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The Science Behind Nutrisystem® DNA Body Blueprint™

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Introduction

The growing field of nutrigenetics is a key area helping drive personalized nutrition recommendations that seek to understand how food and genes interact to influence health outcomes. Advances in genetic testing technology have provided the ability to look at multiple genes using a single sample while making testing affordable with reduced processing time. This allowed genetic testing to become more accessible to the general public. Broadly, consumer awareness and interest regarding genetic testing and adoption rates have increased in recent years. Achievements in efficacy and adoption in the emerging field require transparency in the ethical, legal, and privacy protections afforded to consumers. Recent developments in genomics have enabled large nutrigenetic human studies to elucidate the role genes and nutrition play in weight loss and weight management. Developing scientifically validated tools for personalized nutrition and weight management strategies is one of the largest opportunities for applying nutrigenetic research. The scientific advancements made in this field have allowed Nutrisystem to select specific genetic markers with strong evidence associated with food, dietary patterns and weight-related risk scores. The opportunity to combine our weight loss system with actionable insights developed with scientifically relevant SNPs (single nucleotide polymorphisms) offers unique personalization opportunities for consumers. Nutrisystem has developed a concise customer friendly report providing personalized and actionable recommendations to improve an individual's weight management journey. This innovation offers consumers integrated, personalized solutions that incorporate current and continually evolving nutrigenetics research. Aligning with Nutrisystem's commitment to providing scientifically driven weight management solutions, nutrigenetics based genetic testing also provides an opportunity to collect population-scale personalized data helping forward the collective obesity research knowledge base.

1. Background

Nutrigenetics - Opportunities & Challenges

The field of nutrigenetics is a key area helping inform personalized nutrition recommendations by seeking to understand how food and genes interact to influence health outcomes. One of the biggest opportunities for applying nutrigenetic research is in the development of scientifically-validated tools for personalized nutrition and weight loss strategies. According to the International Society of Nutrigenetics/Nutrigenomics 2016 Personalized Nutrition Position Paper, the value of nutrigenetic information warrants the inclusion of this information to inform personalized diet recommendations. Furthermore, this position paper provides evidence that genetically-informed dietary advice is better understood and more likely to be adhered to than general dietary guidelines. Given the importance of adherence and understanding in driving sustained weight loss outcomes, nutrigenetics can be a beneficial component of holistic weight management solutions.[1]

Although the opportunities are promising, the implementation of nutrigenetic-informed personalized nutrition and weight management strategies are not without challenges. Key challenges currently seeking solutions in the nutrigenetic field include: (1) communicating that genetic outcomes are based on probability not predictability and must be considered with other key data points like environment and lifestyle, (2) developing robust and rapid bioinformatics tools to make better genetically-informed recommendations, (3) need for population-scale controlled clinical nutrigenetic studies investigating primary outcomes associated with weight management. Nutrisystem®'s scientifically-driven approach and large customer base enable it to be one of the leaders driving positive advancement in the nutrigenetic field.[1] [2]

Scientific Basis for DNA Driven Weight Management

Scientific research is driving the advancements in DNA based weight management. According to a NIH Working Group Report on Obesity, multiple genome-wide association studies (GWAS) across various population types have identified approximately 150 genetic markers significantly associated with Body Mass Index (BMI), waist circumference and genetic obesity risk. One of the largest GWAS studies exploring links between genetics and weight loss/regain identified a specific genetic marker associated with weight loss over a four (4) year period. Additionally, scientific research supports a link between the genetics of food choice and consumption behaviors. Successful weight loss programs require inclusion of behavior modification based on the collection of data from physiological and genetic factors such as food preference, satiety, and eating behaviors to affect positive change. These studies and others support the inclusion of genetic information in personalized weight loss reports and plans. [2]

Incorporating genetic testing into corporate weight management programs has previously been implemented with success providing real-life data points to help improve the science. Aetna introduced a year-long pilot study to its employees providing individual genetic reports to deliver personalized nutrition and coaching plans. Results showed that 76% of participants lost weight over the year-long intervention and study authors cited genetic information as a contributing factor to high program enrollee engagement rates.[3]

Consumer Attitudes & Perceptions to Genetic Testing

Since technological advancements have made genetic testing widely accessible, it is experiencing rapid adoption among consumers. During Black Friday weekend in 2017, Ancestry DNA sold approximately 1.5 million genetic tests and 23andMe was among the most popular items purchased on Amazon.[4] [5] Consumer attitudes and perceptions of genetic testing have begun to positively transition from early-adopters to the mainstream. Research by the Genomes to People (G2P) Research Program, appears to validate consumer purchasing trends. Preliminary data from the PeopleSeq project show that individuals are very interested broadly in genetics (99%), curious about genetic make-up (98%), seek to help others via genetic research participation (92%) and want to use genetic information to improve their health (81%).[6] The Impact of Personal Genomics Study (PGen) from G2P, showed similar trends: people want to have the right to access their own information outside medical settings (89.9%), curious about genetics (84%) and genetic tests should be more widely available (i.e. drugstores) (68.3%).[7] [8] Broadly, research has shown positive attitudes towards personalized nutrition based genetic tests too. Encouraged by these results, Nutrisystem sought to ensure genetic testing aligned with customer needs and had positive attitudes and perceptions. Based upon Nutrisystem®'s independently conducted market research, nearly 3 out of 4 diet intenders believe the knowledge provided by genetic testing would increase their motivation for both dieting (73%) and exercise (70%). Nutrisystem received overwhelmingly positive feedback and broad interest on incorporating nutrigenetic testing into its product offerings through personalized reports to help customers better understand their genetic makeup related to weight management.

Legal, Privacy & Ethical Considerations

As genetic testing becomes ubiquitous in consumer and clinical setting, important topics such as legal protection, privacy policies and ethics must be considered. US laws such as Health Insurance Portability and Accountability Act (HIPAA) and the Genetic Information Non-Discrimination Act (GINA) provide protections against misuse of sensitive genetic information.

Privacy is also top of mind with consumers. Each genetic testing company has their own policies in place to protect privacy. Nutrisystem has developed extensive policies and procedures to ensure customer's data remains private and safe. Instituting a de-identified barcode based system ensures no samples can be matched back to the individual, keeping the customers' data private to the genetic testing partners. Interestingly, research from the PGen Study and Scripps Health revealed genetic testing adoptees showed low privacy concerns when purchasing tests or sharing results with healthcare practitioners.[8] [9] However, the PGen Study showed 6-months post testing, over 80% of consumers felt the information should be kept private and non-sharers of genetic information were more likely to have privacy concerns in comparison to sharers.[7] [9] Clearly, it's important to maintain robust privacy policies, IT security systems and enable the customer to control sharing of information.[10] For further information regarding the privacy policies for DNA Body Blueprint™ refer to the Terms and Conditions and Privacy Policy for customers located on the Nutrisystem website.

As the direct to consumer (DTC) genetic testing space continues to rapidly evolve, it is also important to ensure ethical considerations remain a top priority. Nutrisystem is committed to

maintaining transparency and providing easy to understand information for our customers. For more details, we encourage you to read our Terms and Conditions and Privacy Policy.

2. Lab Testing

DNA extraction and SNP genotyping are performed by AKESOgen, Inc. which is a Clinical Laboratory Improvement Amendments (CLIA)-certified and College of American Pathology (CAP) accredited laboratory. DNA isolations will be carried out from buccal (cheek) cells and SNP genotyping is planned on the Illumina Beadchip platform. The Illumina XT Beadchip comprises a custom set of 308 specific genetic SNP markers designed by scientific experts at Genetic Direction and Nutrisystem. These markers have been scientifically validated and shown to be associated with health and weight management traits. The Illumina XT microarray has an accelerated two-day workflow compared to other genotyping products available on the market that allows for faster results to the customer. The marker set allows for a high amount of redundancy for generating calls for each SNP. Samples will meet a quality-control requirement per Illumina's recommendations.

