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MORTALITY

ABSTRACT & COMMENTARY

## You Will 'Nut' Believe It: Nut Consumption Decreases Total and Cause-Specific Mortality

*By Melissa Quick, DO, and David Kiefer, MD*

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Dr. Quick reports no financial relationships relevant to this field of study.

SYNOPSIS: This article examines the association of nut consumption with total and cause-specific mortality by evaluating two large, independent cohort studies of nurses and other health professionals.

SOURCE: Bao Y, et al. Association of nut consumption with total and cause-specific mortality. *N Engl J Med* 2013;369:2001-2011.

Previous studies have suggested that nut consumption has multiple beneficial health effects, specifically in decreasing coronary heart disease.[1,2] In this article, Bao et al sought to further examine the effect of nut consumption on mortality by examining extensive dietary data juxtaposed with 30 years of follow-up.

Two studies were analyzed: the Nurses' Health Study (NHS), a prospective cohort study that started in 1976 consisting of 121,700 female nurses from 11 U.S. states, and the Health Professionals Follow-up Study (HPFS), a prospective cohort study of 51,529 male health professionals from all 50 states that began in 1986. Of the enrolled participants, 76,464 women in the NHS and 42,498 men in the HPFS remained after excluding women and men with a history of cancer, heart disease, and stroke, or participants who did not provide adequate information about nut consumption or sufficient anthropometric data.

Information was collected via validated food-frequency questionnaires that were sent every 2-4 years, beginning in 1980 for the NHS and in 1986 for the HPFS. Participants were asked how often they had consumed a serving of nuts (serving size: 28 g [1 oz]) during the preceding year and were given the choices: never or almost never, one to three times a

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month, once a week, two to four times a week, five or six times a week, once a day, two or three times a day, four to six times a day, or more than six times a day. As the study went on, the wording of the questionnaire changed slightly as participants were asked the same question but with two discrete nut categories consisting of "peanuts" vs "other nuts." "Total nut" consumption was defined as the intake of peanuts and other nuts. Additional questionnaires were sent every 2 years to update medical and lifestyle information.

The primary endpoint of this analysis was death from any cause. Using systematic searches of individual states' vital records and the National Death Index, the authors were able to obtain 98% of death information in each cohort.

Data analysis was adjusted to minimize within-person variation, such as altered dietary patterns before or after a diagnosis of a major illness. Additionally, other data analysis modifications were made to reduce the influence of smokers, diabetics, or those with an extreme body mass index (BMI) — participants were excluded from the analysis if they had ever smoked, had a BMI < 18.5 kg/m$^2$ or > 40 kg/m$^2$, or had a diagnosis of diabetes at baseline.

Inverse associations were observed between nut consumption and most major causes of death, including heart disease, cancer, and respiratory diseases. In the NHS, the authors found during 30 years of follow-up (2,135,482 person-years), there were 16,200 total deaths. For the HPFS, after 24 years of follow-up (903,371 person-years), there were 11,229 documented deaths.

With pooled data from both cohorts in comparison to participants who did not eat nuts, those who consumed nuts less than once a week had a 7% lower death rate (hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.90-0.96); for nut consumption once per week there was an 11% lower death rate (HR, 0.89; 95% CI, 0.86-0.93); for nut consumption two to four times per week a 13% lower death rate (HR, 0.87; 95% CI, 0.83-0.90); for nut consumption five to six times per week a 15% lower death rate (HR, 0.85; 95% CI, 0.79-0.91). Finally, those who consumed nuts seven or more times per week had a 20% lower death rate (HR, 0.80; 95% CI, 0.73-0.86; $P < 0.001$).

A separate analysis between peanuts and tree nuts displayed similar associations with total and cause-specific mortality between the two types of nuts. When consumption of nuts two or more times per week was compared with no nut consumption, the pooled multivariate-adjusted HRs for death were 0.88 (95% CI, 0.84-0.93) for peanuts and 0.83 (95% CI, 0.79-0.88) for tree nuts.

## ■ COMMENTARY

It was only about 20 years ago that nuts were propelled from the "unhealthy" to the "healthy" food category, as their high fat content and high caloric value was unappealing to many consumers. Today, nuts are emerging as one of the most unique, nutrient-dense foods that exists by virtue of their distinctive combination of complex matrices rich in unsaturated fatty, fiber, vitamins, minerals, and multiple bioactive compounds.[3] A common misconception is that foods high in fatty acids, such as nuts, can lead to excess weight gain. However, multiple studies have shown that there is no association between nut consumption and weight gain, and some research suggests nuts can actually help individuals lose weight.[4,5]

