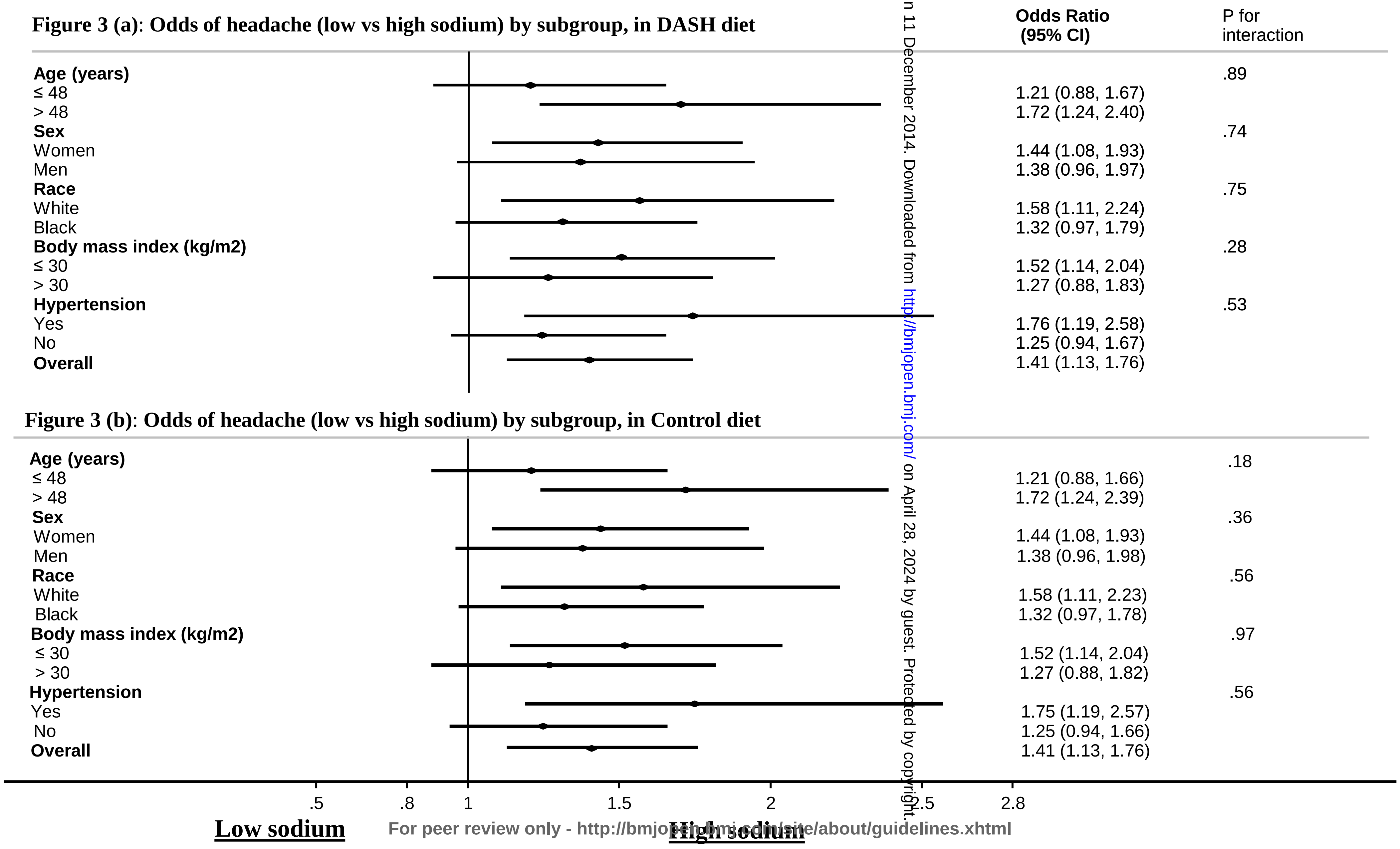

Figure 3 (a): **Odds of headache (low vs high sodium) by subgroup, in DASH diet**

Figure 3 (b): **Odds of headache (low vs high sodium) by subgroup, in Control diet**

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Effects of Dietary Sodium and the DASH Diet on the Occurrence of Headaches: Results from Randomized Multicenter DASH-Sodium Clinical Trial

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Abstract

Objectives: Headaches are a common medical problem, yet few studies, particularly trials, have evaluated therapies that might prevent or control headaches. We, thus, investigated the effects on the occurrence of headaches of three levels of dietary sodium intake and two diet patterns [the **D**ietary **A**pproaches to **S**top **H**ypertension (DASH) diet (rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat) and a control diet (typical of Western consumption patterns).

Design: Randomized multicenter clinical trial.

Setting: Post-hoc analyses of the DASH-Sodium trial in the USA.

Participants: In a multicenter feeding study with three 30 day periods, 390 participants were randomized to the DASH or control diet. On their assigned diet, participants ate food with high sodium during one period, intermediate sodium during another period, and low sodium during another period, in random order.

Outcome measures: Occurrence and severity of headache were ascertained from self-administered questionnaires, completed at the end of each feeding period.

Results: The occurrence of headaches was similar in DASH vs. Control, at high [odds ratio (95% confidence interval) = 0.65 (0.37-1.12); p=0.12)], intermediate [0.57 (0.29-1.12); p =0.10], and low [0.64 (0.36-1.13); p=0.12] sodium levels. By contrast, there was a lower risk of headache on the low, compared to high, sodium level, both on the control [0.69 (0.49 - 0.99); p = 0.05] and DASH [0.69 (0.49-0.98); p=0.04] diets.

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Conclusions: A reduced sodium intake was associated with a significantly lower risk of headache, whilst dietary patterns had no effect on the risk of headaches in adults. Reduced dietary sodium intake offers a novel approach to prevent headaches.

Key words: Headache; Sodium; Dietary Approaches to Stop Hypertension; DASH-Sodium trial

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Strengths and limitations of this study

- Post-hoc analysis of a multicenter randomized clinical trial comparing effects of the two diet patterns using parallel design together with a three-period crossover of three levels of dietary sodium [high (150 mmol), intermediate (100 mmol), low (50 mmol)] on headaches in healthy adults with stage 1 hypertension.
- Three screening and two run-in feeding periods prior to randomization to assess participant's eligibility, compliance with dietary requirements and to estimate caloric requirements to maintain weight during study.
- Vigorous efforts made to promote adherence with assigned diets during feeding periods.
- Lack of information on the prevalence of headaches at baseline as well as type of self-reported headaches experienced by participants at the end of feeding periods.