3. Genetic Direction Scientific Validity

The scientific validity of each carefully selected genetic trait and outcome is a priority for Nutrisystem in this emerging space. After vetting multiple companies in the nutrigenetics space, we chose a partnership with Genetic Direction due to their science bonafides. Through this partnership, we can provide genetics-based personalized weight management programs. Genetic Direction's scientific team focuses on traits related to lifestyle and behavior modifications to support a consumer's overall health and wellness goals. The genetic markers included in our reports undergo a rigorous scientific due diligence process to ensure genetic marker and phenotype associations provide meaningful and proven insights.

The selection of genes and SNPs for each category undergoes an extensive vetting process of peer-reviewed, high quality scientific publications by Genetic Direction's genomics research team comprised of distinguished researchers in nutrigenetics, obesity and general preventative health. Broadly, the types of peer-reviewed scientific publications are: clinical, functional and reviews. Identified genes/SNPs of interest must meet the following scientifically-validated criteria:

1. At least two (2) independent peer-reviewed studies (associations in other intervention studies and/or cross-sectional experimental or observational studies).
2. Generally, study sample size of ≥200 or greater (e.g., POUNDS LOST, Look AHEAD trials).
3. Preference for randomized controlled trials (RCT). However, if RCTs are not available for a trait, evidence from the best designed, standardized intervention, such as a large exercise training study (e.g., HERITAGE Family Study, N~500), or well-established longitudinal observational studies are used (e.g., Framingham Heart Study).

4. Dynamic Traits (e.g., circulating levels, such as Vitamin D, sun sensitivity) used SNPs from the most recent, comprehensive, published genome-wide association analyses (GWAS) meta-analyses (e.g., GIANT or CHARGE consortia). Often, these meta-analyses include data on over 100,000 individuals from over 40 studies, with replication in another tens of thousands of individuals and dozens of studies. Thus, we included only the SNPs with the most up-to-date and strongest evidence of association ($p \leq 5x10\text{-}8$ at a minimum) with these traits.

In addition to the criteria set forth by Genetic Direction's team, Nutrisystem®'s research and development team reviews the science and recommendations in accordance with our internal scientific standards and core philosophy to weight management. Genetic Direction's scientific team is constantly reviewing and assessing genetic markers to ensure relevant and scientifically based information is incorporated into the reports. As new insights become available, Nutrisystem® customers will receive update notifications to learn more.

Nutrisystem's broad customer reach will lead to the creation of one of the largest de-identified genetic and phenotypic information databases. Utilizing this unique resource, we will be able to further identify and validate lifestyle genotype-phenotype associations.

4. Scientific Bulletin

Metabolism

Your Body's Ability to Lose and Maintain Weight

Overview

With obesity rates continuing to climb in the United States, it's no surprise that an estimated 106 million adults are trying to lose weight and 68.3 million that are trying to maintain weight loss.[11] As the obesity epidemic continues it's important that we continue to invest in obesity research and provide innovate, safe and effective solutions based off of the latest insights. The ability to understand how genes play a role in one's ability to lose and maintain weight provides insights previously unknown that may help answer personal questions of "why can't I lose weight easily" and lead to better short and long term outcomes.

Genes Tested: FTO, TCF7L2, MNTR1B, PPARG, BDNF, ABDB11

These genes have been researched and shown to have a statistically significant association with weight loss and weight loss maintenance. Several large studies have shown that people who participated in intensive and long-term diet and exercise programs exhibited significantly larger weight loss responses based upon their genetic profile.[12] [13] [14] [15] Those individuals who carried a specific profile of these 6 genes lost weight with the diet and exercise program—but, on average, they tended to lose less weight compared to other participants who did not carry, or who have fewer markers in this genotype profile. Also, after completing the diet and exercise program, people with more markers of this genotype profile were, on average, also more likely to regain some of the weight that they had lost.

Outcomes and Recommendations:

A Normal outcome suggests that one can expect to successfully lose weight and keep it off by following a well-planned diet with proper portion and calorie control, plus an exercise program which is paramount during the weight maintenance phase. However, this does not mean that losing weight and keeping it off will be effortless.

A Below Average result suggests that one may lose weight and body fat at a slightly slower rate than those with a different genetic predisposition. However, genetics is just one factor that determines success. Optimizing diet, exercise and lifestyle changes support achievable weight loss outcomes.

A Low outcome means that it may be a little harder for one to lose weight than others with a different genetic result. Again, genetics is just one small factor that determines success. Proper diet, exercise and lifestyle changes are very impactful.

Limitations and Warnings:

As suggested in the outcome results, the ability to lose weight and maintain that weight loss is not solely predicted on genetic results. Genetics plays a role in our ability to successfully lose and maintain weight, however proper diet, exercise and healthy lifestyle change remains the most important factor that determines success.

Metabolism and Your Resting Metabolic Rate

Overview:

Metabolism is defined as a combination of chemical processes that keeps cells living to carry out basic functions within the body. These processes include absorbing, transporting and using nutrients, breathing, growing and repairing cells and producing substances the body and major organs need to thrive amongst others. The number of calories the body burns to carry out these functions is known as resting metabolic rate (RMR). RMR accounts for approximately 70% of daily calorie burn in sedentary people and is influenced by age, body size and composition, and gender. RMR typically declines 1-2% each decade after the age of 20 and this is mostly due to loss of fat-free mass.[16] Not surprisingly, genes also affect metabolic factors and can increase or decrease RMR. There are two other factors that determine how many calories the body burns each day, physical activity and thermogenesis. Physical activity accounts for approximately 20% of daily calorie burn and is the most variable factor from day to day. Thermic Effect of Eating (TEE) accounts for about 10% of daily calorie burn and is the number of calories burned by eating, digesting, absorbing and processing the food you consume.

Genes Tested: LEPR, CHRNA3, CRY2

These genes have been shown through several independent studies to be associated with a person's resting metabolic rate (RMR) and how responsive their metabolism is to diet and exercise in terms of burning fat. In a study of overweight and obese women leptin levels and polymorphisms in the leptin receptor (LEPR) gene were associated with energy expenditure. Results showed that the DNA sequence variability of the LEPR gene could affect fat, protein and carbohydrate oxidation and is hypothesized to be due to glucose variability leading to differences in glucose oxidation.[17] In another study of 678 men and women, results indicated that certain

genotypes burned about 100 calories more per day than subjects with different genotypes.[18] Genes influencing resting metabolic rate show potential genes for obesity, diabetes and metabolic syndrome due to their correlation with energy balance and breakdown of macronutrients.

Outcomes and Recommendations:

A Below Average outcome means that one may be less metabolically responsive to diet and exercise in terms of burning fat and RMR is not likely to change too much in response to diet and exercise. This means that one should make a concerted effort to expend more energy in daily life and take other measures to boost RMR like preserving and enhancing lean muscle mass through strength training.

An Average outcome means that one has a normal responsiveness to burning fat when it comes to diet, exercise and RMR. Resting metabolism may respond well to proper diet and exercise, however to assist with weight loss it is still recommended to deliberately expend more calories than consumed.

Having an Above Average metabolism indicate that one likely has a higher resting metabolic rate than people with a different genetic makeup. Because of this, the body may burn fat at a slightly elevated rate when following a diet and exercise plan.

Limitations and Warnings:

Having an Above Average or Below Average metabolism outcome is not an indication that weight loss attempts are not justified. Weight gain is influenced by many factors including diet, environment, sleep, physical activity, stress, hormones and genetic makeup. While it may be true that some individuals have the ability to lose weight more quickly than others, most everyone, except those with rare medical conditions, will lose weight when an energy deficit is created through calorie restriction or physical exercise.