In the last decade, nuts have been gaining popularity in both the media and in the health care realm. In 2003, the FDA deemed nuts "heart healthy" and authorized the claim that "scientific evidence suggests but does not prove that eating 1.5 ounces (43 g) per day of most nuts as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease."[6] Furthermore, multiple epidemiological and clinical studies have shown that frequent nut consumption is associated with improved plasma lipid profiles and decreased risk of coronary heart disease, certain types of cancer, stroke, atherosclerosis, type 2 diabetes, inflammation, and other chronic diseases.[7,8]

## Summary Points

- Nuts (peanuts and tree nuts) are unique, nutrient-dense foods rich in unsaturated fatty acids, fiber, vitamins, minerals, and many bioactive substances.
- Nut consumption is inversely associated with total mortality among women and men with greatest benefit seen when consuming nuts seven or more times a week.
- Scientific evidence suggests that nuts are a cardioprotective food.

Indeed, Bao's study showed that the more a person ate nuts, the less he/she died from most major causes of death, including heart disease, cancer, and cardiovascular diseases. In terms of *overall* nut consumption, the following causes of death were significantly decreased *regardless* of quantity of nut consumption: "all causes" ($P < 0.001$), "cancer" ($P = 0.03$), "cardiovascular disease" ($P < 0.001$), and "heart disease" ($P < 0.001$). For each of these categories, there was an inverse association between amount of nuts eaten and the hazard ratio. The other causes of death did not have consistent inverse associations, nor were the results significant.

With regard to nut-specific results, only two categories of death — all-cause mortality and heart disease — displayed definitive positive effects (meaning a hazard ratio < 1 and a confidence interval not crossing 1) for each type of nut ("any nut," "peanut," or "tree nut"). For cancer as a cause of death, the results were only significant for those who ate "any nut" or "tree nuts." For respiratory disease as a cause of death, results were only significant for those who ate "peanuts."

Overall, these findings are quite promising, and they echo the findings of a recent landmark, randomized, primary prevention study (PREDIMED trial (Prevención con Dieta Mediterránea) published in 2013. The PREDIMED study surprised many in the medical community by demonstrating just how effectively the Mediterranean diet (supplementing with either increased intake of olive oil or mixed nuts) can prevent cardiovascular disease, compared to a low-fat diet.[9] The results of the PREDIMED trial are comparable to Bao's study in that they demonstrated that individuals eating nuts more than three times per week died less often from cardiovascular disease and cancer than those who did not consume nuts.[10] Though encouraging, PREDIMED was limited by a median follow-up of only 4.8 years and a smaller sample size. Accordingly, one of the strengths of Bao's study is a large sample size and longer duration of follow-up. So which nuts should we be eating? Tree nuts are the most common type of nut studied for health benefits. Tree nuts are defined as dry fruits with one seed in which the ovary wall becomes hard at maturity.[2] The most popular tree nuts include almonds (*Prunus* spp.), Brazil nuts (*Bertholletia excelsa* spp.), cashews (*Anacardium occidentale*), hazelnuts (*Corylus avellana*), macadamia nuts (*Macadamia* spp.), pecans (*Carya illinoinensis*), pine nuts (*Pinus* spp.), pistachios (*Pistacia vera*), and walnuts (*Juglans regia*).[7] Consumers often erroneously identify peanuts (*Arachis hypogaea*) as nuts, but they are actually legumes.[7] Peanuts do, however, have a similar nutrient profile as tree nuts.[11] Of note, chestnuts (*Castanea sativa*) are tree nuts as well, but they are generally excluded from the category of "healthy" tree nuts because they are much starchier and have a less favorable nutrient profile.[2]

Many components of tree nuts are responsible for their nutritional value: macronutrients (fat, protein, and carbohydrates), micronutrients (minerals and vitamins), fat-soluble bioactives (monounsaturated fatty acids, polyunsaturated fatty acids, tocopherols, etc.), and bioactive phytochemicals (primarily phenolic acids and carotenoids). Additionally, tree nuts have antioxidant effects, free radical scavenging activity, and anticarcinogenic and antimutagenic effects.[7] Interestingly, a study performed in 2008 compared the antioxidant and antiproliferative properties of common nuts and found that walnuts have the highest total phenolic and flavonoid contents.[12]

One potential limitation of Bao's study is that there was no differentiation between which specific nuts were consumed. In his study, nuts were differentiated into three categories: "peanut," "tree nut," or "any nut," which included both tree nuts and peanuts. While the nutrition profile for nuts is similar overall, each type of nut has varying levels of caloric value, different types of fat, different mineral and vitamin content, and many more factors. In the PREDIMED study, the nut-consuming intervention arm was actually divided into groups: a "walnut" arm (containing polyunsaturated fatty acids and polyphenols) and an "almonds and hazelnuts" arm (containing monounsaturated fatty acids and polyphenols).[9]

Another possible limitation of this study is that participants were not required to recall how the nuts they consumed were prepared (roasted, salted, etc). Of course there is a huge variety in nut preparation. Interestingly, when evaluating raw vs roasted nuts,

it seems roasting does not affect the nutrition profile of the nut. On the other hand, the question of salted vs unsalted nuts leans more favorably toward the unsalted variety, as increased salt can cause harm to those with high blood pressure or other chronic cardiac conditions.

