

ASN Publications

November 2016 Media Alert: *The Journal of Nutrition*

The following articles are being published in the November 2016 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.

[Whole grain consumption lowers diastolic \(resting\) blood pressure in overweight and obese adults](#)

[High-level review links compound in cocoa to potential improvements in cardiovascular health](#)

[Higher-dose vitamin D prenatal supplements may curb maternal inflammation](#)

Whole grain consumption lowers diastolic (resting) blood pressure in overweight and obese adults

Nutrition professionals have long recommended that we include substantial amounts of whole-grain foods in our diets. An example is the 2015 Dietary Guidelines for Americans which suggests that we make "half our grains whole grains." But Americans (and many others around the world) prefer refined grains when it comes to the breads, pastas, breakfast cereals, pastries, and rice they eat on a daily basis. Newly published evidence, which can be found in the November 2016 issue of *The Journal of Nutrition*, suggests however that we reconsider our choices in this regard. In this study, a research team headed up by Dr. John Kirwan (the Lerner Research Institute and Cleveland Clinic) examined what happens to biomarkers of cardiovascular health when overweight and obese adults alternate their consumption of refined and whole-grain products. This research is important because heart disease and stroke constitute today's leading causes of death in the United States, and continuing upward obesity trends suggest this problem is not going away in the near future.

To test their hypothesis that whole-grain foods are more heart-healthy than their refined-grain counterparts, the researchers recruited 33 willing participants (mostly women) for their 26-week-long study. During the first 8 weeks, half of the recruits were provided with meals and snacks prepared with whole-grain wheat or rice. The other half consumed similar meals made with refined wheat or rice. This intervention period was followed by a 10-week "wash-out" period during which the participants prepared their own foods to their own liking. After the wash-out period, each participant was provided for 8 weeks with the dietary treatment they didn't receive in the first intervention period. The whole-grain and refined-grain meal plans were designed to provide similar calories and major nutrients, so that any differential effects could be attributed directly to the type of grain consumed.

The researchers found that, compared to the refined-grain intervention period, consumption of whole-grain foods reduced diastolic blood pressure, which is the pressure our blood vessels experience between heartbeats. In addition, adiponectin (a hormone produced by fat cells and thought to help protect against systemic inflammation) was higher when whole grains were eaten. This was particularly surprising because both dietary interventions resulted in similar weight and body fat loss.

November 29-December 2. [Nutrition Society of Australia 40th Annual Scientific Meeting.](#)
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The researchers concluded that, because high diastolic blood pressure is a risk factor for early death in adults under 50 years of age, increased whole-grain food intake may provide a useful approach to control hypertension and stave off cardiovascular disease.

Reference

Kirwan JP, Malin SK, Scelsi AR, Kullman EL, Navaneethan SD, Pagadala MR, Haus JM, Filion J, Godin J-P, Kochhar S, Ross AB. A whole-grain diet reduces cardiovascular risk factors in overweight and obese adults: a randomized controlled trial. *Journal of Nutrition* 2016;146:2244-51.

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High-level review links compound in cocoa to potential improvements in cardiovascular health

Chocolate is one of the world's most sought-after delicacies, and mounting scientific evidence suggests that it (and the cocoa from which it's made) may be more than delicious - it might also keep the cardiovascular system healthy. The reason for this health benefit is not understood, but some experts believe that it may be due to anti-inflammatory compounds called flavanols. However, not all studies have found anti-inflammatory or heart-healthy effects of cocoa flavanols, and it's important to consider research rigor when evaluating any diet-health claim in this regard. To help discern fact from fiction, Dr. Simin Liu (Director of the Center for Global Cardiometabolic Health at Brown University), Xiaochen Lin (a doctoral candidate), and colleagues from Brigham and Women's Hospital systematically reviewed all previously conducted randomized, controlled, dietary intervention studies focusing on the effect of chocolate, cocoa, or cocoa flavanols on cardiovascular disease risk factors. Their findings can be found in the November 2016 issue of *The Journal of Nutrition*.

After searching several databases of peer-reviewed scientific journals, the research team first identified 326 studies that fit their general criteria. However, after the full text review, all but 19 of these studies were discarded. The remaining 19 unique studies, involving 1131 participants, varied in quality but were all placebo-controlled intervention studies and included information about circulating cardiometabolic biomarkers in blood samples collected before and after the dietary treatments were initiated. After conducting this systematic review of the existing literature, the researchers used mathematical approaches to reconstruct and combine all the data collected in each of the studies so that they could be re-analyzed in a coordinated way - an approach referred to as a meta-analysis.

