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The Journal of Nutrition Media Alerts

The following articles are being published in the April 2017 issue of *The Journal of Nutrition*, a publication of the American Society for Nutrition. Summaries of the selected articles appear below; the full text of each article is available by clicking on the links listed. Manuscripts published in *The Journal of Nutrition* are embargoed until the article appears online either as in press (Articles in Press) or as a final version. The embargoes for the following articles have expired.

- Obesity, Mediterranean diet, and inflammation – how are they linked?
- Nordic and Mediterranean-type diets may benefit colorectal cancer survivors
- Higher dairy intake coupled with vitamin D supplementation associated with stronger bones in original Framingham cohort

Obesity, Mediterranean diet, and inflammation – how are they linked?

Cardiovascular disease is the number-one killer in most parts of theindustrialized world. In the United States, heart disease is the primary causeof death for both men and women, and the US Centers for Disease Control andPrevention estimate that about 610,000 people die of heart disease every year - that's 1 in every 4 deaths. In addition, stroke kills more than 130,000Americans each year - that's 1 out of every 20 deaths. Experts have long knownabout a multitude of cardiovascular risk factors, including being overweight,having high blood pressure, eating a unhealthy diet, and being physicallyinactive. Likely the most studied of these factors is diet – both what we eatand what we do not eat. Although the best diet likely depends on multiplefactors, including the genes we inherit from our parents, it is clear thatcertain dietary patterns may be more beneficial than others. For instance, consuminga diet similar to that traditionally enjoyed around the Mediterranean Sea isassociated with low risk of heart disease and stroke. In general, theMediterranean diet emphasizes fruits, vegetables, fish, whole grains, limitedmeat, and healthy fats – with a healthy splash of wine. But it has beendifficult for scientists to separate out potential *direct* benefits of the Mediterranean diet from the fact thatobesity rates are low and physical activity high among people who eat it. Beingable to do this is critical to understanding the true biology behind theassociation between diet and cardiovascular risk, and therefore what types ofrecommendations should be made to promote public health. To help dissect apartthese confounding factors, a research team led by Dr. Anwar T. Merchant (ArnoldSchool of Public Health) and Dr. Yong-Moon Park (National Institute ofEnvironmental Health Sciences) used a statistical technique referred to as"mediation analysis." You can read more about their study and its findings inthe April 2017 issue of *The Journal ofNutrition*.

The researchers were particularly interested in studying the possibilitythat consumption of a Mediterranean-like diet indirectly decreases inflammationand helps people regulate blood sugar via its direct impact on adiposity. Tostudy this, they utilized data previously collected from 4700 healthy adultswho had participated in the National Health and Nutrition Examination Surveybetween 1988 and 1994. Each person in the study had provided information abouttheir typical dietary intake, and these patterns were given a score reflectinghow well the foods fit a typical Mediterranean diet. Body weight and heightwere recorded, and blood samples were analyzed for substances related to bloodsugar regulation and inflammation. Waist circumference, an indicator ofabdominal obesity, was also measured.

As expected, study participants who consumed diets most similar to theMediterranean pattern had the healthiest blood values, lowest risk for

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obesity,and smallest waist circumferences. Importantly, mediation analysis suggestedthat, in fact, the associations between diet and blood glucose as well as dietand inflammation could be explained by differences in waist circumference.Relationships with body mass index (weight divided by height squared) were notso strong. The researchers concluded that consumption of a Mediterranean-likediet might reduce insulin resistance and inflammation largely by reducingabdominal obesity (i.e., waist circumference). Understanding the physiologybehind this finding will require further study.