How can we encourage our patients to eat more nuts? First, reframing nuts as unique, nutrient-dense nourishment that cannot be found in other foods could encourage individuals to incorporate more nuts into their daily diet. Historically, traditional "food pyramids" or "MyPlates" sponsored by the USDA as a guide to daily nutrition have grouped nuts under the larger "protein" category as part of a meal.[13] However, approximately 60% of nuts consumed in the United States are consumed as snacks.[14] Thus, in an effort to encourage nut consumption in the public, it may be worthwhile for health care providers to reframe the use of nuts as "healthy snacks," and perhaps in the future, to move nuts to their own dietary category.

Overall, Bao's study impressively demonstrates an inverse relationship between those who consume nuts and all-cause mortality and mortality from heart disease. Health care providers should emphasize that any nut is a good nut (including peanuts!) as nutrient profiles overall are very similar. And it seems more nuts are better than fewer nuts. So how many nuts should one eat? Bao's study described a portion of nuts as 28 g (1 oz), whereas the FDA suggests a daily dose of 43 g (1.5 oz). Regardless of the size of one's hand, it seems to safe assume a "healthy handful" of nuts a day should be a friendly reminder to any individuals to promote health and wellness. Do NUT forget it! ■


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## WOMEN'S HEALTH

### ABSTRACT & COMMENTARY

# Spirituality and In Vitro Fertilization


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**Dr Sasser reports no financial relationships relevant to this field of study.**



SYNOPSIS: In a randomized study conducted among Chinese women undergoing in vitro fertilization therapy, those receiving a body-mind-spirit intervention combining well-being, resilience, and spiritual transformation experiences with principles of Chinese philosophy showed significantly lower state and trait anxiety, greater tranquility and resilience, and smaller declines in daily functioning and physical distress, as compared with control participants who received no intervention.



SOURCE: Chan CHY, et al. Incorporating spirituality in psychosocial group intervention for women undergoing in vitro fertilization: A prospective randomized controlled study. *Psychol Psychother* 2012;85:356-373.


A research group in Hong Kong developed an integrated body-mind-spirit (I-BMS) intervention combining typical "Western" elements (well-being, resilience, spiritual transformation) with culturally relevant content from Chinese philosophy. Exercises, usually done

## Summary Points

- Women receiving a body-mind-spirit intervention showed lower anxiety and some other negative symptoms while undergoing in vitro fertilization (IVF) therapy as compared to a no-intervention control group.
- For some symptoms on which all participants worsened during the study, such as physical distress and daily functioning, those in the intervention group declined to a lesser extent.
- There was no significant difference between the study groups in IVF outcomes.

in groups, included meditation, breathing exercises, journaling, and didactic content about the physical processes of stress and relaxation.

To test the I-BMS intervention in a high-stress life setting, the group recruited 339 women who were beginning in vitro fertilization (IVF) treatment. The goal of the study was not to try to influence the outcome of IVF, but rather to use it to provide context for the intervention. Women who agreed to participate were assigned randomly to I-BMS or to a control group that received nothing from the study. Those in the I-BMS study arm attended four weekly sessions, each lasting 3 hours, in groups of 7-10, and did additional exercises at home.

Study outcomes were assessed using the Chinese State-Trait Anxiety Inventory, the Importance of Childbearing Index, the Chinese version of the Kansas Marital Satisfaction Scale, and a Body-Mind-Spirit Well-Being Inventory developed by the investigators. Participants also provided socioeconomic and medical information.
The effect of the I-BMS intervention as compared with the control condition was assessed for the period from study randomization until the day ovarian stimulation began ($T_0$-$T_1$), and from then until embryo transfer was attempted ($T_1$-$T_2$), as well as over the complete study period ($T_0$-$T_2$). A summary of the study findings is shown in Table 1. Briefly, the intervention group improved on key measures of anxiety and spirituality while the control group worsened. On other measures, both groups improved or declined, but the I-BMS group showed more desirable changes. Interestingly, the intervention appeared to be most effective in the short term in dealing with cognitive effects (anxiety, importance of childbearing) and in the longer term with more practical effects (marital satisfaction, physical distress). The fact that some outcomes only showed significant changes when measured over the total study period suggests a gain in the "potency" of I-BMS over time. There was no significant difference by study group in IVF outcomes.