Cocoa flavanol consumption was associated with improvement in some biomarkers of lipid metabolism and insulin resistance, and effects were similar for women and men. However, it is worth noting that the chocolate used in the interventions groups was primarily dark chocolate, and the placebo used in each trial was either white chocolate or beverages with negligible flavanol content. Therefore, the findings from this meta-analysis might not generalize to different sorts of chocolate candies or white chocolates, of which the content of sugar/food additives could be substantially higher than that of dark chocolate. The scientists urge funding of larger, more long-term randomized, controlled, intervention trials to assess whether these effects are manifest in actual clinical outcomes (such as decreased risk of diabetes, heart disease, and stroke) rather than just biomarkers thereof.

Reference

Lin X, Zhang I, Li A, Manson JE, Sesso HD, Wang L, Liu S. Cocoa flavanol intake and biomarkers for cardiometabolic health; a systematic review and meta-analysis of randomized controlled trials. *Journal of Nutrition* 2016;146:2325-33.

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Higher-dose vitamin D prenatal supplements may curb maternal inflammation

Vitamin D, sometimes referred to as the "sunshine vitamin" because the

body can make it when exposed to adequate amounts of sunlight, is involved in myriad functions important for health. Its most well-studied role has to do with chaperoning dietary calcium as it is taken up in the small intestine. Consequently, vitamin D deficiency can lead to calcium deficiency and, in turn, weak bones and teeth. But vitamin D is involved in much more than maintaining skeletal health. It also helps modulate immune function, and may play a key role in suppressing inflammation. This may be particularly important during pregnancy, because maternal inflammation during this important portion of the lifecycle is associated with high blood pressure, pre-eclampsia, premature delivery, and low birth weight. Recent surveys have suggested that vitamin D deficiency is more common than previously thought, affecting up to 69% of American women during pregnancy. In response, researchers and clinicians alike would like to know whether vitamin D supplementation at levels above those common in prenatal supplements are warranted. To help answer this question, a research team led by Dr. Charles Stephensen at the USDA-ARS Western Human Nutrition Research Center and Dr. Bryan Jacoby at the University of California, Davis recruited a group of healthy American women during mid-pregnancy and randomized them to consume either a typical prenatal supplement containing 400 international units (IU) of vitamin D and a placebo pill or the prenatal supplement and an additional pill providing 1600 IU vitamin D daily. Their methods and results, published in the November 2016 issue of *The Journal of Nutrition*, are described briefly here.

This study was carried out as a randomized, double-blind, placebo-controlled, dietary intervention study - the best-case scenario of nutrition research because most of the possible biases are systematically controlled. Women were enrolled during early pregnancy (before 20 weeks) when they began taking their assigned supplements, and then re-evaluated twice thereafter. Blood samples were obtained and analyzed for various forms of vitamin D and a battery of immune and inflammatory markers. Other important outcomes such as the mothers' blood pressure and infant birth weight were also recorded.

Although vitamin D dosage did not impact other maternal or infant outcomes, the higher dose increased circulating vitamin D concentrations. Higher blood vitamin D was correlated with lower circulating tumor necrosis factor- α (TNF- α), an immune substance typically associated with inflammation. Consuming 2000 IU vitamin D each day instead of the more standard 400 IU increased the proportion of immune cells that were producing interleukin 10, an anti-inflammatory compound. The researchers posit that maternal consumption of 2000 IU (rather than 400 IU) of vitamin D may help prevent adverse outcomes caused by excess inflammation during pregnancy, and recommend that additional studies focused on less-well-nourished women be conducted.

Reference Zerofsky MS, Jacoby BN, Pedersen TL, Stephensen CB. Daily cholecalciferol supplementation during pregnancy alters markers of regulatory immunity, inflammation, and clinical outcomes in a randomized controlled trial. *Journal of Nutrition* 2016;146:2388-97.