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Introduction

Worldwide, headache is a common medical problem and amongst the most frequently reported disorders of the nervous system [1-3]. Globally, 46% of adults are estimated to have an active headache disorder (42% for tension-type headaches; 11% for migraines) [2, 4-6]. Headaches affect all age groups, with a higher prevalence in women compared to men [4-6]. The direct cost of health care services, and medications for the management of headaches is likewise substantial [7-11], as are indirect costs. Patients with frequent headaches have a poor quality of life and a higher number of days absent from work, compared with others [12-15]. Hence, successful strategies to prevent and treat headache would confer substantial benefits to afflicted individuals, as well as to society in general.

Available data support a direct association between blood pressure and the occurrence of headache [16-19]. Therefore, it is reasonable to speculate that dietary factors that lower blood pressure (e.g. reduced sodium intake and the DASH diet [20, 21]) might also reduce the occurrence of headache. However, evidence on the relationship of headaches with sodium intake and other dietary factors is sparse, with most attention focusing on the potential role of monosodium glutamate intake [22-24]. In the primary results paper of the DASH-Sodium trial, which focused on the blood pressure effects of the dietary interventions, the authors briefly comment on the occurrence of headaches in the broad context of side effects. They reported that the side effect of headache occurred in 47% of participants during the high, compared to 39 percent during the low, sodium feeding period [21]. In this paper, we expand on these preliminary observations.

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Methods

A detailed description of the rationale, design, and methods of the DASH-Sodium trial has been published [25]. Briefly, DASH-Sodium was a multicenter, randomized clinical trial, conducted between September 1997 and November 1999, designed to compare the effects on blood pressure of three levels of dietary sodium and two diet patterns. The study design incorporated a parallel, two-group, comparison of diet (DASH diet vs. control diet) together with a three-period crossover of the three levels of dietary sodium intake, with a primary outcome of mean systolic blood pressure (Figure 1). The three sodium levels were 1) "high" (150 mmol, at 2100 Kcal caloric intake), reflecting average consumption in the USA, 2) "intermediate" (100 mmol) reflecting the upper limit of current recommendations for adults [26], and 3) "low" (50 mmol). The DASH diet is rich in fruits, vegetables, and low-fat dairy products, high in dietary fiber, potassium, calcium and magnesium, moderately high in protein, and low in saturated fat, cholesterol, and total fat. The control diet is typical of what many in the Western world eat.

Study participants were 412 adults (age ≥ 22 years) with systolic blood pressure between 120 and 159 mm Hg and diastolic blood pressure between 80 and 95 mm Hg (i.e., pre-hypertension or stage 1 hypertension). Major exclusion criteria were diabetes mellitus, evidence of active malignancy, history of cardiovascular event (angina, myocardial infarction, angioplasty, or stroke), renal insufficiency (serum creatinine > 1.2 mg/dL for females or 1.5 mg/dL for males), anemia (hematocrit at least 5 percent below normal range), pregnancy, inflammatory bowel disease, body mass index > 40 kg/m^2, use

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of antihypertensive drugs and corticosteroids, and consumption of more than 14 alcoholic beverages per week.

Three screening visits (each separated by at least seven days) were conducted to assess general eligibility and to collect baseline data. Following the screening visits, eligible participants started a two-week run-in feeding period during which they ate the control diet at the high sodium level. The run-in feeding period was designed to exclude participants who were unlikely to comply with the dietary requirements and to estimate caloric requirements needed to maintain weight. Participants were then randomly assigned (generated using desktop PC at each coordinating center) to one of the two diets using a parallel-group design, and ate each of three sodium levels (feeding periods) for 30 days each, in a randomized crossover design. Participants were not notified of their assigned dietary pattern or sodium sequence.

During feeding periods (run-in and intervention), participants were required to eat at least one meal per day on site at the clinical center, five days per week, and to take food home for other meals. Participants were expected to eat all of their food and were instructed to record the type and amount of any uneaten study food. Caffeinated beverages and alcohol were limited and monitored. Individual energy intake (calorie content) was adjusted so that each participant's weight during each feeding period remained stable.

Data collection staff were masked to randomized sodium and diet sequence. Measurements were obtained during screening and at the end of each feeding period. Blood pressure was measured in a

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seated position, using the right arm of participants. Twenty-four hour urine (for analysis of sodium, potassium, urea nitrogen, and creatinine) and body weight were also collected. Compliance with the feeding protocol was assessed by urinary excretion of sodium, potassium, phosphorus, urea nitrogen, and creatinine, estimated from 24 hour urine collections.

Symptoms (side effects) including headache, bloating, dry mouth, excessive thirst, fatigue or low energy, lightheadedness, nausea, and change in taste, were collected via self-administered questionnaires (see Supplement) completed during the last seven days of each sodium feeding period. For each symptom, potential responses were (1) "none" for not experiencing any symptom, (2) "mild" if symptom occurred but did not interfere with usual activities, (3) "moderate" if symptom occurred and somewhat interfered with usual activities, and (4) "severe" if participants were unable to perform usual activities due to the symptom.

This analysis of the DASH-Sodium trial included 390 (95%) of the 412 randomized participants. Excluded participants were those with missing information on headaches in any of the 3 feeding periods. For the primary analysis in this study, headache was defined as "any headache" (mild, moderate or severe) during the last seven days of each feeding period. Subsequently, we report frequency of headache by severity.

The means and proportions between groups were explored using t-tests and chi-square tests, respectively. A non-parametric test (extension of Wilcoxon rank-sum test) was used for trends in the frequency of headache by sodium intake. Since multiple observations were obtained on each participant,

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we used generalized estimating equation models [27], with a logit link and binomial error and an exchangeable covariance structure, to model the odds of a headache. The adjusted covariates used in this analysis were measured at baseline. Models were adjusted for age, sex, race, clinical site, systolic blood pressure, body mass index, and smoking status. The potential for carryover effects was unavoidable in this trial, however, since the experimental agent was one's diet and participants must eat something during these intervals, statistical (GEE) models were also adjusted for carry-over effects from the previous periods. To address the qualitative consistency and benefit-hazard profiles between participants, subgroup analysis by diet stratified by age, sex, race, obesity (BMI $\geq$ 30 kg/m^2 *v* not) and hypertension (blood pressure $\geq$ 140/90 mmHg *v* not) status at baseline were also performed. Interactions between subgroups were tested by the addition of an interaction term to the main effects model.

Institutional review boards at the participating centers and an external data and safety monitoring committee approved the trial protocol and consent procedures. Each participant provided written, informed consent.

A p-value of $\leq$ 0.05 was considered statistically significant. All analyses were performed using Stata version 12.1 (Stata Corp LP, College Station, Texas, USA).

Results

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The 390 participants included in our analyses were those with completed symptoms questionnaires - 192 (94%) of the 204 participants assigned to the control diet and 198 (95%) of the 208 participants assigned to the DASH diet. Clinical and demographic characteristics of the two groups were similar (Table 1).

