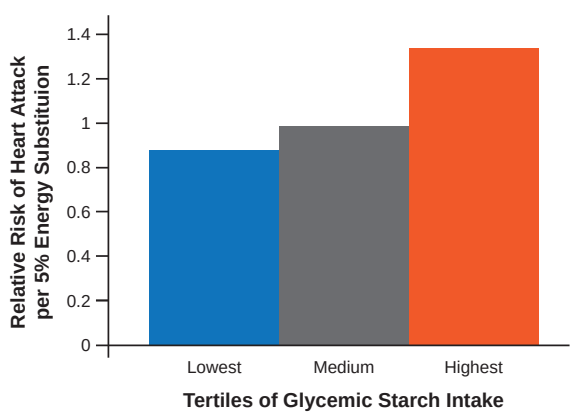
Carbohydrates have a major influence on smaller LDL particles, which have greater entry into the arterial wall and are subjected to faster oxidation. Moderate carbohydrate restriction can improve atherogenic dyslipidemia [Krauss RM et al. *Am J Clin Nutr* 2006].

Epidemiologic evidence to date shows no reduction in heart disease when SFAs are replaced by carbohydrates, and there is some evidence that the risk may be increased. However, the type of carbohydrate may be important. In one study, replacing SFAs with carbohydrates with low-glycemic index values was associated with a lower risk of myocardial infarction (MI; HR, 0.88; 95% CI, 0.72 to 1.07), whereas replacing SFAs with carbohydrates with high glycemic index values was associated with a higher risk of MI (HR, 1.33; 95% CI, 1.08 to 1.64; Figure 2) [Jakobsen MU et al. *Am J Clin Nutr* 2010].

**Figure 2.** Risk of Heart Attack Increases as High Glycemic Index Carbohydrates Are Substituted for SFAs

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A meta-analysis of eight randomized controlled trials indicated that consuming polyunsaturated fatty acids (PUFAs) in place of SFA reduces coronary heart disease [Mozaffarian D et al. *PLoS Med* 2010]. Although challenged in a more recent meta-analysis [Ramsden CE et al. *BMJ* 2013], other evidence is strong that the risk of coronary heart disease is reduced when SFAs are replaced with PUFAs [Astrup A et al. *Am J Clin Nutr* 2011].

Low fat diets in general appear to be healthier. Among persons at high CV risk, a Mediterranean diet (fruits, vegetables, fish, and whole grains) supplemented with extra-virgin olive oil or nuts reduced the incidence of major CV events [Estruch R et al. *N Engl J Med* 2013].

Although studies of specific eating patterns such as the Dietary Approaches to Stop Hypertension (DASH) eating plan and the Mediterranean diet have shown CVD benefits, the actual beneficial element in the diet has not been conclusively identified. The evidence to date shows no clear benefit of substituting carbohydrates for SFAs although there might be a benefit if the carbohydrate is unrefined and has a low glycemic index [Astrup A et al. *Am J Clin Nutr* 2011]. The Women's Health Initiative trial, which assessed diets with reduced total fat intake and increased intakes of vegetables, fruits, and grains, showed no reduction of heart disease risk or stroke [Howard BV et al. *JAMA* 2006]. A meta-analysis of 21 prospective cohort trials supported these findings [Siri-Tarino PW et al. *Am J Clin Nutr* 2010].

It may be that the intake of red meat is responsible for much of the risk of heart disease (and diabetes) attributed to saturated fat. Red meat consumption has been associated with an increased risk of CVD and cancer mortality, while substitution of other healthy protein sources is associated with lower mortality risk [Pan A et al. *Arch Intern Med* 2012]. Elevated trimethylamine-N-oxide (a proatherosclerotic metabolite) levels, found in red meat predict an increased risk of major adverse CV events [Tang WH et al. *N Engl J Med* 2013].

Thus, it is not just the presence of cholesterol and saturated fat in the diet that matters; it is also the foods that are the sources of those factors. Individual SFAs may have different CV effects and major SFA food sources contain other constituents that could influence CVD risk. The combination of multiple biomarkers and the use of clinical endpoints could help substantiate the effects on CVD. In general, fatty fish, nuts, other polyphenol-rich foods, and legumes are good dietary choices, while trans-fats, sugars, and glycemic starches are not [Astrup A et al. *Am J Clin Nutr* 2011].

## Use of Personalized Nutrition Based on Genetic Polymorphisms to Reduce Disease Risk

Written by Maria Vinall

Genetic variations can affect how nutrients are metabolized, while nutrient deficiencies can have an effect on genetic variation. Carl L. Keen, PhD, University of California, Davis, Davis, California, USA, discussed the future challenges and present ethical considerations in the use of personalized nutrition based on genetic polymorphisms that increase an individual's risk for developing, or susceptibility to, marginal nutritional deficiency.

