The American Journal of Clinical Nutrition
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The following articles are being published in the April 2017 issue of *The American Journal of Clinical Nutrition (AJCN)*, a publication of the American Society for Nutrition. Full summaries and analyses are available on the ASN website. Links to the articles are below. Articles published in *AJCN* 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.

Genes, dietary supplements, and bone health: new research reveals a surprising association

Contrary to what they had originally hypothesized, scientists find that women with the greatest genetic risk of having weak bones benefit the least from taking calcium and vitamin D supplements. As such, other treatments should be considered for these at-risk women.

Wang Y, Wactawski-Wende J, Sucheston-Campbell LE, Preus L, Hovey KM, Nie J, Jackson RD, Handelman SK, Nassir R, Crandall CJ, et al. The influence of genetic susceptibility and calcium plus vitamin D supplementation on fracture risk. *American Journal of Clinical Nutrition* 2017;105:970–9.
Civitelli R, Peterson T. Toward personalized calcium and vitamin D supplementation. *American Journal of Clinical Nutrition* 2017;105:777–8.

Sleep, genetics, and obesity—seemingly improbable (but likely) bedfellows

Study finds that association between genetic obesity risk and actually being overweight may be exacerbated by adverse sleep patterns. Alternatively, the potential negative impact of poor sleep on obesity may be worsened by unfortunate genetics.

Celis-Morales C, Lyall DM, Guo Y, Steell L, Llanas D, Ward J, Mackay DF, Biello SM, Bailey MES, Pell JP, et al. Sleep characteristics modify the association of genetic predisposition with obesity and anthropometric measurements in 119,679 UK Biobank participants. *American Journal of Clinical Nutrition* 2017;105:980–90.
Tremblay A, Pérusse L. Obesity, genes, and sleep habits. *American Journal of Clinical Nutrition* 2017;105:779–80.

Folic acid supplements may be beneficial in lowering risk of gout in hypertensive individuals taking blood pressure–lowering medications

Compared with their counterparts who took only a blood pressure–lowering medication, study finds that those who took both the drug and folic acid experienced less pronounced increases in blood uric acid, a compound that can lead to gout.

Qin X, Li Y, He M, Tang G, Yin D, Liang M, Wang B, Nie J, Huo Y, Xu X, et al. Folic acid therapy reduces serum uric acid in hypertensive patients: a substudy of the China Stroke Primary Prevention Trial (CSPPT). *American Journal of Clinical Nutrition* 2017;105:882–9.
Scheepers LEJM. Folic acid: the solution for treating asymptomatic hyperuricemia? *American Journal of Clinical Nutrition* 2017;105:775–6.

Gluten consumption during infancy and toddlerhood not linked to development of celiac disease in preschool years

New report suggests that daily gluten intake during childhood does not generally predict which kids will develop celiac disease. However, high gluten intake was associated with celiac disease in a subset with a very specific genetic variation.

Crespo-Escobar P, Mearin ML, Hervás D, Auricchio R, Castillejo G, Gyimesi J, Martinez-Ojinaga E, Werkstetter K, Vriezinga SL, Korponay-Szabo IR, et al. The role of gluten consumption at an early age in celiac disease development: a further analysis of the prospective PreventCD cohort study. *American Journal of Clinical Nutrition* 2017;105:890–6.

Genes, dietary supplements, and bone health: new research reveals a surprising association

Background As life expectancy continues to increase worldwide, public health experts and clinicians are more and more interested in understanding what we can do to improve quality of life as we age. An important line of research in this regard is maintaining healthy bones, because bone fractures represent an important risk of hospitalization and disability in the elderly. To keep our bones strong, experts agree that we need to consume adequate amounts of bone-building nutrients such as protein, calcium, phosphorus, and vitamin D. However, other factors, such as genetics and physical activity, are also crucial in determining whether the body can use these nutrients to maintain the complex architecture of our skeleton. Indeed, to really understand the relation between diet and bone health, researchers need to also consider genetic predisposition as well as other mediating factors in their studies. The April 2017 issue of *The American Journal of Clinical Nutrition* features the results of a study that did just that. Specifically, this study (led by Heather Ochs-Balcom at the University at Buffalo, The State University of New York) tested the hypothesis that taking calcium and vitamin D supplements is most effective in reducing risk of bone fractures in individuals who are, due to their genetics, at the highest risk.

Study Design To test their hypothesis, the research team leveraged data previously collected from 5,823 postmenopausal women enrolled in the Women's Health Initiative study. These women had been randomly assigned to take either a calcium/vitamin D supplement or placebo daily for 6 to 7 years. Genetic disposition was determined by looking at a series of gene variants known to affect risks of having low bone density or bone fractures.