Figure 2 displays the distribution of headaches by sodium level and assigned diet. The highest occurrence of headache was reported by participants on the control diet with high sodium (47%) and the lowest by participants on the DASH diet with low sodium level (36%). On both diets, the number of headaches reported was greatest for the high sodium level and least on the low sodium level.

Among those assigned to the control diet, mean (SD) urinary sodium excretion was 141 (55), 106 (43) and 64 (37) mmol per 24 hours during the high, intermediate, and low sodium feeding periods, respectively. In the DASH diet group, mean (SD) urinary sodium levels were 144 (57), 107 (52) and 67 (46) mmol per 24 hour during the high, intermediate, and low sodium feeding periods, respectively. On each sodium level, mean urinary sodium excretion was similar in those assigned to the two diets (each $p > 0.05$). Mean urinary potassium and urea nitrogen were higher in the DASH diet group, reflecting the higher vegetable, dairy, and protein content of the DASH diet compared with the control diet, at each sodium level (Table 2).

Table 3 shows differences in the odds of headache by diet and sodium level. Compared to the high sodium level, we observed a lower odds of any headache during the low sodium period both on the control diet (adjusted OR: 0.69, 95% CI: 0.49-0.99) and the DASH diet (adjusted OR: 0.69, 95% CI:

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0.49-0.98). Although the relationship appeared graded (Figure 2), there was no significant difference between the intermediate level of sodium and either the low or high sodium levels, on either diet. There was no significant association of diet pattern (DASH vs. Control) with headache on any sodium level. There was also no significant interaction between diet and sodium on the occurrence of headaches (p-interaction > 0.05). Compared to the control diet with high sodium, there was a reduced risk of a headache on the DASH diet with low sodium (adjusted OR = 0.64, 95% CI: 0.41 – 0.99, p = 0.05).

While on control diet, the number of persons who reported a severe headache was 4 (2.1%) during high, 1 (0.5%) during intermediate, and 1 (0.5%) during low sodium periods, respectively (p for trend = 0.13). On DASH diet, the corresponding number of persons who reported a severe headache was 8 (4%) during high, 2 (1%) during intermediate, and 3 (1.5%) during low sodium periods, respectively (p for trend= 0.08). The frequency of severe headache was similar (p = 0.3) by diet [DASH 8 (4%) and control 4 (2%)] during high sodium feeding period. (Table 4)

There was no evidence that the relationship between sodium levels and headache was modified by age, sex, race, baseline BMI or blood pressure (Figure 3).

Discussion

In this secondary analysis of the DASH-Sodium trial, which enrolled adults with pre- and stage 1 hypertension, a reduced dietary sodium intake was associated with a lower risk of headache, both on the

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control diet and the DASH diet. In contrast, the risk of headache was similar on the DASH and control diets.

The epidemiological literature on headaches in adults is limited [1, 2, 6]. However, it is well-recognized that, compared to normotensive individuals, individuals with hypertension have a higher frequency of headaches [16-19, 28]. Of note, Cooper *et al* reported a direct relationship of headaches with both systolic and diastolic blood pressure [17]. As regards trials, in a pooled analysis that included seven double–blinded, randomized placebo controlled trials of Ibesartan therapy, Hansson *et al* found a direct relationship of diastolic blood pressure with incident headaches in 2673 patients with mild to moderate hypertension [29].

The association between dietary sodium intake and blood pressure is also well recognized [30, 31]. The DASH diet alone and in combination with reduced sodium intake lowers blood pressure in patients with or without hypertension [20, 21]. It is noteworthy that there was no significant relationship between diet pattern and headache. This suggests that a process that is independent of a blood pressure may mediate the relationship between sodium and headaches.

Our results contrast with the popular belief that a diet rich in fruits, vegetables and potassium and low in saturated and total fat may ease the frequency, or even prevent, headache [32]. Several dietary factors, including fasting, alcoholic drinks, chocolate, coffee, and cheese, appear to trigger vascular headache (cluster or migraine) in adults [33- 36]. In some studies, an increased intake of monosodium glutamate is associated with the occurrence of headaches [22-24]. However, a recent review concluded that evidence

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on the relationship of sodium glutamate intake and headaches is inconsistent [37]. In one study of 200 adults (mean age 37.7 years, 81% females), monosodium glutamate was identified as a trigger for migraine headache in only 5 (2.5%) of study participants [36]. However, data on the relationship between sodium intake and any form of headaches are sparse.

The results of this study provide encouraging evidence in support of dietary recommendations to lower sodium intake: recommendations which are currently based on the relationship of sodium intake with blood pressure. The daily intake of sodium in adults living in the United States is already in excess of their physiological need and for many individuals, is much higher than the highest level tested in this study [38, 39]. Our results also support the recent World Health Organization guidelines for reducing sodium intake to less than 87 mmol/day [40] and American Heart Association guidelines for reducing sodium intake to 65 mmol/day [31].

Strengths of our study include its randomized controlled design comparing two diets using a parallel design and a three-period crossover of three levels of dietary sodium (high, intermediate, and low). Dietary intake during the feeding periods was closely monitored and vigorous efforts were made to promote adherence with assigned diets. The participants of this study were healthy, non-institutionalized, racially diverse, middle- and older-aged men and women. Hence we believe that these results are applicable to a large fraction of adults.

Our study also has limitations. Information on the prevalence of headache at baseline from eligible participants was lacking. In addition, there was no information about the type of headache (tension,

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cluster or migraine) experienced by study participants. However, we suspect that most of the headaches were tension headaches. Whether a reduced sodium intake can prevent vascular headache is unknown. Second, the instrument was administered just once in each feeding period and does not allow calculation of an event rate, such as person-days of headaches. Third, these are secondary, post-hoc analyses from a trial that was not explicitly designed to test the effects of dietary factors on headaches. Nonetheless, a rigorously controlled feeding study designed to test the effects of dietary factors on occurrence of headaches would be extremely expensive and logistically challenging. Fourth, our results likely underestimate the relationship of sodium intake with headaches. The range of sodium intake was relatively narrow - the highest sodium group in our trial actually corresponds to the average in the USA and is much lower than the intake in many countries, particularly in Asia. Self-report of symptoms is inherently imprecise and could bias results to the null, given that a validated instrument was not used for patient-reported headache.

In conclusion, a reduced sodium intake was associated with significantly lower risk of headache, while diet patterns had no effect on the risk of headaches. A reduced dietary sodium intake offers a novel approach to prevent headache in adults. Additional studies are needed to replicate these findings and to explore mechanisms that mediate the association between sodium intake and headache.