### ■ COMMENTARY

A number of factors influence how we should assess the results of this study. The first, and most important, is attrition. Over the course of the study, 31 I-BMS and 57 control participants were lost to follow-up, producing attrition rates of 18% and 34.1%, respectively. A portion of these (n = 34) were attributable to IVF-related causes (pregnancy, treatment delay, or termination), but the remainder were voluntary withdrawals from the study. While some dropouts, especially in a no-intervention control group, are to be expected, a rate much above 20% is cause for concern. The investigators found several statistically significant differences between those who dropped out of the study and those who remained, including higher baseline marital satisfaction, lower baseline importance of childbearing, and shorter marital duration among the dropouts. However, they do not report how these characteristics were distributed between dropouts from the intervention and control groups. This makes it difficult to say exactly how attrition may have affected the study's findings, although it raises doubts about the integrity of randomization as a way of making the study groups comparable on potentially confounding factors. It seems appropriate as a consequence to view the results with some suspicion.

A second issue deals with timing. The study investigators describe at what points in the IVF treatment process they measured the various outcomes (study enrollment — presumably before any treatment, the day ovarian stimulation began, and the day embryo transfer took place), but the study intervention is described simply as taking place "before treatment." It is unclear how long the interval between the study intervention and the beginning of IVF was or whether it was roughly the same for all women in the intervention group. This leaves the reader to guess at important clinical details such as the value of practice and internalization after the intervention and before a stressful event, and the likely duration of the treatment effect. This is all the more important given the apparent pattern of changing effects over time. The absence of clear description of the methods limits both the strength and the generalizability of the study's findings.

Two other study design factors are important to note. First, the I-BMS treatment was compared with a no-intervention control. This raises the possibility

Table 1. Study Outcomes by Time Interval and Study Group

| | $T_0$ to $T_1$ | | $T_1$ to $T_2$ | | $T_0$ to $T_2$ | |
|---|---|---|---|---|---|---|
| | I-BMS | Control | I-BMS | Control | I-BMS | Control |
| State Anxiety | - | + | | | - | + |
| Trait Anxiety | - | + | | | - | + |
| Importance of Childbearing | -- | - | | | -- | - |
| Tranquility | + | - | + | - | + | - |
| Disorientation | - | + | | | - | + |
| Marital Satisfaction | | | + | - | + | - |
| Physical Distress | | | + | ++ | + | ++ |
| Daily Functioning | | | | | - | -- |
| Negative Affect | | | + | ++ | + | ++ |
| Positive Affect | | | | | | |
| Resilience | | | | | + | - |

+ Rose, ++ Rose more, - Declined, -- Declined more | $P < 0.01$ (shaded), $P < 0.05$ (unshaded)
$T_0$ Study inception, $T_1$ Day ovarian stimulation began, $T_2$ Day embryo transfer was attempted

of a "nocebo" effect, in which the control group's responses are affected negatively by the awareness that they are not receiving something. The study's results would be more compelling had I-BMS been compared with another active intervention — a point made by the investigators as a goal of future research. Second, the study group was composed of women only. This removed one element of heterogeneity (i.e., raised internal validity), but given that the study focused on IVF, is regrettable. Male spouses/partners were understood to be present in the participants' lives. Had these men at least been assessed, if not included fully in the study, it would have been possible to determine their role in raising or lowering their female partners' levels of stress. We are also left with no concrete sense of how appropriate this intervention would be for male patients.

In its favor, the study tested an integrative intervention that included culturally relevant content and delivery. It combined cross-cultural elements (meditation, guided imagery, physical activity) with Chinese philosophy and a sensitivity to the importance of marriage and childbearing in Chinese culture. This awareness that behavioral and cognitive interventions are tied to (or at least influenced by) specific circumstances aids both in their evaluation and use in practice. This study also took place in the course of a genuine, acute stressor — IVF therapy. This seems to be more demanding a test of the treatment effect than would have been possible in the context of daily "background" stress. While this may not be a wholly generalizable experience, it contains elements common to many stressful situations — high personal stakes, limited control of complex processes, problems in applying routine coping skills to an unfamiliar situation — which does much to show its possible benefits in other contexts.

What should clinicians and patients take away from this study? One clear message seems to be the value of being forearmed. This and similar interventions help those who use them to develop coping resources that can be drawn on later. While this can be seen most readily in how we react to clearly defined, high-stress events, the same techniques can be used to help manage "ordinary" daily stresses.