Likelihood of Regaining Weight

Overview:

Weight management can be a two part process. First, there is the hard work and dedication needed to achieve weight loss. Second, is the even harder task of keeping the weight from coming back. It is observed that approximately 70% will regain at least half of the weight lost within 2 years of successful weight loss attempts and will return to their baseline weight within 3–5 years.[19] What is known is that weight regain is not due to any one factor. Calorie restriction and a now smaller body size can lead to a slower metabolism which makes it difficult to keep the pounds off. After success is achieved, people can become relaxed with calorie and portion control and become less active. It is crucial for successful weight maintenance that diet, exercise and behavior strategies adopted during the weight loss phase become a lifelong part of behavior change. Understanding genetic markers can help identify and adhere to optimal strategies for successful lifestyle change.

Gene Tested: FTO, PPARG, BDNF, NEGR1, TMEM18, KTCD15, GNPDA2

Research shows that these genes play a significant role in weight regain. In one study of 3,234 overweight or obese adults where participants followed an exercise, medication, and/or lifestyle

plan with the goal of losing 7% of their body weight, researchers found three SNPs that were associated with weight regain, regardless of the weight loss method used. Researchers concluded that genetic testing could provide insights on who may require additional support to maintain weight loss after.[14]

In another large-scale study of close to 3,500 overweight or obese adults, researchers identified SNPs associated with the FTO gene that were strongly related to weight regain. Among those who had successfully lost weight after one year, those with specific risk alleles for the FTO gene regained about 3 pounds for every risk allele they carried at the four-year follow-up.[20]

Outcomes and Recommendations:

An outcome of Below Average, Normal, or Above Average reflects whether a result includes genotypes that carry the likelihood of regaining weight.

A Below Average outcome indicates that one will be less likely to regain weight based off their genetic profile. This is a good scenario since keeping weight off is often harder than losing weight, however it is imperative to incorporate a healthy diet, engage in regular exercise, and adopt new lifestyle practices. A Normal outcome indicates a normal chance of regaining weight compared to others with a different genetic profile and an Above Average outcome means one's chance of regaining the weight is highest. However, this does not indicate that weight regain is imminent. It means that it is crucial to continue healthy lifestyle habits for successful weight maintenance.

Limitations and Warnings:

While genetics does play a role in the potential to regain weight lost, it is not the most important factor. Following a continued healthy diet consisting of calorie and portion control, increased exercise, and behavioral changes are most important to combat weight regain. Some successful strategies of weight maintenance are consistency, frequent self-weighing, adequate sleep, and stress management, increased exercise with incorporation of strength training and controlling hunger with proper meal spacing.

Risk for Being Overweight

Overview:

The genetics of weight gain are complex. However, when it comes to obesity, the FTO or "obesity gene" as it became known after its discovery in 2007, has by far the strongest association with the risk of becoming overweight or obese as an adult. How the "obesity gene" triggers weight gain is still not entirely known, but it appears to impact the functioning of the hypothalamus of the brain, which is the area responsible for regulating appetite and satiety. Simply, those with the risk-associated FTO allele are genetically prone to have higher circulating levels of ghrelin, otherwise known as the "hunger hormone," in their blood, have a greater appetite for high calorie foods, and feel less full and satisfied after eating.

Genes Tested: FTO

This gene has been shown to have significant associations with a person's likelihood of being overweight or obese in adulthood. In one genome wide study involving 38,759 participants, researchers found that those carrying two copies of a variant in the FTO gene—about 16% of the population—were about 1.7 times likely to be obese.[21] The gene also appears to increase risk

across various ethnic populations, according to a meta-analysis including 59 studies and more than 111,500 people of a variety of ethnic backgrounds.[22] In a study of more than 9,500 overweight or obese adults, researchers found that even people carrying the most high risk variant of the FTO gene lost weight at the same rate, regardless of weight loss method they used, as those with more favorable genotypes.[23]

Outcomes and Recommendations:

An outcome of Average, Above Average or Well Above Average indicates whether a genotype result includes those that carry the likelihood of becoming overweight or obese.

An Average result indicates that one is less likely to be overweight or obese than those with a different genetic profile. While an Above Average or Well Above Average result indicates that there is a greater risk of being overweight or obese when compared to others with a different genetic profile. It's important to remember that with any of these outcomes that this does not impact the ability to lose weight.

Limitations and Warnings:

While genetics does play a significant role in obesity risk, it is not the most important factor. A healthy diet, exercise, and lifestyle are most important to combat excessive weight gain. It is also important to remember that while the FTO gene plays an important role in gaining weight, research shows that the gene doesn't appear to interfere with weight loss.

Eating Behaviors

How Strong is Your Sweet Tooth

Overview

A craving for sweeter foods is commonly referred to as having a "sweet tooth". There is a wide variation in the general public's preferences for sweet foods influenced by many factors including lifestyle, environment, and psychological influences. However, there does appear to be a genetic component to the body's ability to sense how much sugar we are taking in and to regulate our food intake accordingly.

Added sugar intake above the recommended daily value can have negative health consequences including increasing the risk of obesity, diabetes, and heart disease. The USDA and Health and Human Services recommend eating less than 10 percent of calories from added sugar. Added sugar is defined as sugars not naturally occurring in foods.

Genes Tested: SLC2A2 (GLUT2)

The glucose transporter type 2 protein (GLUT2) regulates sugar in the body and has been found in connection with controlling food intake. GLUT2 protein is encoded by the SLC2A2 gene. A variant in the SLC2A2 gene correlated with a higher preference for sweet foods and a higher likelihood of overconsuming sugar suggesting an underlying food intake regulation mechanism. A study conducted in over 680 men and women found that a variation in the SLC2A2 gene corresponded with over 20 grams more of sugar consumption each day when compared to those without the variation.[24]

Outcomes and Recommendations

A report outcome of Normal does not have the genetic variant present that increases risk of over consumption of sugar. Without the genetic variant there is a lower likelihood of over consuming sugar and to crave and overeat sugary foods. However, this does not mean one will not over consume sugar. Most Americans eat too much sugar due to various environmental and lifestyle stimuli. Sugar is also linked to an increase in feel-good brain chemicals like serotonin and dopamine increasing the likelihood of over consumption.

Those with an Above Average outcome have an increased risk of over consuming sugar. Individuals can benefit from some lifestyle and behavior strategies to prevent excess sugar in the diet. Knowing one's genetic risk alone can help them adopt success strategies to limit daily sugar intake to stay within the recommended ranges.

Limitations and Warnings

No limitations or warnings to report.

How Likely You Are to Overeat

Overview

Food desire and an individual's motivation to consume food is measured by researchers in comparison to another individuals' motivation to consume food. How hard someone is willing to work to obtain food is influenced not only by the foods palatability, but a person's food environment. Behavioral scientists put subjects through a series of tasks that test motivation, categorizing participants by levels of food/reward associations. The brain's reward pathways control response to perceived rewards such as food by releasing chemicals that elicit good feelings.[25] This basic biological system keeps us alive by rewarding us for behaviors needed for survival, such as eating. This feedback system plays a role in our risk of overeating and our inability to resist foods that provide us with the reward of feel good hormones. Further, it has been researched that food desire and motivation has a genetic association.[25]

Genes Tested: DRD2

Dopamine is a neurotransmitter that is responsible for the brain's reward and pleasure centers. DRD2 is the gene responsible for the dopamine receptor associated with dopamine signaling. A variant on this gene has been associated with weaker dopamine signaling. An initial study further found the variation of the DRD2 gene may interact with food reinforcement to influence energy intake.[27] This gene also has a significant association with smoking cessation. Smoking cessation is related to other behaviors that involve high-reward system stimulating activities like food reward and overeating.[26] [27]

Outcomes and Recommendations

Those with a Normal outcome lack the genetic variant related to food desire and motivation and are less likely to succumb to addictive behaviors like overeating. However, behaviors are also influenced by environment and lifestyle. Practicing moderation can help change lifestyle behaviors related to obesity.