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Table 1: Baseline characteristics of participants in DASH-Sodium trial [Number (percentage) or mean (standard deviation)]

Characteristic	Control Diet (n=192)	DASH Diet (n=198)	Total (n=390)
Age (years)	49 (10)	47 (10)	48 (10)
Females, n (%)	104 (54)	118 (60)	222 (57)
Race, n (%)			
Caucasian	78 (41)	81 (41)	159 (41)
African American	109 (57)	114 (57)	223 (57)
Other	5 (3)	3 (2)	8 (2)
Body Mass Index, (kg/m^2)	30 (5)	29 (5)	29.2 (5)
Systolic Blood Pressure (mm Hg)	135 (9)	134 (9)	135 (9)
Diastolic Blood Pressure (mm Hg)	86 (4)	85 (5)	86 (4)
Hypertension, n (%) †	76 (40)	79 (40)	155 (40)
Current Smoker, n (%)	21 (11)	21 (11)	42 (11)

†Hypertension was defined as an average systolic blood pressure of 140 mm of Hg or an average diastolic blood pressure of 90 mmHg during the three screening visits.

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Table 2: Urinary excretion according to sodium level and diet [Mean (standard deviation)]

	Level of sodium					
	High		Intermediate		Low	
	DASH (n=198)	Control (n=192)	DASH (n=198)	Control (n=192)	DASH (n=198)	Control (n=192)
Sodium						
gram/day	3.3 (1.3)	3.2 (1.3)	2.5 (1.2)	2.4 (0.9)	1.5 (1.1)	1.5 (0.8)
mmol/day	144 (57)	141 (55)	107 (52)	106 (43)	67 (46)	64 (37)
Potassium						
gram/day	3.0 (1.1)	1.6 (0.5)	3.2 (1.2)	1.6 (0.5)	3.2 (1.1)	1.6 (0.5)
mmol/day	76 (27)	40 (14)	82 (31)	41 (14)	81 (29)	41 (14)
Urea Nitrogen gram/day	11.5 (4)	9.5 (3.2)	12.4 (4.5)	9.7 (3.4)	12 (4)	10 (3.3)
Creatinine gram/day	1.4 (0.5)	1.5 (0.5)	1.5 (0.6)	1.5 (0.6)	1.4 (0.5)	1.5 (0.6)

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Table 3: Odds ratio of headaches by diet and sodium sequence

	Odds ratio (95 %CI)	*p* value
Sodium effects on the DASH diet		
Intermediate *v* high sodium	0.72 (0.51-1.01)	0.06
Low *v* intermediate sodium	0.96 (0.68-1.37)	0.85
Low *v* high sodium	0.69 (0.49-0.98)	0.04
Sodium effects on the control diet		
Intermediate *v* high sodium	0.81 (0.57-1.15)	0.24
Low *v* intermediate sodium	0.86 (0.59-1.24)	0.42
Low *v* high sodium	0.69 (0.49-0.99)	0.05
Diet effects (DASH vs Control) at each sodium level		
On high sodium	0.65 (0.37-1.12)	0.12
On intermediate sodium	0.57 (0.29-1.12)	0.10
On low sodium	0.64 (0.36-1.13)	0.12
Low Sodium on DASH vs High Sodium on Control	0.64 (0.14-0.99)	0.05

Models adjusted for age, sex, race, site, systolic blood pressure, BMI, smoking status and carry over effects from the previous period. CI =confidence interval.

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Table 4: Occurrence and severity of headache by sodium level and diet, n (%)

	Level of sodium					
	High		Intermediate		Low	
	DASH (n=198)	Control (n=192)	DASH (n=198)	Control (n=192)	DASH (n=198)	Control (n=192)
Mild	60 (30)	70 (36)	43 (22)	62 (32)	53 (27)	53 (28)
Moderate	17 (9)	17 (9)	31 (16)	16 (8)	16 (8)	21 (11)
Severe	8 (4)	4 (2)	2 (1)	1 (0.5)	3 (1)	1 (0.5)

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FIGURE LEGEND:

Figure 1: DASH-Sodium Trial Flow Diagram

Figure 2: Frequency of headache by diet and sodium level.

Figure 3

(a): Odds of headache (low vs high sodium) by subgroup, in the DASH diet

(b): Odds of headache (low vs high sodium) by subgroup, in the Control diet

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Effects of Dietary Sodium and the DASH Diet on the Occurrence of Headaches: Results from Randomized Multicenter DASH-Sodium Clinical Trial

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Abstract

Objectives: Headaches are a common medical problem, yet few studies, particularly trials, have evaluated therapies that might prevent or control headaches. We, thus, investigated the effects on the occurrence of headaches of three levels of dietary sodium intake and two diet patterns [the **D**ietary **A**pproaches to **S**top **H**ypertension (DASH) diet (rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat) and a control diet (typical of Western consumption patterns).

Design: Randomized multicenter clinical trial.

Setting: Post-hoc analyses of the DASH-Sodium trial in the USA.

Participants: In a multicenter feeding study with three 30 day periods, 390 participants were randomized to the DASH or control diet. On their assigned diet, participants ate food with high sodium during one period, intermediate sodium during another period, and low sodium during another period, in random order.

Outcome measures: Occurrence and severity of headache were ascertained from self-administered questionnaires, completed at the end of each feeding period.

Results: The occurrence of headaches was similar in DASH vs. Control, at high [odds ratio (95% confidence interval) = 0.65 (0.37-1.12); p=0.12)], intermediate [0.57 (0.29-1.12); p =0.10], and low [0.64 (0.36-1.13); p=0.12] sodium levels. By contrast, there was a lower risk of headache on the low, compared to high, sodium level, both on the control [0.69 (0.49 - 0.99); p = 0.05] and DASH [0.69 (0.49-0.98); p=0.04] diets.

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Conclusions: A reduced sodium intake was associated with a significantly lower risk of headache, whilst dietary patterns had no effect on the risk of headaches in adults. Reduced dietary sodium intake offers a novel approach to prevent headaches.

Key words: Headache; Sodium; Dietary Approaches to Stop Hypertension; DASH-Sodium trial

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Strengths and limitations of this study

- Post-hoc analysis of a multicenter randomized clinical trial comparing effects of the two diet patterns using parallel design together with a three-period crossover of three levels of dietary sodium [high (150 mmol), intermediate (100 mmol), low (50 mmol)] on headaches in healthy adults with stage 1 hypertension.
- Three screening and two run-in feeding periods prior to randomization to assess participant's eligibility, compliance with dietary requirements and to estimate caloric requirements to maintain weight during study.
- Vigorous efforts made to promote adherence with assigned diets during feeding periods.
- Lack of information on the prevalence of headaches at baseline as well as type of self-reported headaches experienced by participants at the end of feeding periods.