Results In contrast to what they had expected, the scientists found a protective effect of calcium and vitamin D supplementation on risk of fracture only in women with the lowest genetic predisposition for having weak bones. In fact, fracture risk in these women who were assigned to calcium and vitamin D supplementation was 40% lower than that of women assigned to placebo.

Conclusions The researchers posit that perhaps the genetic variations that predispose some women to having weak bones may also somehow prevent their bodies from utilizing calcium and vitamin D in dietary supplements. This is a great example of how "precision medicine" might someday be used to better understand which individuals can (and cannot) benefit from specific interventions, such as nutritional supplementation. In this case, because there appears to be no benefit of taking calcium and vitamin supplements in women with high genetic risk of weak bones, other treatments should be considered.

References

Wang Y, Wactawski-Wende J, Sucheston-Campbell LE, Preus L, Hovey KM, Nie J, Jackson RD, Handelman SK, Nassir R, Crandall CJ, et al. The influence of genetic susceptibility and calcium plus vitamin D supplementation on fracture risk. *American Journal of Clinical Nutrition* 2017;105:970–9.

Civitelli R, Peterson T. Toward personalized calcium and vitamin D supplementation. *American Journal of Clinical Nutrition* 2017;105:777–8.

For more information

For the complete article, please go to the following URL:

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Sleep, genetics, and obesity—seemingly improbable (but likely) bedfellows

Background Burgeoning rates of obesity have become an international health crisis, and although experts agree that genetics can affect a person's risk of becoming obese, other more malleable factors are clearly driving these trends. For instance, even the strongest genetic predisposition toward obesity will not cause a person to gain weight if food is scarce. Conversely, even weak genetic variations might result in high risk of obesity in populations with unlimited access to inexpensive, high-fat foods coupled with physical inactivity. Researchers describe this sort of situation as an "interaction" because the effect of one factor (in this case genetics) on health can be modified by another factor (in this case food availability or exercise). Sleep patterns are also emerging as being important in terms of obesity risk. Indeed, both inadequate and excessive sleep are associated with higher chances of weight gain. It is also possible that sleep and genetics interact in this regard, but until recently this had not been rigorously studied. An article published in the April 2017 issue of *The American Journal of Clinical Nutrition*, however, provides the first evidence for such an interaction. Details of this study and its results are provided here.

Study Design The study involved nearly 120,000 adults living in England, Scotland, or Wales who had participated in the UK Biobank study, an international project that recruited 500,000 people (40–69 years old) between 2006 and 2010. Since enrollment, participants have provided blood, urine, and saliva samples and detailed information about themselves, including sleep patterns and work schedules. In addition, they have been weighed and measured and have agreed to have their health followed over time. Here, a research team led by Jason Gill (University of Glasgow, United Kingdom) investigated whether sleep patterns and genetic predisposition interacted to predict body mass index (BMI, body weight divided by height-squared), an indicator of obesity risk.

Results and Conclusions As anticipated, there was a strong interaction between genetic obesity risk and sleep on BMI measurements. For instance, subjects who rarely napped generally had lower BMI values than those who usually napped, but the effect was greater in those with the highest genetic risk. Similar findings were apparent for those who reported doing nightshift work, and both short and long sleep durations were most predictive of high BMI in the genetically high-risk groups. Interestingly, participants characterizing themselves as "evening people" generally had higher BMI values than those self-described as "morning people," but this relation was only significant in participants who had median or higher genetic risk of obesity. The scientists concluded that the association between genetic risk of obesity and actually becoming overweight is exacerbated by adverse sleep patterns. They could have also concluded that the potential impact of poor sleep on obesity is exacerbated by unfortunate genetics.

References

Celis-Morales C, Lyall DM, Guo Y, Steell L, Llanas D, Ward J, Mackay DF, Biello SM, Bailey MES, Pell JP, Gill JMR. Sleep characteristics modify the association of genetic predisposition with obeity and anthropometric measurements in 119,679 UK Biobank participants. *American Journal of Clinical Nutrition* 2017;105:980–90.

Tremblay A, Pérusse L. Obesity, genes, and sleep habits. *American Journal of Clinical Nutrition* 2017;105:779–80.

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Folic acid supplements may be beneficial in lowering risk of gout in hypertensive individuals taking blood pressure–lowering medications

Background Gout is a form of arthritis characterized by sudden burning pain, stiffness, and swelling—often in the big toe. Most commonly seen in men, gout is caused by a buildup of the compound uric acid in the blood, a condition referred to as hyperuricemia. When this happens, uric acid crystals can accumulate—potentially harming joints, tendons, and other tissues. Hyperuricemia is also associated with increased risk of high blood pressure, diabetes, kidney disease, stroke, and heart disease. As such, clinicians and researchers continue to search for ways to prevent hyperuricemia and its damaging sequelae. There are several drugs available, but their side effects make them less than desirable. There is also some evidence that taking supplements of folic acid (a synthetic form of the essential vitamin folate) might decrease gout. However, results have been mixed. To help address the possibility that folic acid supplements might be beneficial, Fan Fan Hou (Southern Medical University, Guangzhou, China) and colleagues randomly assigned 15,364 hypertensive patients to take the antihypertensive drug enalapril alone or with folic acid. Their results, suggesting a potentially beneficial effect of folic acid, are published in the April 2017 issue of *The American Journal of Clinical Nutrition*.