Those with the genetic variant may be more likely to engage in behaviors related to overeating and are less likely to resist tempting foods. Knowing one's risk can be the first step in behavior modification. Adopting strategies that mimic the effects of the good feeling reward system like exercise can help with lifestyle change. Identifying key positive behaviors that can replace negative ones can help change habits long term.

Limitations and Warnings

Studies have been performed on subjects concerned with smoking cessation.

How's Your Impulse Control Around Fatty Foods

Overview

Eating disinhibition is the tendency to overeat in response to emotional distress or when being presented with foods that are perceived as tempting. It has been reported to be strongly associated with weight gain over time in adults. The tendency to overindulge in calorie-dense, fatty foods is a common problem in society. In a study, the strongest correlation of weight gain in adults was overeating in response to the habitual environment.[28] Fatty foods stimulate the reward center of your brain encouraging over consumption. As we age we may experience changes in impulse control and taste responsiveness. All of these environmental factors may correlate with weight gain over time in adults. A hereditary link has been investigated to explore genetic predispositions to increase consumption of fatty foods over time.[29]

Genes Tested: FTO

FTO is the fat mass and obesity associated gene and carries several variants related to our risk for obesity. A common risk variant of the FTO gene may have an impact on longitudinal changes in impulsivity and dietary patterns over time. The Baltimore Longitudinal Study of Aging reported that individuals with a specific genetic variation found in the FTO gene had reduced activity in the brain that controls impulse and dictates taste preference leaving them at risk for over consumption of high calorie fatty foods. This study also found carriers of the risk variant were at a 67% higher risk for becoming obese.[30]

Outcomes and Recommendations

While some people are aware of their impulses, many people are unaware and regularly overeat. The genetic component underlying some of this behavior can provide awareness allowing the individual to employ strategies to overcome the risk.

An outcome of Normal indicates that one does not have the risk variant associated with a decrease in impulse control and decline in taste responsiveness over time. The likelihood to exhibit an average level of impulse control and the risk for consuming high calorie fatty foods with age is not elevated. However, this does not mean one does not need to be mindful of food choices and portion sizes. People with good impulse control can slip into mindless eating as our environment and habits also play a role in our behavior.

Those with the risk genotype indicating a Slightly Below Average and Below Average ability to resist tempting foods may find success in scientifically proven techniques to increase mindfulness and portion control when eating. For those who are aware of impulsive behaviors, environmental changes may also be beneficial. Knowing one's risk factor can allow them to

seek out strategies to increase success on a weight loss program. Impulse control is essential for maintaining a healthy, portion-controlled diet.

Limitations and Warnings

Study was conducted in an older White population. Environmental factors may play a key role in predicting weight gain with age due to increased impulsivity and consumption of fatty foods.

Caffeine Metabolism

Overview

Caffeine is a natural stimulant. It acts in the body on a receptor to block adenosine which regulates the body's wake/sleep cycles. This increases alertness and brain activity to reduce tiredness. It also increases epinephrine which is a hormone responsible for the body's fight or flight response.

Not everyone responds to caffeine equally. Some experience negative side effects such as jitters, irritability, sleep issues, increased heart rate, and GI distress. The ability to process caffeine is largely hereditary. Caffeine is absorbed into the bloodstream and peaks after about 90 minutes and drops off in about 3 to 4 hours. Genetic predisposition may determine how quickly caffeine is metabolized.

Genes Tested: AHR, RP11-10017.3-001, ARID3B, CYP1A1

The genes influencing caffeine metabolism include intergenic regions that are stretches of DNA sequences located between genes that may control other genes nearby. Caffeine is broken down in the liver by enzymes that metabolize the chemical. A series of genes affect how efficiently caffeine is broken down. One study of 9,876 individuals found variants in several genes associated with slow caffeine metabolism leaving caffeine in the system longer than those that process the caffeine at a normal rate.[31] Having caffeine linger in the system may have adverse effects such as increasing blood pressure or risk of heart attack. The Journal of American Medical Association has reported that slow caffeine metabolizers who drank 2 to 3 cups of coffee a day had a 36 percent increased risk of heart attack, and a 64% increased risk at 4 cups a day.[32]

Outcomes and Recommendations

A normal rate of caffeine metabolism means the liver breaks down the caffeine at a normal rate and it does not linger in the body longer than average. One is more likely to enjoy the benefits of caffeine such as having increased alertness and performance. The recommended intake remains at 400 milligrams per day for normal metabolizers.

Having a slow rate of caffeine metabolism leaves one less likely to benefit from the stimulant, while also increasing risk for elevated blood pressure and heart attacks. It is recommended to abstain from caffeine or consume a maximum of 200 mg per day.

Limitations and Warnings

Being a normal caffeine metabolizer does not mean one is immune to some of the negative side effects experienced by consumers of caffeine. Jitteriness and gastrointestinal distress may still result, so it is important to listen to the body. Going above 600 mg may have adverse effects

regardless of genotype. Certain groups, such as people with hypertension and the elderly, may be more susceptible to the adverse effects of caffeine. Pregnant and breastfeeding women should always limit intake to a maximum of 200 to 300 mg/day of caffeine (the amount in two to three cups of coffee).

Food Breakdown

The Body's Ability to Utilize Carbohydrates

Overview

Genetics may influence a person's insulin sensitivity and the effects carbohydrates have on weight loss and maintenance. Carbohydrates are converted into glucose during digestion and are the primary source of fuel for the body and brain. Glucose is transported into our cells to be used for energy and insulin is needed to help shuttle the glucose into the cells. Insulin resistance occurs when the cells no longer respond optimally to insulin's signals resulting in high blood sugar. Insulin resistance is the most common metabolic disorder associated with obesity. Having an optimal response to insulin in the body is important to weight management. Therefore, glucose is an important nutrient that must be maintained in homeostasis for good health.

Genetic variants that affect insulin signaling have been identified along with their relationship to diet and exercise. A diet higher in carbohydrates is not clearly related with obesity or diabetes, however what's more clearly related is the type of carbohydrate consumed. Dietary interventions are beneficial for weight loss and insulin action but the effect of varying macronutrient content is not uniform. Several large epidemiological studies have shown that increased carbohydrate intake may lead to a lower risk of diabetes. The difference in response to diet may have a genetic link.[33]

Genes Tested: IRS1

This gene may influence insulin resistance and how the body responds to carbohydrates. The insulin receptor substrate gene codes for IRS1, a mediator in the insulin signaling pathway. A common genetic variant identified in a recent genome-wide association is associated with insulin resistance, hyperinsulinemia, and type 2 diabetes.[34] The POUNDS LOST study found that people with the variant of IRS1 gene had lower levels of insulin resistance and greater weight loss when consuming a high carbohydrate, low fat diet filled with healthy complex carbs such as fiber and whole plant foods when compared to eating a lower carb, higher fat diet.

Outcomes and Recommendations

A higher carbohydrate diet with lower fat intake may be more conducive for weight loss in the presence of the IRS1 gene variant. The outcome for this gene may be Normal or Enhanced. An outcome of Enhanced has the gene variant present. Individuals may experience improved insulin sensitivity and weight loss from a diet higher in complex carbs and slightly lower fat. Including more whole unprocessed plant foods and fiber is recommended. Those with a Normal outcome do not have the variant present and may experience similar amounts of weight loss when on a reduced calorie diet regardless of what percentage of complex carbohydrates are consumed. The

types of carbohydrates consumed are important. Processed, refined carbs are more likely to release greater amounts of insulin in the body and could have an effect on insulin resistance.

Limitations and Warnings

Carbohydrates contain essential nutrients like fiber and B vitamins. Consuming the right kind of carbohydrates can help control blood sugar and support healthy weight loss.