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Introduction

Worldwide, headache is a common medical problem and amongst the most frequently reported disorders of the nervous system [1-3]. Globally, 46% of adults are estimated to have an active headache disorder (42% for tension-type headaches; 11% for migraines) [2, 4-6]. Headaches affect all age groups, with a higher prevalence in women compared to men [4-6]. The direct cost of health care services, and medications for the management of headaches is likewise substantial [7-11], as are indirect costs. Patients with frequent headaches have a poor quality of life and a higher number of days absent from work, compared with others [12-15]. Hence, successful strategies to prevent and treat headache would confer substantial benefits to afflicted individuals, as well as to society in general.

Available data support a direct association between blood pressure and the occurrence of headache [16-19]. Therefore, it is reasonable to speculate that dietary factors that lower blood pressure (e.g. reduced sodium intake and the DASH diet [20, 21]) might also reduce the occurrence of headache. However, evidence on the relationship of headaches with sodium intake and other dietary factors is sparse, with most attention focusing on the potential role of monosodium glutamate intake [22-24]. In the primary results paper of the DASH-Sodium trial, which focused on the blood pressure effects of the dietary interventions, the authors briefly comment on the occurrence of headaches in the broad context of side effects. They reported that the side effect of headache occurred in 47% of participants during the high, compared to 39 percent during the low, sodium feeding period [21]. In this paper, we expand on these preliminary observations.

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Methods

A detailed description of the rationale, design, and methods of the DASH-Sodium trial has been published [25]. Briefly, DASH-Sodium was a multicenter, randomized clinical trial, conducted between September 1997 and November 1999, designed to compare the effects on blood pressure of three levels of dietary sodium and two diet patterns. The study design incorporated a parallel, two-group, comparison of diet (DASH diet vs. control diet) together with a three-period crossover of the three levels of dietary sodium intake, with a primary outcome of mean systolic blood pressure (Figure 1). The three sodium levels were 1) "high" (150 mmol, at 2100 Kcal caloric intake), reflecting average consumption in the USA, 2) "intermediate" (100 mmol) reflecting the upper limit of current recommendations for adults [26], and 3) "low" (50 mmol). The DASH diet is rich in fruits, vegetables, and low-fat dairy products, high in dietary fiber, potassium, calcium and magnesium, moderately high in protein, and low in saturated fat, cholesterol, and total fat. The control diet is typical of what many in the Western world eat.

Study participants were 412 adults (age ≥ 22 years) with systolic blood pressure between 120 and 159 mm Hg and diastolic blood pressure between 80 and 95 mm Hg (i.e., pre-hypertension or stage 1 hypertension). Major exclusion criteria were diabetes mellitus, evidence of active malignancy, history of cardiovascular event (angina, myocardial infarction, angioplasty, or stroke), renal insufficiency (serum creatinine > 1.2 mg/dL for females or 1.5 mg/dL for males), anemia (hematocrit at least 5 percent below normal range), pregnancy, inflammatory bowel disease, body mass index > 40 kg/m^2, use of antihypertensive drugs and corticosteroids, and consumption of more than 14 alcoholic beverages per week.

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Three screening visits (each separated by at least seven days) were conducted to assess general eligibility and to collect baseline data. Following the screening visits, eligible participants started a two-week run-in feeding period during which they ate the control diet at the high sodium level. The run-in feeding period was designed to exclude participants who were unlikely to comply with the dietary requirements and to estimate caloric requirements needed to maintain weight. Participants were then randomly assigned (generated using desktop PC at each coordinating center) to one of the two diets using a parallel-group design, and ate each of three sodium levels (feeding periods) for 30 days each, in a randomized crossover design. The sodium feeding periods were separated by feeding breaks of up to 5 days in duration, which were not intended as "washout" periods. Participants were not notified of their assigned dietary pattern or sodium sequence.

During feeding periods (run-in and intervention), participants were required to eat at least one meal per day on site at the clinical center, five days per week, and to take food home for other meals. Participants were expected to eat all of their food and were instructed to record the type and amount of any uneaten study food. Caffeinated beverages and alcohol were limited and monitored. Individual energy intake (calorie content) was adjusted so that each participant's weight during each feeding period remained stable.

Data collection staff were masked to randomized sodium and diet sequence. Measurements were obtained during screening and at the end of each feeding period. Blood pressure was measured in a seated position, using the right arm of participants. Twenty-four hour urine (for analysis of sodium, potassium, urea nitrogen, and creatinine) and body weight were also collected. Compliance with the

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feeding protocol was assessed by urinary excretion of sodium, potassium, phosphorus, urea nitrogen, and creatinine, estimated from 24 hour urine collections.

Symptoms (side effects) including headache, bloating, dry mouth, excessive thirst, fatigue or low energy, lightheadedness, nausea, and change in taste, were collected via self-administered questionnaires (see Supplement) completed during the last seven days of each sodium feeding period. For each symptom, potential responses were (1) "none" for not experiencing any symptom, (2) "mild" if symptom occurred but did not interfere with usual activities, (3) "moderate" if symptom occurred and somewhat interfered with usual activities, and (4) "severe" if participants were unable to perform usual activities due to the symptom.

This analysis of the DASH-Sodium trial included 390 (95%) of the 412 randomized participants. Excluded participants were those with missing information on headaches in any of the 3 feeding periods. For the primary analysis in this study, headache was defined as "any headache" (mild, moderate or severe) during the last seven days of each feeding period. Subsequently, we report frequency of headache by severity.

The means and proportions between groups were explored using t-tests and chi-square tests, respectively. A non-parametric test (extension of Wilcoxon rank-sum test) was used for trends in the frequency of headache by sodium intake. Since multiple observations were obtained on each participant, we used generalized estimating equation models [27], with a logit link and binomial error and an exchangeable covariance structure, to model the odds of a headache. The adjusted covariates used in this

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analysis were measured at baseline. Models were adjusted for age, sex, race, clinical site, systolic blood pressure, body mass index, and smoking status. The potential for carryover effects was unavoidable in this trial, however, since the experimental agent was one's diet and participants must eat something during these intervals, statistical (GEE) models were also adjusted for carry-over effects from the previous periods. To address the qualitative consistency and benefit-hazard profiles between participants, subgroup analysis by diet stratified by age, sex, race, obesity (BMI ≥ 30 kg/m^2 *v* not) and hypertension (blood pressure ≥ 140/90 mmHg *v* not) status at baseline were also performed. Interactions between subgroups were tested by the addition of an interaction term to the main effects model.

Institutional review boards at the participating centers and an external data and safety monitoring committee approved the trial protocol and consent procedures. Each participant provided written, informed consent.

A p-value of ≤ 0.05 was considered statistically significant. All analyses were performed using Stata version 12.1 (Stata Corp LP, College Station, Texas, USA).