Reference Park YM,Zhang J, Steck SE, Fung TT, Hazlett LJ, Han K, Ko SH, Merchant AT. ObesityMediates the Association between Mediterranean Diet Consumption and Insulin Resistanceand Inflammation in US Adults. *Journal ofNutrition* 147: 563-571.
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Nordic andMediterranean-type diets may benefit colorectal cancer survivors

Of themany cancers affecting both men and women, colorectal cancer is the third most-commontype of cancer and the second leading cause of cancer-related death amongAmericans: over 136,000 people are diagnosed with colorectal cancer each year.Understandably, the majority of research conducted to date on this disease hasfocused on how to prevent and treat it. For instance, observational studieshave suggested that risk for colorectal cancer may be lower in people whoconsume low levels of fat, red meat, refined sugar, and alcohol. Conversely, highintake of fiber, fruits, and vegetables may be protective. With increasingsuccess in preventing and treating the disease, however, some researchers havebegun to redirect their efforts toward finding ways to improve survival for peoplewho have successfully completed colorectal cancer treatment. One such study,published in the April 2017 issue of *TheJournal of Nutrition*, provides new evidence that diets featuringtraditional Mediterranean or Nordic foods just might just fit this bill.

Thestudy was led coordinately by Drs. Wolfgang Lieb and Sabrina Schlesinger (Christian-Albrechts-Universityof Kiel and Imperial College London). A total of 1404 adults who had been previouslydiagnosed with colorectal cancer were studied over a period of about 7 years. Dietswere assessed using a food frequency questionnaire and categorized as to theirresemblance to Mediterranean and Nordic consumption patterns. For instance, forthe Mediterranean food intake pattern, diets higher in vegetables, fruits, nuts,legumes, cereals, and fish received a higher score and those with higheramounts of meat, poultry, and dairy foods a lower score. For the Nordic foodintake pattern, diets high in cabbage, root vegetables, rye bread, oatmeal,apples, pears, fish, and shellfish got the highest scores. The researchers theninvestigated whether consumption of these two ethnic food patterns was relatedto the participants' risk of death during the study.

Individualswho scored highest in terms of consuming a Mediterranean-like diet were 52%less likely to die during the study than those with the lowest scores.Similarly, consuming Nordic foods was associated with a 37% lower risk ofdeath. The researchers concluded that consumption of either of these foodpatterns might improve survival in long-term survivors of colorectal cancer.

Reference RatjenI, Schafmayer C, di Giuseppe R, Waniek A, Plachta-Danielzik S, Koch M, NöthlingsU, Hampe J, Schlesinger S, Lieb W. Postdiagnostic Mediterranean and Healthy NordicDietary Patterns Are Inversely Associated with All-Cause Mortality in Long-TermColorectal Cancer Survivors. *Journal ofNutrition* 147: 636-644.
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Higher dairyintake coupled with vitamin D supplementation associated with stronger bones inoriginal Framingham cohort

Maintaining a healthy skeleton as we age is important because weak andbrittle bones can lead to more fractures, difficulty with mobility, and illness– all of which are associated with decreased quality of life and even earlydeath. Many factors are related to risk of bone deterioration in olderindividuals, including unfortunate genetics and physical inactivity. Butnutrition likely plays one of the most critical roles in this regard. Forinstance, because the bone's architecture is largely composed of protein,consuming a diet with high-quality (complete) protein helps keep bones strong.In addition, getting adequate amounts of calcium and phosphorus is critical tomaintaining bone density and strength. Vitamin D, which can be produced in thebody if it is exposed to sufficient sunlight but is also found in

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a limitednumber of foods, is also important because it stimulates dietary calciumabsorption from the intestine. As such, protein- and mineral-rich dairyproducts, particularly if they are fortified with vitamin D, are generallyconsidered some of the best foods to keep bones strong throughout the lifespan.In an article published in the April issue of *The Journal of Nutrition*, new research findings underscore theimportance of vitamin D intake in terms of realizing the benefits of dairyintake on bone health in older individuals.

This research, led by Dr. Shivani Sahni (Institute for Aging Research,Hebrew SeniorLife, Israel Deaconess Medical Center, and HarvardMedical School), was one of the hundreds of projects associated with the FraminghamHeart Study, initiated in 1948. This famous and important study, a jointproject of the National Heart, Lung, and Blood Institute and Boston University,was originally designed to identify common lifestyle and biological factorscontributing to cardiovascular disease by following its development over a longperiod of time in a large group of participants. Since its inception, however,the Framingham Study has expanded to explore many other conditions, including bonehealth and osteoporosis. Here, Dr. Sahni and colleagues report relationships amongtypical dairy food intakes, vitamin D supplementation, and changes in bonemineral density in a subset of the original Framingham participants now 67-93years old.