The Body's Ability to Utilize Fat

Overview

How our bodies respond to and process dietary fat can differ. Research has examined how genetics correlate to dietary fat intake and what impact they have on our weight. Studies report significant genetic associations with dietary fat and weight loss while participating in lifestyle interventions. By examining the risk variants of each gene one can know the effect dietary fat will have on weight loss and provide diet recommendations.

Genes Tested: PPARG, TCF7L2, APOA5, CRY2, MTNR1B, PPM1K

The PPARG gene encodes a transcription factor that regulates fat storage. In studies the consumption of dietary fat was monitored for the impact it may have on weight loss, BMI, waist circumference, fat mass, and blood triglycerides. Studies have shown variants that both protect from and predict obesity related to dietary fat intake.[20] [35] [36] [37]

The TCF7L2 gene encodes a transcription factor implicated in blood glucose homeostasis and has been associated with increased risk of type 2 diabetes. The POUNDS LOST trial reported those with the risk genotype may reduce body fat by consuming a low fat reduced calorie diet.[38]

The APOA5 gene encodes an apolipoprotein involved in the regulation of triglycerides in the blood. A variant in this gene may change the effect dietary fat has on these triglycerides, BMI, and obesity. Reduced fat intakes have shown consistent interaction with reduced BMI in the risk variant.[39] [40] [41] Studies suggest the non-risk variant may protect from obesity even when consuming a high-fat diet.[42]

The CRY2 and MTNR1B genes are related to glucose metabolism and a balance between energy expenditure and intake. Variants on these genes were observed to modify the effect dietary fat intake has on energy expenditure during weight-loss diets.[43]

PPM1K gene is associated with amino acid metabolites. Significant interaction was found in a 2-year prospective dietary intervention trial between PPM1K gene variant and weight loss.[44]

Outcomes and Recommendations

Genetic information may help identify people who need specific tools and support to lose weight and maintain weight loss.[20] A genetic profile with a Normal result suggests that your body will utilize dietary fat as expected. By reducing calories, one can expect to lose similar amounts of weight on a low or moderate fat diet. Those with low utilization may be sensitive to total fat and/or saturated fat in the diet and may benefit from a low fat, reduced calorie diet for weight loss.

Limitations and Warnings

The definition of a low fat diet is not clear. The Institute of Medicine recommends an intake of 20-35% of total daily calories come from dietary fat and that no more than 10% of those calories come from saturated fat. A low fat diet may also be considered 15-25% of daily calories. Not all fats are created equal and the source of fat is still important.

The Body's Ability to Utilize Protein

Overview

Protein is essential in our diets for muscle building, wound healing, healthy hair, healthy skin, and proper immune function. Protein is comprised of amino acids which are broken into two categories, essential and non-essential. There are twenty amino acids, nine essential which must be consumed in the diet and eleven non-essential which can be made by the body. Complete proteins contain all nine essential amino acids in adequate amounts and are found in animal sources and soy. Most plant foods are incomplete proteins and therefore vegetarians and vegans must ensure they are consuming a variety of plant based proteins. Amino acids in our foods are used by our bodies to produce proteins, enzymes, hormones, and other tissues. Protein has also been proven to help one feel fuller, longer and therefore plays an important role in weight loss. Our bodies process protein differently and the amount of protein consumed in the diet may have effects directly related to weight loss due to individual genetic variants.

Genes Tested: FTO

The FTO gene is also known as the "fat mass and obesity associated gene". It was one of the first genes to be associated with obesity and body mass. A large study found that people with one genotype of the FTO gene who dieted lost more weight, body fat, and fat around their mid-section when consuming a moderate-to-high protein diet regardless of fat and carbohydrate intake. These subjects also lost more muscle with weight loss even with high protein and exercise. Protein sensitivity leads to a likelihood of increased weight loss, fat loss and a risk of muscle loss on a moderate-to-high protein, reduced calorie diet.[14] Another study suggested individuals at risk for being overweight and obese based on their FTO genotype may benefit from a high protein diet for weight loss and weight maintenance.[13]

Outcomes and Recommendations

Genetic outcomes may suggest a Normal, Slightly enhanced, or Enhanced protein utilization.

Normal outcomes reflect a low probability that weight loss and lean body mass will be influenced by the percentage of protein in the diet. The minimum amount of protein recommended for adults is 10% of total daily calories when consuming an energy balanced diet. When consuming a lower calorie diet the percentage of protein consumed may need to be increased. The average recommendation is to consume 0.8-1 gram of protein per 1 kilogram of body weight.

Genotypes with an outcome of Slightly Enhanced indicates a likelihood of better weight loss response to a calorie reduced diet consisting of a higher percentage of protein. Aiming for 25% of total calories from protein may produce optimal weight loss. People with this outcome also

experienced higher amounts of muscle loss while dieting and are recommended to include resistance training as part of a regular exercise routine.

Enhanced genotypes may lose more weight on a moderate to high percentage of protein. These individuals should consume 25% to 30% of calories from protein.

Limitations and Warnings

Individuals with slightly enhanced and enhanced protein utilization are also at risk for muscle loss and should include resistance training as part of a regular exercise routine.

Vitamins and Minerals

Vitamin D

Overview

Vitamin D acts as a hormone in the body and is produced from exposure to ultraviolet rays from the sun. The best source of vitamin D is sun exposure, however adequate intake may be achieved through diet and supplementation.

Vitamin D is essential for skeletal health and low levels have been linked to diabetes, cancer and all-cause mortality. It is essential for the absorption of calcium and calcium metabolism. Low circulating levels of vitamin D in the body can lead to risk of bone fracture, decreased muscle function and a decrease in immunity. Heritability of vitamin D blood levels are estimated to be as high as 53%. Other factors influencing blood levels are sun exposure, diet, age and lifestyle.

Genes Tested: CYP2R1, GC, NADSYN1

Several SNPs have been identified in large genome wide association studies as being linked to low levels of vitamin D in the body. These genes may play a role in the conversion and transportation of vitamin D throughout the body.

Each of the genes influences a step in the process of converting vitamin D into its circulating form, 25-hydroxyvitamin D (25-OH). NADSYN1 encodes the enzyme that is used in the pathway synthesizing vitamin D3. CYP2R1 encodes Vitamin D 25-hydroxylase, the key enzyme involved in the hydroxylation of vitamin D in the liver; a critical first step in vitamin D metabolism. The gene GC encodes vitamin D binding protein (VDR) made in the liver that binds and transports vitamin D.[45]

Outcomes and Recommendations

Outcomes can range from Normal, Below Average, and Low. These outcomes do not determine actual blood levels.

A Normal outcome does not mean blood levels are optimal. One's genotype is associated with a low risk of being deficient assuming adequate sun exposure and dietary intake of vitamin D. Below Average and Low outcomes may warrant a blood test to determine actual levels.

Those living in the southern latitudes during the summer are likely to have higher levels of vitamin D. However, it is not uncommon for those with lots of sun exposure to still experience

low levels. It has been suggested that approximately 5-30 minutes between 10 AM and 3 PM without sunscreen at least two times a week can lead to adequate synthesis of Vitamin D.[46]

Vitamin D can also be obtained through foods such as oily fish, egg yolks and fortified milks.

Limitations and Warnings

These studies were conducted in primarily white individuals of European descent and may not apply to other ethnicities. It is not clear if genetic predisposition modifies the response to sun exposure. As always, it's important to practice sun safety while following recommendations. It is important to discuss supplementation with a health care provider.