A second clear message is the need to choose treatment strategies carefully. The attention the investigators in this study paid to cultural and situational factors certainly improved the fit between the intervention and those who received it. It is worthwhile to consider where and for whom an intervention was developed — one size does not fit all. Many interventions have been validated in

various ethnic, linguistic, gender, and age groups, and this information is usually readily available. (A good source for this information for mind-body interventions is the National Registry of Evidence-Based Programs and Practices, a website sponsored by the Substance Abuse and Mental Health Services Administration of the U.S. Department of Health and Human Services. It can be found at www.nrepp.samhsa.gov.) It is also important to note that interventions with many parts may need to be viewed as integrated units — in other words not as menus from which selected parts can be extracted.

Finally, it is important for both clinicians and patients to be aware that coping strategies can be effective — and should be employed — even if they do not alter the outcome of the event creating the stress. In this case, IVF outcomes were no different with or without I-BMS. Even so, the intervention gave the women who received it a way of managing part of a situation that was largely outside their control. Regardless of the IVF outcome, they gained a means of thinking about and reacting to it. This is valuable whenever clinician and patient must confront difficult and uncertain prognoses. ■

## DIABETES

ABSTRACT & COMMENTARY

# Prevention of Diabetes with Mediterranean Diet

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**Dr. Pantuso reports no financial relationships relevant to this field of study.**

SYNOPSIS: Previously, the authors reported the preliminary data from one of the 11 PREDIMED sites demonstrated that the Mediterranean diets enriched with high-fat vegetable foods decreased the incidence of diabetes. In this subgroup analysis, the authors report the data from all 11 PREDIMED sites demonstrating a decreased risk of diabetes with the use of a Mediterranean diet pattern in persons with high risk of cardiovascular disease.

SOURCE: Salas-Salvado J, et al. Prevention of diabetes with Mediterranean diets: A subgroup analysis of a randomized trial. *Ann Intern Med* 2014;160:1-10.

Lifestyle modifications have demonstrated efficacy in the prevention of diabetes. Limited studies have investigated whether dietary pattern changes without energy restriction and increased physical activity also may be an effective intervention in the prevention of diabetes. The Mediterranean dietary pattern has been associated with a decreased risk of diabetes.[1] The Mediterranean dietary pattern consists of large quantity and variety of plant-derived foods including whole grains and cereals, raw and cooked vegetables, fresh and dried fruits, fish, with nuts and olive oil as added fats, and a moderate intake of meat and dairy products with moderate amount of wine during meals.[2]

### Summary Points

- After controlling for confounding variables, a 30% relative risk reduction for diabetes was found in the merged Mediterranean diet groups vs the control diet.
- The mean scores of both the Mediterranean diet groups' adherence increased compared to the control group for all yearly comparisons ($P < 0.010$).

### METHODS

The PREDIMED study is a parallel-group, randomized, primary cardiovascular prevention trial conducted in Spain at 11 recruiting centers. The study included persons at high risk but without cardiovascular disease (CVD) at baseline. Participants were randomized to one of three of the following nutrition interventions: Mediterranean diet supplemented with extra-virgin olive oil (EVOO), Mediterranean diet supplemented with mixed nuts, or a control diet with the guidance to reduce intake of all types of fat. There were no energy restrictions or physical activity recommendations for any of the intervention groups.

The participants consisted of community-dwelling men (aged 55-80) and women (aged 60-80) without CVD who had either type 2 diabetes or at least three or more of the following cardiovascular risk factors: hypertension, hypercholesterolemia, low high-density lipoprotein (HDL) cholesterol levels, current

smoking, overweight or obese, and family history of premature CVD. A total of 7447 eligible participants were enrolled in the trial from October 2003 to June 2009. Each participant was randomized to one of the three nutrient interventions by computer-generated random numbers at the recruitment site.

This subgroup study only included participants who did not have diabetes at baseline and had adequate follow-up. The authors calculated that 1130 participants were needed per group to obtain a statistical power greater than 90% with a two-tailed $\alpha = 0.05$. The expected proportions of new diabetes cases were 11% and 7% in the control and intervention groups, respectively (relative risk, 0.64).

### MEDITERRANEAN DIET INTERVENTION

Dieticians gave personalized advice in both individual and group formats to participants regarding their dietary intervention at baseline and quarterly thereafter. A 14-item questionnaire was used to evaluate dietary adherence at each session and personalized advice was given to increase adherence to the Mediterranean diet interventions. Participants enrolled in the Mediterranean plus nut group received 30 g/day of mixed nuts (15 g of walnuts, 7.5 g of hazelnuts, and 7.5 g of almonds) and the EVOO group received 50 mL/day of EVOO at no cost to the participants.