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The Journal of Nutrition: Editor's Picks

[MicroRNAs derived from cow's milk partially resist digestion in the stomach and are possibly bioaccessible](#)
[Very preterm births lead to low levels of glucocorticoids in breast milk](#)
[Personal characteristics, environment, and lifestyle impact the extent of serum vitamin D elevations resulting from a year-long supplement program](#)

MicroRNAs derived from cow's milk partially resist digestion in the stomach and are possibly bioaccessible

MicroRNAs are small non-coding RNA species that are highly conserved across mammals and have been shown to influence various physiological processes. As a result, the levels of microRNAs have been demonstrated to be associated with several disease states. Importantly, recent

evidence supports the concept of transfer of microRNA between species and even absorption of those derived from plant and animal foods in the diet. Transfer may occur through several pathways, but one putative pathway includes the release and uptake of extracellular vesicles containing the microRNA. These observations allude to the possibility of diet-derived microRNAs having an impact on host health and support the need to conduct studies that evaluate how digestion may influence microRNA stability and accessibility for absorption. Benmoussa and colleagues have started to answer these questions and report results derived from a study using an in vitro digestion model in a paper published in the November 2016 issue of *The Journal of Nutrition*. To conduct this work, they used a computer-controlled in vitro digestion model that simulates digestion in the stomach, duodenum, jejunum, and ileum. Their experiments used commercially available dairy milk as a source of microRNA. Samples were collected from each of the four digestion compartments at baseline, 30, 60, and 120 minutes after starting digestion. Samples were used to detect microRNA using quantitative PCR analyses and to determine the presence of proteins that would indicate whether exosomes were present in the aliquots containing the microRNA. In addition, they compared these results to non-digested samples of the same starting material that underwent similar exosome isolation procedures.

Dairy milk contained 8.3×10^9 copies of the bta-miR-223 and 3.8×10^{10} copies of the bta-miR-12b at baseline, as well as several other microRNA species. After 30 minutes of digestion, those amounts were decreased to 64% and 23% of the value prior to digestion for bta-miR-223 and bta-miR-12b microRNA, respectively. There was little change in the level of these two microRNA after 120 minutes of digestion. Some of the undigested microRNA were associated with exosomes, which may have helped to protect them from digestion. However, the majority of these microRNA were associated with particles that were not thought to be exosomes.

The authors concluded that microRNA in dairy milk are associated with extracellular vesicles that are exosomes, and that their ability to resist digestion is because they are linked to these extracellular vesicles, protein complexes or lipids present in milk. Because a large fraction of the microRNA present in the dairy milk resist digestion, and are therefore, available for absorption in the small intestine, there is a possibility for these small nucleotides to influence health. Therefore, more work is needed to explore the nature of these large extracellular vesicles and their ability to transport and protect microRNA from digestion, and thus their potential to influence various physiological processes.

Reference

Benmoussa A, Lee CHC, Laffont B, Savard P, Laugier J, Boilard E, Gilbert C, Fliss I, Provost P. Commercial dairy cow milk microRNAs resist digestion under simulated gastrointestinal tract conditions. *Journal of Nutrition* 2016;146:2199-15.

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Very preterm births lead to low levels of glucocorticoids in breast milk

The accepted gold standard for neonatal nutrition is the provision of breast milk. However, very preterm deliveries often occur before it is possible for the mother to produce milk. As a result, a common approach is to provide donor milk from women who have delivered at term when it is available. The stage of lactation influences not only the nutrition components of breast milk, but also the non-nutrient components, such as hormones. Use of breast milk produced at later stages of lactation has been associated with postnatal growth restriction in the very preterm neonate (<32 weeks of gestational age). One class of hormones in breast milk are the glucocorticoids, cortisol and cortisone, which are supportive of intestinal epithelium development. Many very preterm neonates, especially those that are ill, have quite low levels of cortisol, when compared to term neonates. These observations

suggest the need to better understand glucocorticoid concentrations in breast milk of preterm and term mothers, and whether there are any fluctuations in those levels. This topic was addressed in a paper published by van der Voorn and colleagues in the November 2016 issue of The Journal of Nutrition.

This paper reports the results of two separate studies. In the first study, 10 mothers who delivered at term (>37 weeks) and 10 mothers that delivered very preterm babies (<32 weeks) were recruited. Milk samples were collected weekly during the first month after delivery being careful to collect samples at the same time of day each time. Foremilk was collected using a breast pump just prior to every feeding occasion. The goal of this study was to compare the concentration of cortisol, cortisone and their ratio at these time points for the preterm and term mother's breast milk. The goal of the second study was to determine the diurnal variation in these variables in term delivery mothers over a 24-hour period 4 weeks after delivery. Paired breast milk and saliva samples were collected to monitor diurnal variation and to compare the levels in milk and saliva at the same time point.