Over time the benefits expected from a healthy diet have evolved from prevention of illness due to deficiencies in essential nutrients (eg, rickets, scurvy), to the reduction in the onset/progression of select cancers and age-related diseases, to concepts such as the Barker Hypothesis, which proposes an association between

maternal diet generational health, and most recently to the belief that healthy diets promote "optimal health". Although the exact definition of optimal health remains elusive, it has been variously characterized as a sense of well-being, achievement of one's genetic potential, the absence of disease, and the ability to retain excellent visual acuity, reaction time, and fine motor control well into old age. The success of nutritional genomics will be defined by the targets that are set.

Single-nucleotide polymorphisms (SNP) can determine how nutrients are processed in the body and may be useful in determining which foods to consume and in what quantities. The enzyme 5, 10-methylenetetrahydrofolate reductase (MTHFR) is involved in folate metabolism. Polymorphisms of the MTHFR gene are associated with higher rates of neural tube defects [Kirke PN et al. *BMJ* 2004], which can result in a higher risk of infants born with spina bifida in women who have these genetic defects [De Wals P et al. *N Engl J Med* 2007]. Food fortification with folic acid has been shown to significantly reduce the rate of neural-tube defects in newborns.

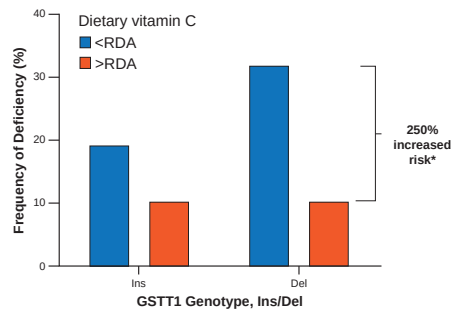
Other nutrient-gene interactions that reduce manganese and copper have been identified that lead to ataxia prolonged bleeding, lysosomal dysfunction, cardiomyopathy, and lung failure in mice and sheep, scoliosis in chickens [Voglis S et al. *Am J Respir Crit Care Med* 2009; Yoshida M et al. *Lab Invest* 2009; Huang L et al. *Nat Genet* 1999; Opsahl W et al. *Science* 1984], and conditions such as Menkes disease, occipital horn syndrome, and Wilson's disease, in humans [Kodama H et al. *Brain Dev* 2011].

Low levels of vitamin C are linked to increased risk of heart disease, type 2 diabetes, and cancer. The utilization of vitamin C can be affected by variations in the glutathione S-transferases (GSTs) T1 gene that protects against serum ascorbic acid deficiency. Individuals with the GSTT1 deletion gene variant have an increased risk of ascorbic acid deficiency if they do not meet the Recommended Dietary Allowance for vitamin C (Figure 1) [Cahill LE et al. *Am J Clin Nutr* 2009].

It is generally accepted that sodium intake is associated with hypertension; however, the impact is not the same for everyone. Blood pressure response to high salt intake is greater in individuals with ACE I/D and 11βHSD2 G534A polymorphisms (Figure 2) [Poch E et al. *Hypertension* 2001].

The Costa Rica Heart Study [Cornelis MC et al. *JAMA* 2006] looked at the association between coffee intake and the risk of myocardial infarction (MI), and whether the polymorphic cytochrome P450 1A2 (CYP1A2) enzyme modifies this association. Caffeine intake was associated with an increased risk of nonfatal MI, but only in individuals with AC or CC CYP1A2 genotype (slow caffeine metabolizers; Figure 3).

**Figure 1. GSTT1 Genotype, Vitamin C Adequacy and Ascorbic Acid Deficiency**




*Relative risk of deficiency for those with the "deletion" variant who do not meet the RDA for vitamin C compared with those who do meet the RDA.

Del=deletion; INS=insertion; RDA=recommended daily allowance.

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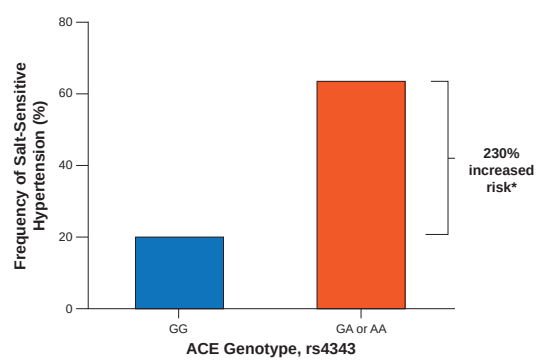
Adding to the complexity of gene-nutrient interactions is the human microbiome, which contains 100 times as many genes as the human genome. The microbiome produces vitamins, maintains intestinal structure, protects from pathogens, helps maintain immune function, and affects host metabolism and secretion of hormones from the gut. It is significantly impacted by mode of infant feeding (formula vs breast feeding), host genotype, diet, and gut biotics.

**Figure 2. Salt-Sensitive Hypertension by ACE Genotype**




*Relative risk of salt-sensitive hypertension with the GA or AA genotype compared with the GG genotype.