Results

The 390 participants included in our analyses were those with completed symptoms questionnaires - 192 (94%) of the 204 participants assigned to the control diet and 198 (95%) of the 208 participants assigned to the DASH diet. Clinical and demographic characteristics of the two groups were similar (Table 1).

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Figure 2 displays the distribution of headaches by sodium level and assigned diet. The highest occurrence of headache was reported by participants on the control diet with high sodium (47%) and the lowest by participants on the DASH diet with low sodium level (36%). On both diets, the number of headaches reported was greatest for the high sodium level and least on the low sodium level.

Among those assigned to the control diet, mean (SD) urinary sodium excretion was 141 (55), 106 (43) and 64 (37) mmol per 24 hours during the high, intermediate, and low sodium feeding periods, respectively. In the DASH diet group, mean (SD) urinary sodium levels were 144 (57), 107 (52) and 67 (46) mmol per 24 hour during the high, intermediate, and low sodium feeding periods, respectively. On each sodium level, mean urinary sodium excretion was similar in those assigned to the two diets (each $p > 0.05$). Mean urinary potassium and urea nitrogen were higher in the DASH diet group, reflecting the higher vegetable, dairy, and protein content of the DASH diet compared with the control diet, at each sodium level (Table 2).

Table 3 shows differences in the odds of headache by diet and sodium level. Compared to the high sodium level, we observed a lower odds of any headache during the low sodium period both on the control diet (adjusted OR: 0.69, 95% CI: 0.49-0.99) and the DASH diet (adjusted OR: 0.69, 95% CI: 0.49-0.98). Although the relationship appeared graded (Figure 2), there was no significant difference between the intermediate level of sodium and either the low or high sodium levels, on either diet. There was no significant association of diet pattern (DASH vs. Control) with headache on any sodium level. There was also no significant interaction between diet and sodium on the occurrence of headaches (p-

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interaction > 0.05). Compared to the control diet with high sodium, there was a reduced risk of a headache on the DASH diet with low sodium (adjusted OR = 0.64, 95% CI: 0.41 – 0.99, p = 0.05).

While on control diet, the number of persons who reported a severe headache was 4 (2.1%) during high, 1 (0.5%) during intermediate, and 1 (0.5%) during low sodium periods, respectively (p for trend = 0.13). On DASH diet, the corresponding number of persons who reported a severe headache was 8 (4%) during high, 2 (1%) during intermediate, and 3 (1.5%) during low sodium periods, respectively (p for trend= 0.08). The frequency of severe headache was similar (p = 0.3) by diet [DASH 8 (4%) and control 4 (2%)] during high sodium feeding period. (Table 4)

There was no evidence that the relationship between sodium levels and headache was modified by age, sex, race, baseline BMI or blood pressure (Figure 3).

Discussion

In this secondary analysis of the DASH-Sodium trial, which enrolled adults with pre- and stage 1 hypertension, a reduced dietary sodium intake was associated with a lower risk of headache, both on the control diet and the DASH diet. In contrast, the risk of headache was similar on the DASH and control diets.

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The epidemiological literature on headaches in adults is limited [1, 2, 6]. However, it is well-recognized that, compared to normotensive individuals, individuals with hypertension have a higher frequency of headaches [16-19, 28]. Of note, Cooper *et al* reported a direct relationship of headaches with both systolic and diastolic blood pressure [17]. As regards trials, in a pooled analysis that included seven double–blinded, randomized placebo controlled trials of Ibesartan therapy, Hansson *et al* found a direct relationship of diastolic blood pressure with incident headaches in 2673 patients with mild to moderate hypertension [29].

The association between dietary sodium intake and blood pressure is also well recognized [30, 31]. The DASH diet alone and in combination with reduced sodium intake lowers blood pressure in patients with or without hypertension [20, 21]. It is noteworthy that there was no significant relationship between diet pattern and headache. This suggests that a process that is independent of a blood pressure may mediate the relationship between sodium and headaches.

Our results contrast with the popular belief that a diet rich in fruits, vegetables and potassium and low in saturated and total fat may ease the frequency, or even prevent, headache [32]. Several dietary factors, including fasting, alcoholic drinks, chocolate, coffee, and cheese, appear to trigger vascular headache (cluster or migraine) in adults [33- 36]. In some studies, an increased intake of monosodium glutamate is associated with the occurrence of headaches [22-24]. However, a recent review concluded that evidence on the relationship of sodium glutamate intake and headaches is inconsistent [37]. In one study of 200 adults (mean age 37.7 years, 81% females), monosodium glutamate was identified as a trigger for migraine headache in only 5 (2.5%) of study participants [36]. However, data on the relationship between sodium intake and any form of headaches are sparse.

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The results of this study provide encouraging evidence in support of dietary recommendations to lower sodium intake: recommendations which are currently based on the relationship of sodium intake with blood pressure. The daily intake of sodium in adults living in the United States is already in excess of their physiological need and for many individuals, is much higher than the highest level tested in this study [38, 39]. Our results also support the recent World Health Organization guidelines for reducing sodium intake to less than 87 mmol/day [40] and American Heart Association guidelines for reducing sodium intake to 65 mmol/day [31].

Strengths of our study include its randomized controlled design comparing two diets using a parallel design and a three-period crossover of three levels of dietary sodium (high, intermediate, and low). Dietary intake during the feeding periods was closely monitored and vigorous efforts were made to promote adherence with assigned diets. The participants of this study were healthy, non-institutionalized, racially diverse, middle- and older-aged men and women. Hence we believe that these results are applicable to a large fraction of adults.

Our study also has limitations. Information on the prevalence of headache at baseline from eligible participants was lacking. In addition, there was no information about the type of headache (tension, cluster or migraine) experienced by study participants. However, we suspect that most of the headaches were tension headaches. Whether a reduced sodium intake can prevent vascular headache is unknown. Second, the instrument was administered just once in each feeding period and does not allow calculation of an event rate, such as person-days of headaches. Third, these are secondary, post-hoc analyses from a trial that was not explicitly designed to test the effects of dietary factors on headaches. Nonetheless, a

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rigorously controlled feeding study designed to test the effects of dietary factors on occurrence of headaches would be extremely expensive and logistically challenging. Fourth, our results likely underestimate the relationship of sodium intake with headaches. The range of sodium intake was relatively narrow - the highest sodium group in our trial actually corresponds to the average in the USA and is much lower than the intake in many countries, particularly in Asia. Self-report of symptoms is inherently imprecise and could bias results to the null, given that a validated instrument was not used for patient-reported headache.

In conclusion, a reduced sodium intake was associated with significantly lower risk of headache, while diet patterns had no effect on the risk of headaches. A reduced dietary sodium intake offers a novel approach to prevent headache in adults. Additional studies are needed to replicate these findings and to explore mechanisms that mediate the association between sodium intake and headache.