Vitamin B12

Overview

B vitamins are important nutrients that contribute to DNA synthesis and methylation. Vitamin B12 assists with red blood cell formation, cognitive and neurological function. B vitamins are also involved with the reduction of homocysteine levels which is an amino acid associated with inflammation and heart disease when present at high levels. Deficiencies in B12 have been associated with an increased risk of heart disease and cancer.[46]

Diet, environment, and genetics all play a role in circulating levels of B12 and homocysteine. Absorption of B12 requires the secretion of specific proteins from the gastrointestinal cells to bind to vitamin B12 for adequate absorption within the gastrointestinal tract.[46]

Genes Tested: FUT2

The FUT2 gene codes for an enzyme involved in gut bacteria. Variants have been shown to influence antigens associated with the growth of gastrointestinal bacteria such as H. pylori. Gastric bacteria are associated with vitamin B12 deficiency due to its impact on absorption.[46] In multiple genome-wide association studies, FUT2 was associated with vitamin B12 levels.

Outcomes and Recommendations

Outcomes range from Normal to Low. An outcome of Normal suggests that a diet adequate in B12 will likely produce normal blood levels. However, this does not mean there are low levels of B12 present. Only a blood test can determine actual levels.

An outcome of Low suggests a risk for having blood levels that are at the low end of normal. Again, this does not determine a deficiency. Many other factors may influence blood levels of B12 including age and presence of gastrointestinal disorders. Deficiency in vitamin B12 has been most often associated with poor intestinal absorption rather than dietary deficiency.[47]

Consuming foods rich in B12 is important regardless of genetic outcome. Foods like lean meats and dairy are good sources of B12 and plant-based yogurts are often fortified with B12. Vegans and vegetarians are at a higher risk of low B12 and are recommended to discuss supplementation with a health care provider.

Limitations and Warnings

Associations were detected in a Caucasian population and may not apply to other ethnicities. Only a blood test can determine actual levels of B12. It is important to discuss supplementation with a health care provider.

Calcium

Overview

Calcium is a well-known mineral often associated with bone and teeth health. Although most calcium is stored in the skeletal bones and teeth, it is used by almost every cell in the body for biological processes like nerve function, muscle contraction, hormone release and heart health.

Calcium levels in the blood are tightly regulated and need to stay within a certain range for homeostasis. Because of its essential role, if blood levels drop below adequate levels, the body will pull calcium from bone to ensure that the cells have enough to maintain proper function. Overtime, calcium depletion will lead to weakened bones.

Calcium levels are influenced by lifestyle and environmental factors such as diet, digestion, phosphate levels, vitamin D levels, and hormones. Recently, research has also shown that genetics may play a role in blood calcium levels.

Genes Tested: CASR, DGKD, GCKR, LINC00709, CARS, LOC105370176, CYP24A1

A large study of 39,400 men and women showed variations in these genes were related to blood calcium levels. The heritability of serum calcium levels is estimated to be 33%.[48]

The genes DGKD, GCKR, CASR, and CYP24A1 are associated with bone mineral density and their expression is influenced by dietary calcium intake. DGKD is a variant that encodes for an enzyme and plays an important role in calcium signaling in parathyroid (PTH) cells. CASR is also linked to the hormonal control of serum calcium in relationship to its role with PTH concentrations and signaling. CYP24A1 codes for an enzyme responsible for detoxification and is implicated in the vitamin D pathway and on PTH concentrations. CARS is a gene that has been linked to hypocalcemia and hypercalciuria.[48]

Outcomes and Recommendations

An outcome of Normal indicates a likelihood of having optimal levels of calcium in the blood if intake is within the recommended dietary guidelines. This does not mean that levels are adequate, only a blood test can indicate that. Other factors may affect calcium levels such as lifestyle, digestion, and age. It is important to consume a balanced diet rich in calcium containing foods.

An outcome of Below Average means there is a risk for having inadequate amounts of calcium in the blood. If levels are low, the body will be more likely to pull calcium from bones, however only a blood test can confirm low levels of calcium. It is important to consume foods rich in calcium. The US Dietary Guidelines for Americans recommend three servings of dairy (excellent sources of calcium), per day to obtain the recommended amount.

Calcium does not build bones efficiently without vitamin D, so it is recommended to include a diet rich in vitamin D foods like fortified dairy and fatty fish.

Limitations and Warnings

Only a blood test can determine actual levels of calcium. It is important to discuss supplementation with a health care provider.

Vitamin C

Overview

Vitamin C is an essential water-soluble vitamin that must be consumed in the diet. Vitamin C might best be known for its association with immune function. It acts as an antioxidant and helps prevent oxidative damage that may contribute to chronic diseases such as atherosclerosis, type 2 diabetes, and cancer. It plays an important role in skin health, helping to synthesize collagen and hormones. Vitamin C in the diet is also important for iron absorption. Severe deficiencies can cause scurvy, a disease characterized by bleeding gums and a reduced rate of healing wounds.

Genes Tested: SLC23A1

A three-part study was designed to research genetic associations of the SLC23A1 gene and circulating vitamin C levels. This large study examined the relationship in a discovery phase, replication phase and meta-analysis to validate findings. The SLC23A1 gene encodes an active vitamin C transporter, SVCT1. It is hypothesized that a variant in the gene affects active transport of vitamin C in the body and is related to lower levels of vitamin C.[49]

Outcomes and Recommendations

An outcome of Normal indicates a likelihood of having normal levels of vitamin C if consuming adequate amounts of vitamin C rich foods. Below Average and Low outcomes indicate a likelihood of having lower levels of vitamin C in the blood even if dietary intake is adequate. This does not mean that blood levels are low, as only a blood test can indicate actual levels. Monitoring intake of vitamin C rich foods may be beneficial. Consuming fresh, raw fruits and vegetables are important because vitamin C may be destroyed by heat and oxygen.

Vitamin C levels are also influenced by lifestyle and environmental factors. Smoking depletes the body's supply of vitamin C and therefore it is crucial to obtain recommended amounts daily.

Limitations and Warnings

The research is limited to a population of European decent. Only a blood test can indicate a deficiency. It is important to discuss supplementation with a health care provider. Caution should be taken given that high doses of vitamin C supplementation may cause gastrointestinal distress.

Iron

Overview

Iron is an essential nutrient responsible for key biological processes in the body. It is often associated with energy because it is a key component of hemoglobin, a part of red blood cells that carry oxygen throughout the body. Adequate iron levels are needed to maintain healthy cells, skin, hair, nails and support the immune system.

Iron balance within the body is tightly regulated. Low iron intake can lead to an iron deficiency or anemia, while too much iron can lead to iron toxicity increasing risk for organ damage, diabetes, heart attack and other conditions. It is important to keep iron intake adequate and follow the recommended dietary guidelines. Many environmental and lifestyle factors influence iron levels including diet, gender and age, as well as genetics.

Genes Tested: TRF2, HFE, TMPRSS6

Several genes can impact the risk for iron status in the blood affecting how the body absorbs, transports and recycles iron. Genome wide association studies have investigated genetic variants that impact serum iron levels. The top two genetic variants were examined in the Women's Health and Aging Study (WHAS) I and II for replication of previous findings. It has been found that the TMPRSS6 gene is essential for normal iron homeostasis in humans.[50] The TMPRSS6 gene was found to have the strongest association with lower serum levels in these studies. It codes for an enzyme that promotes iron absorption and recycling.[51] A genetic variant of TMPRSS6 has an inhibitory effect and is associated with a decreased efficiency in iron absorption.[52] [53] The HFE gene is linked to the regulation of iron uptake in the small intestine. Two variants on the HFE gene have been linked to increased uptake and risk for iron overload.[54] TRF2 is a gene that codes for the protein transferrin which is responsible for transferring iron in the body and variants of this gene may affect iron efficiency.[55]

Outcomes and Recommendations

Reported outcomes are based on the combination of these genes. A result of Normal indicates a likelihood of normal iron status but does not determine actual blood levels. This is also dependent on adequate dietary intake as well as other environmental and lifestyle factors. Eating a healthy diet that includes iron-rich foods such as lean meat, poultry, and fish is important.