When all the data were combined, the researchers found no associationbetween dairy foods consumption and bone mineral density. However, when onlyvitamin D supplement users were included in the analysis, higher consumption ofmilk, yogurt, and cheese was in fact associated with denser bones. Higher dairyintake was also associated with lower risk of bone loss over the years. Theresearchers concluded that dairy intake remains important in maintaining bonehealth as we age, but the effects might only be realized if sufficient vitaminD is also consumed. Indeed, nutrients do not work by themselves in the body.Instead, many of them work in elegant and coordinated ways. This is one of thereasons why dietary variety is fundamental to optimal health.

Reference SahniS, Mangano KM, Kiel D, Tucker KL, Hannan MT. Dairy Intake Is Protective againstBone Loss in Older Vitamin D Supplement Users: The Framingham Study. *Journal of Nutrition* 147:645-652.
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The Journal of Nutrition Editor's Picks

- Afternoon or evening samples are most representative of breast milk vitamin content
- Food insecurity has a negative impact on subjective well-being among individuals, regardless of the income classification of the country where they reside
- Elevations in homocysteine induced by folate deficiency contribute to a positive feedback loop that promotes folate receptor expression

Afternoon or evening samples are most representative of breast milk vitamin content

Appropriate sampling techniques are necessary for theaccurate characterization of any samples. Milk nutrient content can be affected by circadian rhythms, period of timeafter feeding initiation, and the impact of maternal diet. Accurately determining the micronutrientcontent of breast milk is necessary when establishing recommendations for infantvitamin intake. Hampel and colleaguesexplored the inherent variability in micronutrient content in breast milksamples to determine the optimal collection protocols. The results of their work are published inthe April issue of *The Journal ofNutrition*

They recruited 18-26 year old women (n=18) in DhakaBangladesh that were between 2 and 4 months of starting lactation. Breast milk was collected from the samebreast during each feeding over a 24-hour period during 3 days. Aliquots were taken during the first 2minutes of feeding, during the remainder of the feeding, and another aliquotwas prepared by mixing the other two aliquots. The mothers were asked to take either a single dose or two doses of avitamin supplement at breakfast on the second or third day of the trial. The samples were analyzed for thiamin,riboflavin, niacin and vitamins B-6, B-12, A and E as well as the fat content.

Vitamins B-6 and B-12 were relatively similar among thealiquots, however, there were small but significant differences in theconcentration of the remaining vitamins

among the aliquots. There was significant variability in theconcentration of all vitamins except for fat-adjusted vitamin A and E caused bythe effects of circadian rhythm. Afternoon and evening breast milk samples were most representative ofdaily vitamin content. Supplementationinduced an acute effect on the concentrations of thiamin, riboflavin, as wellas vitamins B-6 and A between 2 and 4 hours after taking the vitamin. However, only 0.1 and 6.17% of the vitaminsin the supplement were found to pass into the milk. The authors concluded that differences invitamin content of breast milk from these Bangladesh mothers were small andthat sampling milk from the afternoon or evening milk supply would provide themost representative vitamin content.

Reference

Hampel D, Shahab-Ferdows S, Islam MM, Peerson JM, Allen LH. Vitamin concentrations in human milk varywith time within feed, circadian rhythm, and single-dose supplementation. *Journalof Nutrition* 147:603-611, 2017.

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Food insecurity has a negative impact on subjective well-being among individuals, regardless of the income classification of the country where they reside

Quality of life is affected by multiple factors includingphysical health, psychological state, and relationships. Subjective well-being denotes satisfactionwith one's life, and is one attribute contributing to individual perceptions ofquality of life. Food insecurity iscreated through the lack of resources to acquire the desired quantity or qualityof food. It includes components of foodavailability, access, utilization, and stability. Lack of quality food contributes todecrements in physical and psychological health, which would decrease theperceived quality of life. Globally, 805million people are chronically undernourished, and are thus food insecure. However, it is not currently known if theassociations between food insecurity and subjective well-being are similarthroughout the world and across the 4 World Bank income classes of countries. The work published in the April issue of *The Journal of Nutrition* by Frongillo andcolleagues addresses this question.