The median concentrations of cortisol was 4.3 nmol/L in breast milk for term delivery mothers and was 3.2 nmol/L in milk from the very preterm delivery mothers. For cortisone, the median concentrations were 29.6 nmol/L and 20.5 nmol/L in the term and very preterm breast milk samples. The resulting ratio was 0.86 for term breast milk and was 0.87 for the very preterm breast milk. When the time of sample collection was included in the analyses, there was a 50% reduction in cortisol and a 53% reduction in cortisone in very preterm breast milk. An apparent rhythmicity in the data from the first study led the authors to evaluate the 24 hour pattern of both milk and saliva glucocorticoid levels. Peak cortisol and cortisone concentrations in the term breast milk occurred at approximately 0700 hours. Milk and saliva glucocorticoids were correlated. The authors concluded that there was a need to conduct a larger study that not only further explores the diurnal rhythmicity, but also examines the impact of the differences in glucocorticoids caused by very preterm births on the health of the developing newborn.

Reference van der Voorn B, de Waard M, van Goudoever JB, Rotteveel J, Heijboer AC, Finken MJJ. Breast-milk cortisol and cortisone concentrations follow the diurnal rhythm of maternal hypothalamus-pituitary-adrenal axis activity. *Journal of Nutrition* 2016;146:2174-79.

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Personal characteristics, environment, and lifestyle impact the extent of serum vitamin D elevations resulting from a year-long supplement program

Although in 2010 the National Academy of Medicine suggested that the majority of the US population is meeting their vitamin D requirements, other estimates suggest that 25% have inadequate serum concentrations and 8% are deficient. Existing literature suggests an association between an inadequate level of vitamin D and health decrements, such as bone fractures and cancer. Many factors are known to influence vitamin D status, and they include sun exposure, skin pigmentation, body mass index, and medications. However, little is known about how personal, medical, environmental, lifestyle and genetic factors influence the response to vitamin D supplementation. To address this void in our understanding of how best to overcome inadequate or deficient vitamin D status in individuals, Rees and colleagues conducted a study in a large number of healthy older adults that is reported in the November 2016 issue of The Journal of Nutrition.

Participants in the study (n=2187 men and women) were recruited from 11 centers across the United States and Puerto Rico as part of a randomized, double blind, placebo-controlled trial to test the effects of cholecalciferol (inactive form of vitamin D) and/or calcium on large bowel adenoma recurrence. Subjects were between 45 and 75 years of age and were not vitamin D deficient. They were assigned to receive either a placebo treatment, or daily treatments of 1000 IU of cholecalciferol, 1200 mg calcium carbonate, or a combination of vitamin

D and calcium. Blood was collected at enrollment and 1 year later to determine blood levels of 25-hydroxyvitamin D [25(OH)D]. Samples were also collected to determine the presence of several single nucleotide polymorphisms in subject DNA, with an emphasis on genes involved in vitamin D metabolism.

At enrollment (baseline), 69% of subjects assigned to the vitamin D supplement groups had adequate serum vitamin D levels, whereas only 54% of those assigned to the non-vitamin D supplement groups had adequate levels. Seventeen factors that reflect personal characteristics, such as nutrition, behavioral and lifestyle factors, as well as sun exposure were able to explain 32% of the variability in serum vitamin D levels at baseline. After 1 year of supplementation, serum 25(OH)D was elevated from 24.6 to 30.9 ng/mL, whereas it declined from 24.5 to 23.4 ng/mL in those not receiving the vitamin D supplement. Factors contributing to the greater proportional increase in serum 25(OH)D occurring with the supplement included lower baseline serum 25(OH)D, being female, season during which the blood was collected, using protective clothing to limit sun exposure, moderate activity levels, adherence to supplement intake and use of personal supplements.

Together, these factors explained 50% of the variability in response to supplement use by these subjects. After 1 year of supplementation, 94% of those receiving the vitamin D supplement had adequate serum levels whereas only 72% of those not receiving the supplement had adequate levels of 25(OH)D. The genetic polymorphisms monitored in this study did not add significantly to the predictive models, even though several produced results that the authors thought deserved further investigation. A unique discovery of this study was that women exhibited a greater increase in serum 25(OH)D with supplementation than did men.

Reference Rees JR, Mott LA, Barry EL, Baron JA, Bostick RM, Figueiredo JC, Bresalier RS, Robertson DJ, Peacock JL. Lifestyle and other factors explain one-half of the variability in the serum 25-hydroxyvitamin D response to cholecalciferol supplementation in healthy adults. *Journal of Nutrition* 2016;146:2312-24.

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