An outcome of Above Average does not mean one has iron toxicity. However, iron levels and iron intake should be monitored because of the genetic risk for having blood iron levels at the higher end of the normal range. Focusing on a diet filled with plant-based sources of iron may be beneficial because they are not absorbed as efficiently as animal based sources of protein.

Regardless of outcome, women generally need more iron than men. Those with high levels of physical activity also have increased needs. A vegan or vegetarian diet may not provide adequate iron levels because plant-based foods contain non-heme iron which is harder for the body to absorb than animal based foods containing heme iron. You can boost your iron absorption from plant-based foods by pairing them with vitamin C rich foods. Vitamin C can nearly triple plant-based iron absorption. Avoiding foods that may block iron absorption such as tea, coffee, and red wine is also recommended if iron intake is of concern.

Limitations and Warnings

Results do not determine actual blood levels of iron. Only a blood test can determine actual ranges of iron. It is important to discuss supplementation with a health care provider.

Vitamin B6

Overview

Vitamin B6, also known as pyridoxine, is a water-soluble vitamin that plays an important role in nerve cell function, energy metabolism, and the production of hormones. In the United States, deficiency is rare because most people consume adequate amount in their diets. However, genetic variants are associated with blood levels of vitamin B6. Deficiencies of the vitamin may increase the production of an amino acid homocysteine which is an independent risk factor for heart disease.

Genes Tested: NBPF3

The NBPF3 gene has been found in multiple genome-wide association studies to predict differences in vitamin B levels in the blood. The exact function of this gene is not fully understood.[46]

Outcomes and Recommendations

Regardless of genetic profile, a diet rich in vitamin B6 should be consumed. Predictors of this gene produce outcomes of Normal, Below Average and Low. A genetic response of Normal indicates a likelihood of having normal blood levels of vitamin B6 if a well-balanced diet complete with the recommended amount of the nutrient is consumed. A genetic response of Below Average or Low reflects a risk for having lower circulating levels of vitamin B6 in the blood.

These outcomes do not determine actual levels as only a blood test can do that. Consuming adequate amounts of foods rich in vitamin B6 is important regardless of genetic predisposition.

Vitamin B6 rich foods include pistachios, pinto beans, wheat germ, bananas, watermelon, carrots, spinach, peas and avocados.

Limitations and Warnings

Results do not determine actual blood levels of vitamin B6. Only a blood test can determine if a deficiency is present. It is important to discuss supplementation with a health care provider.

Vitamin E

Overview

Vitamin E is a fat soluble vitamin is an antioxidant and has many biological benefits such as protecting the heart and eyes. Vitamin E helps the body make red blood cells and may help prevent some chronic diseases such as cardiovascular disease, diabetes and cancer. It is found in human blood and commonly referred to as alpha-tocopherol. Lower concentrations of vitamin E has been found in overweight and obese individuals due to an association with abdominal fat deposition.[56]

Genes Tested: ZPR1, SCARB1, CYP4F2

Beyond dietary and absorption impacts on vitamin E status, genetics have been associated with a role in the metabolism of this nutrient. Genome-wide association studies show significant relations between genetic markers and serum vitamin E levels. ZPR1 is a gene involved in encoding proteins responsible for vitamin E homeostasis. The SCARB1 gene encodes for a

protein that effects the transfer of vitamin E from good cholesterol (HDL) to tissues and CYP4F2 is a gene that impacts a family of enzymes involved in vitamin E metabolism.[57] [58]

Outcomes and Recommendations

An outcome of normal suggests one is more likely to have adequate levels of vitamin E in the blood. However, it is important that a balanced diet is consumed including optimal amounts of vitamin E rich foods. The Recommended Dietary Allowance (RDA) for vitamin E in adults is 15 milligrams. It is important to consume some healthy fat with vitamin E rich foods to optimize absorption.

An outcome of above average or well above average does not mean a decrease in vitamin E rich foods is recommended. These outcomes indicate a genetic predisposition that may provide a health boost due to vitamin E's beneficial antioxidant properties. Responsiveness of vitamin E supplementation is increased and does come with some risks. It is important to focus on food sources of vitamin E as part of a well-balanced diet.

Eating whole grain foods, nuts, seeds, and cooked green leafy veggies are good sources of vitamin E.

Limitations and Warnings

Results do not determine actual blood levels of vitamin E. Only a blood test can determine if a deficiency is present. There are a limited number of foods that are rich in vitamin E. Supplementation has shown to have both benefits and risks. Therefore, it is best to consume vitamin E through food sources and important to discuss supplementation with a health care provider. It's also important to understand that diseases or conditions that affect fat absorption may lead to vitamin E deficiencies.

Vitamin A

Overview

Vitamin A is a fat-soluble vitamin that is naturally found in many foods. This vitamin promotes good vision, is involved in protein synthesis that affects skin and cell tissue, and helps to support reproduction and growth. It is also critical for immune system function and the regulation of gene expression. Vitamin A is found in plant foods as its precursor form, beta-carotene. Beta-carotene is then converted in the body into active forms of Vitamin A, as needed. The active forms are known as retinol, retinal, and retinoic acid.[59]

Deficiencies in micronutrients may affect functions in the body involved in regulating body weight. Low concentrations of serum retinol have been found in overweight and obese individuals.[60]

Genes Tested: BCM01

The BCMO1 gene encodes an enzyme that converts beta-carotene to retinal, which is a precursor of vitamin A. In a preliminary study that showed statistical significance, two common variants in the BCMO1 gene were identified as having a probability of reduced activity to code for the enzyme needed for conversion.[61]

Outcomes & Recommendations

Genetic risk outcomes may be Normal, Below Average, or Low. This suggests one's ability to convert beta-carotene into an active form of vitamin A may be unlikely to be reduced or more likely to be reduced based on their genotype.

Normal genotypes do not possess the allele combination that shows a diminished response to converting high doses of beta-carotene from a supplement into its active form within the body.

Having a genotype for a risk of Below Average or Low suggests less beta-carotene in supplement form is converted into the active form. The research suggests that even when taking high doses of a beta-carotene supplement the ability to convert the nutrient into an active form of vitamin A may be reduced.[59]

A balanced, healthy diet should include rich sources of beta-carotene. Some foods rich in vitamin A are broccoli, dark leafy greens, carrots, butternut squash, sweet potato, and cantaloupe.

Limitations & Warnings

A result of normal or low does not indicate an actual low level of vitamin A in the body. The outcome reports on a predisposition to have lower levels of vitamin A due to diminished enzyme activity. Only a blood test can determine actual levels. Food recommendations are made to optimize intake of vitamin A and should be modified based on other factors. Caution should be taken with supplementation to not exceed recommended levels as toxicity can occur since vitamin A is fat-soluble. It is recommended to always discuss supplementation with a health care provider.

Zinc

Overview

Zinc is an essential mineral that plays a key role in immune function, protein synthesis, wound healing, insulin function, reproduction, thyroid function, blood clotting, growth, taste, vision and smell. It is the second most common mineral in the body and is found in every cell. The body does not store zinc making it essential to consume in the diet. The recommended dietary allowance (RDA) for adults is 8 milligrams for women and 11 milligrams for men.

Zinc deficiency may hinder immunity and has been linked to cardiovascular disease and diabetes. Literature also suggests a relationship between zinc and obesity and inflammation. Analysis of the National Health and Nutrition Examination Survey (NHANES) found that 35-45% of adults over the age of 60 had zinc intakes below the recommended RDA.[62] At risk populations include the elderly, those experiencing food insufficiency, vegetarians, and vegans. Red meat and poultry provide the majority of zinc in the American diet as zinc from plant sources is harder to absorb.