### CONTROL GROUP INTERVENTION

The same 14-item questionnaire as in the Mediterranean diet intervention was used yearly in the control group. The control group received guidance to reduce intake of dietary fat from animal and plant sources. Through 2006, participants in the control group only received a leaflet describing the low-fat diet. In 2007, participants in the control group also received personalized dietary advice and were invited to group sessions with the same intensity and frequency as those in the Mediterranean groups. A separate nine-item questionnaire was used to assess dietary adherence to the recommended low-fat diet.

A number of questionnaires were used to evaluate diet, physical activity, and other lifestyle factors at baseline and yearly during follow up. A 137-item validated semi quantitative food frequency questionnaire was used to evaluate diet. The Minnesota Leisure time physical activity questionnaire, which was validated in Spanish, was used to evaluate physical activity. A 47-item questionnaire regarding education, lifestyle, medical history, and medication use was used.

### STATISTICAL ANALYSIS

To assess hazard ratios (HR) for Mediterranean diet groups in comparison to the control group, the authors used Cox regression models. They also conducted a crude age- and sex-adjusted model, and two other multivariate models were used for analysis to control for multiple variables. In the multivariate model A, age, sex, and body mass index (BMI) were adjusted. In the multivariate model B, age, sex, baseline smoking (never, current, former), fasting glucose level, presence of dyslipidemia or hypertension, total energy intake level (kcal/d), adherence to Mediterranean diet (14-item questionnaire), physical activity level, education level, and alcohol intake were adjusted.

All $P$ values are 2-tailed at $< 0.050$. All analyses were performed using SPSS version 19 and Stata version 12.1.

At baseline, participants underwent a number of clinical and laboratory assessments including: electrocardiography, anthropometric measurements, and blood pressure measurements. Fasting blood and spot urine were assessed at baseline and follow-up years 1, 3, 5, and 7. Urine hydroxytyrosol and plasma alpha-linolenic acid were used as biomarkers to assess supplemental diet adherence during the first 5 years and follow up.

New onset diabetes was diagnosed during the follow-up period (October 1, 2003 to December 1, 2010) using the American Diabetes Association criteria: fasting plasma glucose levels ≥ 126.1 mg/dL or a 2-hour fasting blood glucose levels of ≥ 200.0 mg/dL after a 75 g oral glucose load.

### RESULTS

A total of 7447 participants were enrolled in the PREDIMED study and 3833 did not have diabetes at baseline. A total of 3541 of the 3833 participants had available information during follow-up to determine if they had diabetes and were eligible for this subgroup analysis.

A total of 252 participants were lost to follow-up for more than 2 years: 4.1% in the Mediterranean supplemented with EVOO, 6.9% in the Mediterranean supplemented with nuts, and 10.5% in the control diet groups.

At baseline, clinical characteristics of age, sex, BMI, weight, mean waist circumference, mean waist-height ratio, tobacco use, marital status, education level, hypertension status, dyslipidemia status, medication use (antihypertensives, statins, or other hypolipidemic drugs), fasting glucose level, total cholesterol, HDL and low-density lipoprotein cholesterol, triglycerides, non-HDL cholesterol, mean physical activity level, mean total caloric

Table 1. Incidence of Diabetes

| Groups | Med Diet + EVOO | Med Diet + nuts | Control Diet |
|---|---|---|---|
| n = | 1154 | 1240 | 1147 |
| New Cases of Diabetes | 80 (6.9%) | 92 (7.4%) | 101 (8.8%) |
| Cumulative incidence (95% CI) | 6.93 (5.53-8.55) | 7.42 (6.02-9.02) | 8.81 (7.23-10.60) |

intake, and mean Mediterranean diet adherence scores were similar in all groups.

DURING THE FOLLOW-UP PERIOD

After a median follow-up of 4.1 years, 273 participants were diagnosed with new-onset diabetes — 80 participants in the Mediterranean diet plus EVOO (6.9%), 92 participants in the Mediterranean plus mixed nuts (7.4%), and 101 participants in the control group (8.8%) (*see Table 1*).

The HRs for diabetes in the Mediterranean diet group supplemented with EVOO compared to the control diet group were 0.60 (95% confidence interval [CI], 0.43-0.85) after adjusting for potential confounding variables (*see Table 2*).The Mediterranean diet group supplemented with nuts compared to the control diet group had a HR of 0.82 (CI, 0.61-1.10) after adjusting for potential confounding variables (*see Table 2*).

After controlling for confounding variables, a 30% relative risk reduction for diabetes in the merged Mediterranean diet groups vs control (HR, 0.70; CI, 0.54-0.92) was found (*see Table 2*).

The mean scores of both the Mediterranean diet groups' adherence increased in both Mediterranean diet groups compared to the control group for all yearly comparisons ($P < 0.010$). As would be expected, both the Mediterranean diet groups had more participants with a diet score of ≥ 10 than in the control group ($P < 0.010$) indicating that the participants in the Mediterranean groups were adhering to their diets and that there were no significant changes in the control group diet.