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Contribution statement: All three authors (Muhammad Amer, Mark Woodward, and Lawrence Appel) have -substantially contributed to the conception, ~~equally participated in the~~ drafting, ~~and~~ editing and revising for the important intellectual content of the manuscript. Muhammad Amer and Mark Woodward were responsible for ~~, did~~ analyses of the data. All three authors participated in the interpretation of the analysis and agreed for the final approval of the version to be published. Authors are in agreement to be accountable for all aspects of the work related to this manuscript and responsible for the integrity of any part of the work shown in this post-hoc analysis of the DASH-Sodium clinical trial.

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Table 1: Baseline characteristics of participants in DASH-Sodium trial [Number (percentage) or mean (standard deviation)]

Characteristic	Control Diet (n=192)	DASH Diet (n=198)	Total (n=390)
Age (years)	49 (10)	47 (10)	48 (10)
Females, n (%)	104 (54)	118 (60)	222 (57)
Race, n (%)			
Caucasian	78 (41)	81 (41)	159 (41)
African American	109 (57)	114 (57)	223 (57)
Other	5 (3)	3 (2)	8 (2)
Body Mass Index, (kg/m^2)	30 (5)	29 (5)	29.2 (5)
Systolic Blood Pressure (mm Hg)	135 (9)	134 (9)	135 (9)
Diastolic Blood Pressure (mm Hg)	86 (4)	85 (5)	86 (4)
Hypertension, n (%) †	76 (40)	79 (40)	155 (40)
Current Smoker, n (%)	21 (11)	21 (11)	42 (11)

†Hypertension was defined as an average systolic blood pressure of 140 mm of Hg or an average diastolic blood pressure of 90 mmHg during the three screening visits.

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Table 2: Urinary excretion according to sodium level and diet [Mean (standard deviation)]

	Level of sodium					
	High		Intermediate		Low	
	DASH (n=198)	Control (n=192)	DASH (n=198)	Control (n=192)	DASH (n=198)	Control (n=192)
Sodium						
gram/day	3.3 (1.3)	3.2 (1.3)	2.5 (1.2)	2.4 (0.9)	1.5 (1.1)	1.5 (0.8)
mmol/day	144 (57)	141 (55)	107 (52)	106 (43)	67 (46)	64 (37)
Potassium						
gram/day	3.0 (1.1)	1.6 (0.5)	3.2 (1.2)	1.6 (0.5)	3.2 (1.1)	1.6 (0.5)
mmol/day	76 (27)	40 (14)	82 (31)	41 (14)	81 (29)	41 (14)
Urea Nitrogen gram/day	11.5 (4)	9.5 (3.2)	12.4 (4.5)	9.7 (3.4)	12 (4)	10 (3.3)
Creatinine gram/day	1.4 (0.5)	1.5 (0.5)	1.5 (0.6)	1.5 (0.6)	1.4 (0.5)	1.5 (0.6)

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Table 3: Odds ratio of headaches by diet and sodium sequence

	Odds ratio (95 %CI)	*p* value
Sodium effects on the DASH diet		
Intermediate *v* high sodium	0.72 (0.51-1.01)	0.06
Low *v* intermediate sodium	0.96 (0.68-1.37)	0.85
Low *v* high sodium	0.69 (0.49-0.98)	0.04
Sodium effects on the control diet		
Intermediate *v* high sodium	0.81 (0.57-1.15)	0.24
Low *v* intermediate sodium	0.86 (0.59-1.24)	0.42
Low *v* high sodium	0.69 (0.49-0.99)	0.05
Diet effects (DASH vs Control) at each sodium level		
On high sodium	0.65 (0.37-1.12)	0.12
On intermediate sodium	0.57 (0.29-1.12)	0.10
On low sodium	0.64 (0.36-1.13)	0.12
Low Sodium on DASH vs High Sodium on Control	0.64 (0.14-0.99)	0.05

Models adjusted for age, sex, race, site, systolic blood pressure, BMI, smoking status and carry over effects from the previous period. CI =confidence interval.

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Table 4: Occurrence and severity of headache by sodium level and diet, n (%)

	Level of sodium					
	High		Intermediate		Low	
	DASH (n=198)	Control (n=192)	DASH (n=198)	Control (n=192)	DASH (n=198)	Control (n=192)
Mild	60 (30)	70 (36)	43 (22)	62 (32)	53 (27)	53 (28)
Moderate	17 (9)	17 (9)	31 (16)	16 (8)	16 (8)	21 (11)
Severe	8 (4)	4 (2)	2 (1)	1 (0.5)	3 (1)	1 (0.5)

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FIGURE LEGEND:

Figure 1: DASH-Sodium Trial Flow Diagram

Figure 2: Frequency of headache by diet and sodium level.

Figure 3

(a): Odds of headache (low vs high sodium) by subgroup, in the DASH diet

(b): Odds of headache (low vs high sodium) by subgroup, in the Control diet

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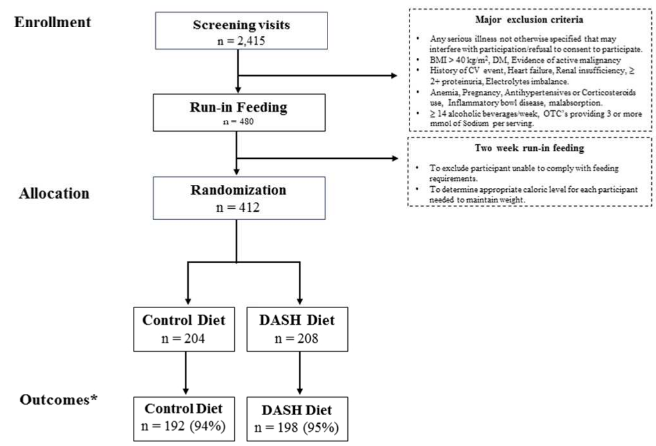
Figure 1: DASH-Sodium Trial Flow Diagram



*Participants with complete questionnaire data on headaches in all 3 periods.