This study used data collected with an 8-item FoodInsecurity Experience Scale (FIES) as part of the 2014 Gallup World Poll that wasconducted in 147 countries. Phone interviews were conducted in 38 countries andface-to-face interviews were performed in 111 other countries with individualsthat were over the age of 15. Well over100,000 data points were available to assess daily experiences and indexes of well-being.

Foodinsecurity was associated with household income, shelter and housing, andemployment status. When controlling forother measures of living conditions, food insecurity was associated with poorphysical health and subjective well-being. The greatest association of subjective well-being with any factormeasured was found for food insecurity. Theassociation was found among individuals in all 4 World Bank income classcountries, with the greatest differences occurring in the higher-incomeclasses. Data collected using the FIESwas reliable at the country level, and had acceptable reliability at the individuallevel. The authors concluded these data suggestthe FIES is a valid measure of food insecurity and the associations discoveredusing it support the expected negative impact that food insecurity has onsubjective well-being.

Reference

Frongillo EA, Nguyen HT, Smith MD, Coleman-Jensen A. Food insecurity is associated with subjectivewell-being among individuals from 138 countries in the 2014 Gallup World Poll. *Journalof Nutrition* 147:680-687, 2017.

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Elevations in homocysteine induced by folate deficiencycontribute to a positive feedback loop that promotes folate receptor expression

Folate deficiency is known to have a negative impact onfetal development. In addition, there isan increase in homocysteine levels with prolonged deficiency, and thecombination can induce endothelial cell injury, inflammation and other negativehealth outcomes. Expression of folatereceptor is elevated in response tofolate deficiency, however, the mechanisms contributing to the upregulation of folatereceptor a is not fullyappreciated. Previous work suggests thathomocysteine binds to heterogeneous nuclear ribonucleoprotein E1 (hnRNP-E1),effectively uncovering an mRNA binding site in hnRNP-E1. Binding of hnRNP-E1 with folate receptor a mRNA leads to an upregulation of thereceptors expression. Once homocysteinebinds to hnRNP-E1, it undergoes degradation with a half-life of 52 hours,indicating a need to synthesize new hnRNP-E1. It is not clear what regulates

the maintenance of hnRNP-E1 expressionduring periods of prolonged folate deficiency. A study conducted by Tang and colleagues addresses this void in ourunderstanding of folate receptor expression regulators, and results of theirwork, along with a commentary by Mayanil are published in the April issue of *The Journal of Nutrition*.

Placental cells were cultured to determine if homocysteinylatedhnRNP-E1 binds to *hnRNP-E1* mRNA, andif this binding enhanced translation. Specificity of the proposed binding site was demonstrated byincorporating single nucleotide mutations in the putative bindingsequences. The relevance of thoseoutcomes were verified using an athymic mouse model in which HeLa tumor cellswere implanted. Expression of both thefolate receptor and hnRNP-E1 were monitored in the tumor xenografts developedin mice consuming a folate deficient diet.

The work demonstrated that elevated homocysteine levels ledto a dose-dependent interaction between hnRNP-E1 and the *hnRNP-E1* mRNA binding site. This interaction led to a proportionalincrease in the translation of hnRNP-E1 in placental cells. The approaches used to interfere with bindingled to reduced synthesis of hnRNP-E1. Folate deficiency, in either placental cells or the mice, inducedupregulation of both the folate receptor and hnRNP-E1. The authors concluded that these resultsdemonstrate the presence of a positive feedback loop that amplifiestranscription of hnRNP-E1 during prolonged folate deficiency in order tomaximize folate receptor expression. Through this mechanism cells attempt to achieve more normal folatehomeostasis.

Reference

Tang Y-S, Khan RA, Xiao S, Hansen DK, Stabler SP, KusumanchiP, Jayaram HN, Antony AC. Evidencefavoring a positive feedback loop for physiologic auto upregulation of hnRNP-E1during prolonged folate deficiency in human placental cells. *Journalof Nutrition* 147:482-498, 2017.

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Mayanil CSK. Thatwhich is bad can trigger good in the human body – Homocysteine-bound hnRNP-E1as a molecular sensor of physiologic folate deficiency.*Journalof Nutrition* 147:471-472, 2017.

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