URINARY HYDROXYTYROSOL AND PLASMA ALPHA-LINOLENIC ACID BIOMARKER LEVELS

Participants in the Mediterranean diet with EVOO had increased urinary hydroxytyrosol levels compared to baseline at 3-year follow-up ($P < 0.050$), indicating that they were consuming the EVOO. The plasma alpha-linolenic acid levels increased in the Mediterranean diet with mixed nuts group at 3-year follow-up ($P < 0.050$) indicating that the participants were consuming the mixed nuts.

No changes were found in urinary hydroxytyrosol or plasma alpha-linolenic acid in the control group. No significant difference in body weight, waist circumference, physical activity levels, or medications

Table 2. Hazard Ratios of Diabetes

| | Raw Data HR (95% CI) | Adjusted for Age and Sex HR (95% CI) | Multivariate A* Adjusted HR (95% CI) | Multivariate B** Adjusted HR (95% CI) |
|---|---|---|---|---|
| Med Diet + EVOO vs Control Diet | 0.69 (0.51-0.92) | 0.68 (0.51-0.92) | 0.68 (0.51-0.92) | 0.60 (0.43-0.85) |
| Med Diet + Nuts vs Control Diet | 0.81 (0.61-1.08) | 0.80 (0.60-1.06) | 0.82 (0.61-1.09) | 0.82 (0.61-1.10) |
| Both Med Diets vs Control Diet | 0.75 (0.58-0.96) | 0.74 (0.58-0.95) | 0.75 (0.58-0.96) | 0.70 (0.54-0.92) |

*Multivariate A Model adjusted for age, sex, and BMI.
**Multivariate Model B adjusted for age, sex, baseline smoking (never, current, former), fasting glucose level, presence of dyslipidemia or hypertension, total energy intake level (kcal/d), adherence to Mediterranean diet (14-item questionnaire), physical activity level, education level, and alcohol intake.

that could potentially affect the development of diabetes (estrogens, corticoids, antiepileptic drugs, statins, and antihypertensives) were found between groups.

■ COMMENATARY

This subgroup analysis demonstrates more evidence that a Mediterranean diet decreases the incidence of type 2 diabetes in older white persons at high risk for CVD, without addressing physical activity or energy restrictions. However, the study has a number of limitations, including that it is a subgroup analysis and it was a secondary endpoint of the PREDIMED study, with the primary endpoint being CVD risk.

In addition, participants who withdrew from the study had a worse cardiovascular risk profile at baseline than the participants who completed the study, which may have affected the data. The study personnel and participants were not blinded to group allocation, as there were noticeable food differences. The PREDIMED investigators who diagnosed new-onset diabetes were blinded. The authors also state that they "cannot discard measurement errors affecting physical activity and alcohol intake during follow up." Overall, the strengths of this trial outweigh the limitations in that it was randomized, the treatment groups were well powered and balanced, and the authors did control for confounding variables. There was an adequate follow-up time of 4.1 years.

One interesting finding of this study is the adherence to the Mediterranean diet groups increased compared to the control group in yearly comparisons. This study had regular meetings between the participants and the dieticians, the participants also filled out questionnaires frequently to ascertain their adherence to the diet, and the Mediterranean groups had access to the EVOO and mixed nuts. This appears to be a great strategy in teaching patients and increasing their adherence to the Mediterranean diet pattern for the prevention of not only diabetes, but for a long, healthy life.

There do not appear to be any reasons not to recommend the Mediterranean diet pattern to both healthy people and those at risk for diabetes or cardiovascular disease. The addition of good quality olive oil and mixed nuts may increase food costs and should be taken into account on a patient-by-patient basis. In addition, should these research results be extrapolated to patients who already have diabetes, the Mediterranean diet pattern may need to be altered slightly by determining the ideal amount of carbohydrates in a specified portion size for individual patients. Also, patients who currently are taking medications will need to have adequate follow up to ensure that their blood sugar values are within the recommended range. The Mediterranean diet is a good recommendation as a healthy dietary pattern, and in conjunction with proper portion control and exercise, it can be safely recommended to most patients. ■


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SHORT REPORT

# Garlic Effective for Blood Pressure Reduction in Stage 1 Essential Hypertension


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**Dr. Decker reports no financial relationships relevant to this field of study.**



SYNOPSIS: A significant reduction in systolic and diastolic blood pressure was observed in individuals with newly diagnosed stage 1 hypertension treated with garlic. Increasing effects were observed in a dose- and duration-dependent manner.


SOURCE: Ashraf R, et al. Effects of *Allium sativum* (garlic) on systolic and diastolic blood pressure in patients with essential hypertension. *Pak J Pharm Sci* 2013;26:859-863.