338x190mm (96 x 96 DPI)

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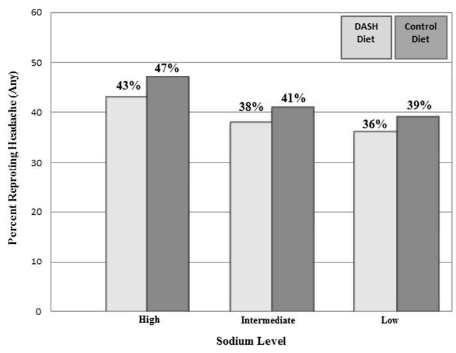
Figure 2: Frequency of headache by diet and sodium level



338x190mm (96 x 96 DPI)

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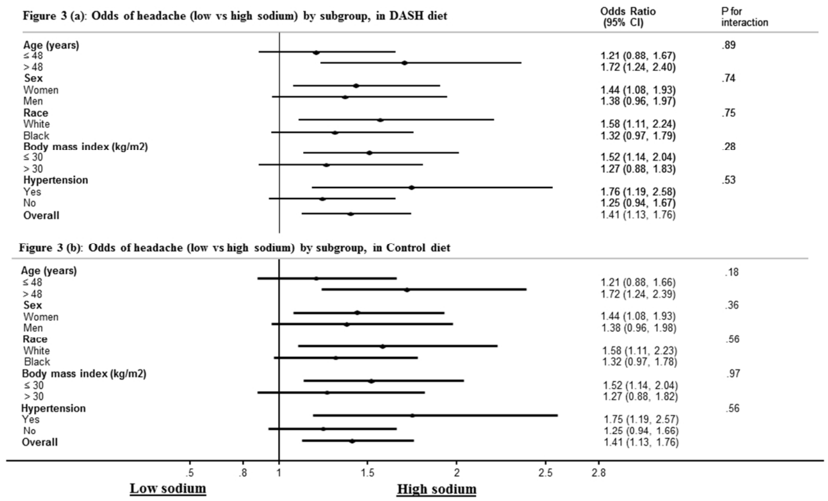

338x190mm (96 x 96 DPI)

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Analysis Guide

January 31, 2001

DATASET: SIDEEFF

Side effects (symptoms) data. One record per randomized participant per visit (collected at SV3, RI, IV1, IV2 and IV3). Use AN_ID as the participant ID for all Data Release Requests and for all analysis data sets that leave CHR.

Variable	Description	Format	Range	Notes
AN_ID	id for analysis datasets	text		Numeric portion of original alphanumeric ID. First digit identifies clinic site.
APPETITE	poor appetite	severity*	1 - 4	= 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
BLOATING	bloating / uncomfortably full	severity*	1 - 4	included in GI symptoms, = 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
CONSTIP	constipation	severity*	1 - 4	included in GI symptoms, = 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
DIARRHEA	diarrhea / loose stools	severity*	1 - 4	included in GI symptoms, = 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
DRYMOUTH	dry mouth	severity*	1 - 4	= 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
EXTHIRST	excessive thirst	severity*	1 - 4	= 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
FATIGUE	fatigue or low energy	severity*	1 - 4	= 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
FELT	overall past two weeks	felt*	1 - 5	
HEADACHE	headache	severity*	1 - 4	= 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
ITCHYSKI	itchy skin or hives	severity*	1 - 4	= 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
LITEHEAD	lightheadedness when standing up	severity*	1 - 4	= 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
NAUSEA	nausea or upset stomach	severity*	1 - 4	included in GI symptoms, = 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
SERIOUS	serious illness in past month	yesnoft*	1 - 4	
STUFFNOS	stuffy nose	severity*	1 - 4	= 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
TASTE	change in taste	severity*	1 - 4	= 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe
VISIT	visit	visitft*	4 - 8	= 4 if SV3, = 5 if RI, = 6 if IFP 1, = 7 if IFP 2, = 8 if IFP 3
WHEEZING	wheezing	severity*	1 - 4	= 1 if did not occur, = 2 if mild, = 3 if moderate, = 4 if severe

* custom format, see list of formats at end of this section.

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Variable Formats

January 31, 2001

DATASET: SIDEEFF

Dataset	Format:	Value Range:	Label:
SIDEEFF	FELT	. -	NO ANSWER
		1 -	MUCH WORSE
		2 -	WORSE THAN USUAL
		3 -	THE SAME AS USUAL
		4 -	BETTER THAN USUAL
		5 -	MUCH BETTER
	SEVERITY	. -	NO ANSWER
		1 -	DID NOT OCCUR
		2 -	MILD
		3 -	MODERATE
		4 -	SEVERE
	VISITFT	1 -	PSV
		2 -	SV1
		3 -	SV2
		4 -	SV3
		5 -	RI
		6 -	INT1
		7 -	INT2
		8 -	INT3
		9 -	COMPLT. FEEDING
	YESNOFT	0 -	No
		1 -	Yes
		2 -	No
		3 -	Unsure

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SideEff Dataset 10 Sample Observations 1

Obs	AN_ID	APPETITE	BLOATING	CONSTIP	DIARRHEA	DRYMOUTH	EXTHIRST	FATIGUE	FELT	HEADACHE	ITCHYSKI	LITEHEAD	NAUSEA	SERIOUS	STUFFNOS	TASTE	VISIT	WHEEZING
1	20847	1	1	1	1	1	1	1	3	1	1	1	1	2	1	1	4	1
2	20847	1	1	1	1	1	1	1	3	2	1	1	1	1	1	1	5	1
3	20847	1	2	1	1	2	1	1	5	1	1	1	1	2	1	1	6	1
4	20847	1	1	1	1	2	1	1	3	1	1	1	1	2	1	1	7	1
5	20847	1	1	1	1	1	1	1	3	1	1	1	1	2	1	1	8	1
6	10933	1	1	1	1	1	1	2	3	1	1	1	1	2	2	1	4	1
7	10933	2	2	2	2	2	3	2	3	1	2	1	1	2	3	1	5	1
8	10933	2	2	1	2	2	3	2	3	2	2	1	2	2	4	1	6	1
9	10933	3	2	3	3	2	2	2	3	3	2	3	3	2	3	1	7	2
10	10933	3	2	2	1	3	2	3	3	2	2	3	2	2	4	3	8	1

DASH-SODIUM Data Release (DTR-19)
PROGRAM: WLDTR1901.sas
ANALYST: W. Li -- Jan 31, 2001

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Manuscript: bmjopen-2014-006671

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	YES
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	YES
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	YES
	2b	Specific objectives or hypotheses	YES
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	YES
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	YES
Participants	4a	Eligibility criteria for participants	YES
	4b	Settings and locations where the data were collected	YES
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	YES
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	YES
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	N/A (post-hoc analysis)
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	YES
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	YES
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Coordinating center staff
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Participants

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		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	YES
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	YES
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	YES
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	YES. N/A for this study
	13b	For each group, losses and exclusions after randomisation, together with reasons	YES
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Time line not dates
	14b	Why the trial ended or was stopped	Planned stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	YES
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	YES
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	YES
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Used Odds Ratio's
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	YES
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A in post hoc analysis
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	YES
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	YES
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	YES
Other information			
Registration	23	Registration number and name of trial registry	YES
Protocol	24	Where the full trial protocol can be accessed, if available	YES
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	YES

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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