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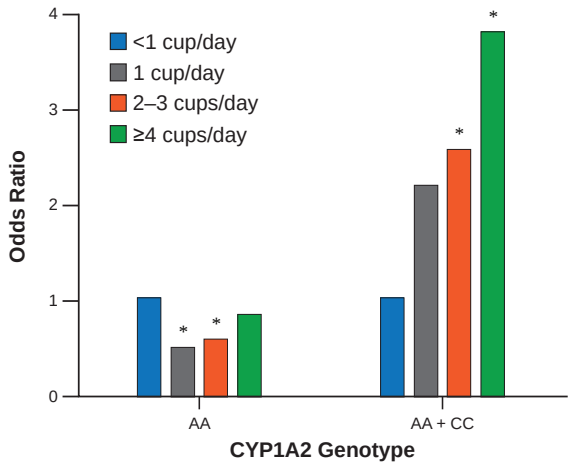
Major issues for the future will be the identification of more genetic polymorphisms that increase an individual's risk for developing, or susceptibility to, marginal nutritional deficiency, as well as toxicity, states. Once this information is obtained, attention will need to be paid to the determination of the epigenetic, or persistent, consequences associated with mild micronutrient deficiencies during early development and how these persistent effects contribute to the risk of age-related chronic diseases.

**Figure 3.** Coffee Intake, MI, and CYP1A2 Genotype




*p<0.05.

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## The Breakfast Controversy

Written by **Phil Vinall**

Although most people will say they believe it is the most important meal of the day and lay publications often link it with increases in metabolism, weight loss, and improvements in mood and the immune system, Americans frequently skip breakfast. Heather J. Leidy, PhD, School of Medicine, University of Missouri, Columbia, Missouri, USA, discussed the potential relationship between skipping breakfast and the rise in obesity in America and the benefits of eating a daily breakfast.

Fifty years ago breakfast was a staple in the American diet. Today ~30% of young people skip their morning meal [Deshmukh-Taskar PR et al. *J Am Diet Assoc* 2010]. Data from several studies indicate that the gradual decline in breakfast eating has mirrored the rise in obesity (Figure 1) [Haines PS et al. *J Am Diet Assoc* 1996; Siega-Riz AM et al. *Am J Clin Nutr* 1998; Timlin TM et al. *Pediatrics* 2008]. An analysis of cross-sectional data from the National Health and Nutrition Examination Survey (1999-2006) of children and adolescents showed that individuals who consume cereal at breakfast had lower intakes of total fat and cholesterol and higher intakes of total carbohydrate, dietary fiber, and several micronutrients ($p<0.05$ for all) than breakfast skippers. Breakfast skippers also had a higher body mass index (BMI) than cereal consumers ($p<0.05$) [Deshmukh-Taskar PR et al. *J Am Diet Assoc* 2010]. Breakfast skippers consume more sweets (40%), chips (55%), soft drinks (55%), and white bread (40%), and less vegetables (45%), fruit (30%), milk (60%) and whole grains (65%) [Sjoberg A et al. *Eur J Clin Nutr* 2003; Haire-Joshu D et al. *J Am Diet Assoc* 2011]. Among adolescents, there is an inverse relationship between increased BMI and breakfast frequency (Figure 2) [Timlin MT et al. *Pediatrics* 2008].

**Figure 1.** Relationship Between Reduced Breakfast Consumption and Obesity

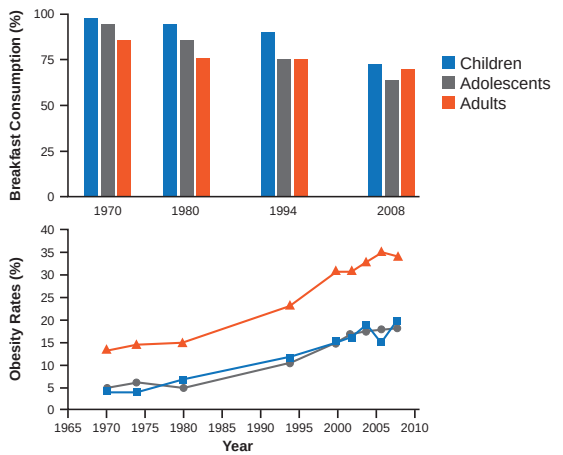


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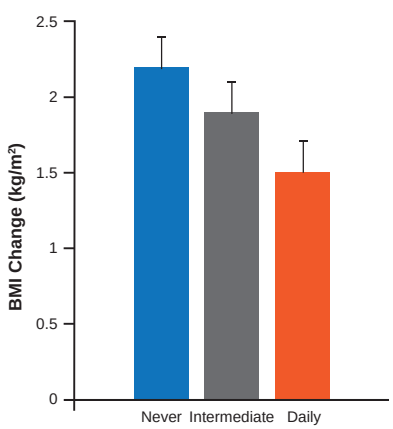
**Figure 2.** Time 2 Breakfast and BMI Change (Adjusted for Baseline BMI and Breakfast Category, Age, and Gender)

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Although there is much observational evidence that breakfast skipping leads to overeating, poor diet control, poor food choices, cravings, weight gain, and hunger, there are few well designed randomized controlled trials (RCT). One RCT examined how the daily timing of increased dietary protein influences the feelings of fullness during energy balance and restriction in male adults [Leidy HJ et al.