Garlic (*Allium sativum*) is a substance with many traditional uses in medicine, including action as an antimicrobial and digestive agent, as well as various effects pertaining to the cardiovascular system including cholesterol and blood pressure modulation. Studies have shown conflicting evidence pertaining to the use of garlic as an antihypertensive, possibly attributable to dosage or garlic formulation, treatment duration, or population differences.

## Summary Point

- Garlic is shown to have a dose- and duration-dependent effect on reducing systolic and diastolic blood pressure, with maximum reductions of 5.23% in systolic and 6.74% in diastolic measurements seen at doses of 1500 mg and 1200 mg after 24 weeks.

A population of 210 individuals with newly diagnosed stage 1 essential hypertension, age ranging between 20-70 years old, were the subjects of this study. Individuals with other known illness or heart disease, with liver or kidney dysfunction, who were pregnant or lactating, or who were taking other drugs known to interact with antihypertensives were excluded from this study.

Participants were divided into seven groups: five groups were given Kwai garlic tablets at doses of 300 mg, 600 mg, 900 mg, 1200 mg, or 1500 mg per day; one group received atenolol 100 mg single dose; and the final group given a placebo. Each of these treatments was continued for a period of 24 weeks, with blood pressure measurements taken at 12 and 24 weeks. Participants were instructed to not introduce any other diet or lifestyle changes or prescriptions during the study. A total of 192 patients completed the study.

Significant differences ($P < 0.005$) in both systolic and diastolic blood pressure were seen with garlic as compared with placebo. Both systolic and diastolic blood pressure decreased with garlic treatment in a dose- and duration-dependent manner, although the difference was not significant at all doses. The maximum reduction seen with garlic was 5.23% (1500 mg) in systolic and 6.74% (1200 mg) in diastolic blood pressure, as compared to reductions of 6.22% and 9.27%, respectively, with 100 mg atenolol. Adverse effects reported by three individuals who dropped out of the study from one of the garlic treatment groups were sensations of heartburn; however, the dosage at which these side effects were experienced was not stated. Additionally, the specific dosing of garlic (with or without food), spacing of divided doses, and allicin content were not explicitly stated. ■



### *Pharmacology Watch* and *Clinical Briefs* Available Online

The April 2014 issues of *Pharmacology Watch* and *Clinical Briefs in Primary Care* are available exclusively by e-mail or online. You can access these two valuable supplements to *Integrative Medicine Alert* at http://www.ahcmedia.com/supplements/. We will send PDF copies of these supplements to you by e-mail if you prefer. Please send an e-mail with your name and/or subscriber number to customerservice@ahcmedia.com with Digital AHC Supplements in the subject line. We welcome your feedback and appreciate your continued support as a subscriber to *Integrative Medicine Alert*.

### CME OBJECTIVES

**Upon completion of this educational activity, participants should be able to:**

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and;
- describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

## CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.

2. Scan the QR code to the right, or log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.

3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

## CME QUESTIONS

**1. Attrition was an important limitation of the IVF and spirituality study because:**

a. it made it impossible to find statistically significant results.

b. it altered the study groups and introduced the potential for bias due to confounding.

c. it removed those participants who were most likely to benefit from the intervention.

d. it removed those participants who were least likely to benefit from the intervention.

**2. Which of the following is *true* regarding nut consumption?**

a. Peanuts should be avoided because they differ from tree nuts.

b. Though healthy, nut consumption usually corresponds with weight gain.

c. The FDA concludes that eating 1.5 ounces (43 g) of nuts daily "may reduce the risk of heart disease."

d. Roasting nuts decreases their nutritive value.

**3. Which of the following is *true* regarding the biomarkers urinary hydroxytyrosol and plasma alpha-linolenic acid?**

a. Both biomarkers were used as additional laboratory tests to measure adherence to the Mediterranean diet interventions.

b. Urinary hydroxytyrosol was used to measure the participants in the Mediterranean diet supplemented with mixed nuts adherence.

c. These biomarkers were used to evaluate diabetes risk in participants in the trial.

d. Plasma α-linolenic acid is a biomarker to measure participants in Mediterranean diet supplemented with EVOO.

**4. Garlic has been shown to have an effect of reducing blood pressure in individuals with stage 1 essential hypertension with:**

a. the greatest reduction in both systolic and diastolic blood pressure at the smallest dose.

b. reductions observed in systolic but not diastolic blood pressure.

c. reductions observed in diastolic but not systolic blood pressure.

d. a trend of increasing reduction in systolic and diastolic blood pressure with dosage.

## [IN FUTURE ISSUES]

Integrative therapies for anxiety | Yoga and fatigue | Diet and health in aging | Exercise and mortality