Study Design This experiment was carried out as part of the China Stroke Primary Prevention Trial, designed primarily to examine the independent and interactive effects of elanapril and folic acid on incidence of stroke. The dose of elanapril (10 mg/day) represented a standard amount in terms of hypertension treatment. To get the daily dose of folic acid consumed (0.8 mg/day), however, would require consumption of anywhere from 4–12 servings of enriched, ready-to-eat breakfast cereal. After about 4.5 years of treatment, the researchers evaluated whether taking the folic acid had any effect on concentrations of uric acid in the blood. It is noteworthy that these concentrations were expected to naturally increase during the study because of high blood pressure.

Results Compared with their counterparts who took only elanapril, those who took both the drug and folic acid experienced less pronounced increases in blood uric acid concentrations during the study. This combination treatment also lowered risk of developing hyperuricemia.

Conclusions The scientists concluded that elanapril–folic acid therapy can “significantly reduce the magnitude of the increase of uric acid concentrations in hypertensive adults.” Additional studies will be needed to see if the same effects can be garnered from consuming higher amounts of naturally occurring folate and whether risk of gout is reduced.

References Qin X, Li Y, He M, Tang G, Yin D, Liang M, Wang B, Nie J, Huo Y, Xu X, et al. Folic acid therapy reduces serum uric acid in hypertensive patients: a substudy of the China Stroke Primary Prevention Trial (CSPPT). *American Journal of Clinical Nutrition* 2017;105:882–9.

Scheepers LEJM. Folic acid: the solution for treating asymptomatic hyperuricemia? *American Journal of Clinical Nutrition* 2017;105:775–6.

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Gluten consumption during infancy and toddlerhood not linked to development of celiac disease in preschool years

Background Celiac disease is a sometimes-serious autoimmune disorder whereby eating gluten, typically found in wheat, rye, and barley, severely damages the small intestine. In children, untreated celiac disease can lead to diarrhea, bloating, vomiting, and even poor growth. Adults with celiac disease also commonly report depression and anxiety. In all cases, poorly managed celiac disease can lead to secondary iron deficiency. Although it is likely underdiagnosed, celiac disease is thought to affect about 1 in 100 people worldwide, and why some people develop celiac disease remains, in large part, a mystery. Although experts have generally believed that introducing infants to gluten-containing foods in the first year of life is important for developing tolerance to it, results of several recent studies have contradicted this long-held belief. Importantly, a study published recently (April 2017) in *The American Journal of Clinical Nutrition* found no relation between early gluten consumption (even high amounts) and development of celiac disease in childhood.

Study Design This study represents a secondary analysis of a randomized, controlled trial in which infants with high genetic risk of celiac disease received gluten or placebo from 4 to 6 months of life. From 6 months until 10 months, parents were asked to follow a prescribed schedule whereby their infants were introduced to increasing amounts of dietary gluten. From 10 months onward, unrestricted gluten consumption was allowed according to national dietary habits. It is noteworthy that the scientists previously reported no effect of the age of gluten introduction on development of celiac disease. For this second phase of the study, the research team (led by Paula Crespo-Escobar, Medical Research Institute La Fe, Valencia, Spain) went one step further: they painstakingly quantified the infants' gluten intake (from foods) from 10 months until 36 months of age using detailed food records coupled with a food composition database detailing gluten content of commonly consumed foods. The scientists then evaluated whether variation in dietary gluten intake was related to development of celiac disease during the first 5 years of life.

Results and Conclusions Average daily gluten intakes were not different between children who did or did not develop celiac disease. However, the researchers identified one genetic variation that seemed to be important: higher gluten intake increased risk of developing celiac disease in infants with this gene variant. They concluded that, at least in most individuals, gluten consumption from 11 months until 3 years of life does not influence celiac disease risk during the first 5 years of life. Additional studies are needed, however, to determine how genetics might interact with gluten consumption to manipulate this risk.

Reference

Crespo-Escobar P, Mearin ML, Hervás D, Auricchio R, Castillejo G, Gyimesi J, Martinez-Ojinaga E, Werkstetter K, Vriezinga SL, Korponay-Szabo IR, et al. The role of gluten consumption at an early age in celiac disease development: a further analysis of the prospective PreventCD cohort study. *American Journal of Clinical Nutrition* 2017;105:890–6.

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