Genes Tested: CA1, PPCDC, LINC01420

CA1 is a gene that codes for carbonic anhydrases. Carbonic anhydrases are zinc containing enzymes that account for nearly all the zinc in our cells. Changes in expression of CA1 may be associated with zinc concentrations. PPCDC may affect zinc status through changes in vitamin B5 metabolism. An analysis of over 12,000 adults reported that genetic variations accounted for 8% of the variations in our blood levels. These variations may affect absorption, distribution and/or excretion of zinc.[63]

Outcomes and Recommendations

Combinations of genes may produce an outcome of Normal, Below Average, and Above Average. These outcomes relate to zinc levels in the blood.

A genetic profile with a Normal status does not mean one's diet includes adequate amounts of zinc for your blood levels to be optimal. Normal status suggests that if one is meeting the RDA for zinc through diet, blood levels should be within the optimal range.

Those with a risk of Below Average are suggested to increase the amount of foods rich in zinc to ensure they meet the RDA.

An Above Average outcome does not indicate a need for reducing zinc intake in the diet. If one continues to eat a balanced diet rich in zinc containing foods the likelihood of maintaining optimal blood levels of zinc are genetically favored.

Limitations and Warnings

It is important for vegetarians and vegans to be mindful of their zinc intake as plant sources containing zinc are harder for the body to absorb. Meat and shellfish are the best sources of zinc and the most bioavailable. Only a blood test can determine zinc levels in the body. Caution should be taken with supplementation as over consumption can lead to toxicity. It is recommended to always discuss supplementation with a doctor.

Magnesium

Overview

Magnesium is a mineral that plays a critical role in blood sugar control, muscle contractions and heart rhythm. It is also required for energy production, bone development, the synthesis of DNA, and to make the antioxidant, glutathione.[64] This important mineral is involved in more than three hundred biochemical reactions in your body. Low serum magnesium levels are associated with chronic diseases such as diabetes, hypertension and osteoporosis. NHANES reports that at least half the US population has inadequate magnesium intake. Lifestyle, environment and genetics can impact magnesium levels.[65]

Genes Tested: MUC1, ATP2B1, DCDC5, TRPM6, SHROOM3, MDS1

The MUC1 gene assists in formation of the mucosal barrier in the intestine and changes in gene expression may affect absorption of magnesium. The TRPM6 gene is involved in magnesium transportation that affects active magnesium absorption and reabsorption. ATP2B1 gene is responsible for the removal of calcium ions from cells and may be dependent on magnesium intake and has previously been identified in genome-wide association study as a factor affecting

blood pressure. SHROOM3, DCDC5, and MDS1 are genes that have been identified in genome-wide association studies for having a correlation with serum magnesium even after adjusting for differences in kidney function. It is estimated that serum magnesium concentrations are about 27% heritable.[66]

An additional genome-wide association study conducted in the African-American population showed three of the six loci were associated with serum magnesium levels. The effects of genetic associations were even more pronounced in post-menopausal women using progestin and people with lower fasting insulin levels.[67]

Outcomes and Recommendations

A combination of alleles within the six genes referenced produce predictor outcomes of Normal, Below Average and Above Average serum magnesium levels.

It is recommended regardless of genetic predisposition to eat a diet with a variety of magnesium rich foods. These include nuts, fatty fish, yogurt, beans, whole grains, dark leafy greens and pumpkin seeds.

Even with an Above Average outcome predicting higher levels of efficiency, environmental factors may affect magnesium levels. Magnesium absorption also decreases with age. Intake of coffee, soda and alcohol are also linked to low magnesium levels.

Predictors of Below Average absorption may warrant supplementation if recommended by a health care provider.

Limitations and Warnings

A genetic risk of low magnesium levels does not mean a deficiency is present as only a blood test can determine actual levels in the body. It is important to discuss supplementation with a health care provider.

Folate

Overview

Folate is a water-soluble B vitamin with important roles in the body including DNA creation, repair, cell growth, development and energy metabolism. Low levels of folate have been associated with the risk for neural tube defects in infants. Folate also plays a role in biochemical processes that affect the metabolism of an amino acid, homocysteine and has implications on many diseases including congenital birth defects, neurodegenerative, osteoporosis and cancer. The amount of folate the body can absorb differs between individuals. Beyond environmental factors, absorption of dietary folate is shown to have a genetic link.

Genes Tested: MTHFR

MTHFR gene produces an enzyme needed for folate absorption and usage in the body. It converts folate to an active form needed for biological processes. The C677T variant in the MTHFR gene has been associated with folate or vitamin B9 status by changing enzyme activity. This may lead to reduced levels within the body and a risk of folate deficiency. Folate deficiency is a concern because of its vital role in many biological processes and can lead to higher levels of homocysteine which is a risk factor for heart disease.

NHANES showed an association with lowered serum folate levels in a study that included 6,000 Hispanic, African, and Caucasian Americans. In studies on the MTHFR gene, people who carried the most unfavorable pairs of alleles had only 10-20% efficiency at processing dietary folate, while those with a below average allele had a 60% efficiency.[68] [69]

Outcomes and Recommendations

Regardless of genetic profile, a diet rich in folate should be consumed. Adequate and increased dietary folate has been shown to have an impact on reducing the negative effects of this genetic variant. Women of child bearing age should focus on folate intake due to its correlation with neural tube defects and other congenital birth defects and supplementation of folic acid is recommended. If one does not eat a diet rich in whole grains, vegetables and fruits, blood levels may be low regardless of a favorable genotype.

Predictors of this gene produce outcomes of normal, below average, and lower levels of efficiency. Those with an outcome of lower may process folate at 10% to 20% efficiency while those with an outcome of below average may process folate at 60% efficiency. These differences in efficiency may warrant increased intake of folate in the diet. Excellent sources of folate-rich foods include lentils, pinto beans, asparagus, and broccoli.

Limitations and Warnings

Poor ability to process folate has been estimated in 53% of women and increases risk of high homocysteine and low vitamin B12 levels. If one has a below average or low genetic risk score outcome it may be beneficial to have vitamin B12, homocysteine, and folate levels tested by a doctor. Other factors including environment, lifestyle, and age can have an impact on folate levels in the body. Smoking can decrease folate levels as well as the ability to digest and absorb nutrients in the digestive tract.

5. Adherence to Programs and Lifestyle Change

Genetic testing and Diet Adherence

In recent years it has been recognized that “one size does not fit all” in terms of the optimal diet for weight loss. Further adding to this view, an expert panel in obesity and weight management that was convened in 2013 concluded that strong evidence exists to support a variety of dietary approaches to achieve clinically significant weight loss results, given the diet is providing an energy deficit and it part of a comprehensive lifestyle intervention.[70]

While many dietary approaches hold promise for weight loss, it will be the dietary approach that one can adhere to over the long term to help maintain weight loss that will be optimal for the individual. Adding a level of personalization to a diet plan through recommendations based on an individual’s genetic variation may support engagement and enhance adherence over time lending to healthier lifestyle behaviors for weight management. Consumers perceive genomics-based dietary advice to be easier to understand compared to general population-based recommendations and report that they are more motivated to make dietary changes if recommendation are personalized to their genetics.[71] Further studies have shown that diet and lifestyle recommendations based on one’s own genetic profile have the potential to enhance

weight loss programs through greater program engagement and adoption of healthy lifestyle behaviors compared to individuals receiving a standard "one-size-fits-all" approach.[72] [73] [74]

However, it is naïve to think that provision of genetic information alone will result in enhanced engagement and the motivation necessary for behavior change and subsequent weight loss. Provision of genetic information alone has been shown to enhance an individual's readiness to change; however, little, if any, actual behavior changes were adopted.[75] An National Institutes of Health (NIH) Working Group reported that the ability to communicate a personalized strategy that motivates behavior change will be a necessity of genomic interventions seeking to support successful weight loss.[76] Controlled studies have supported this statement, demonstrating that the use of higher-quality genetic interventions that provide actionable recommendations informed by genetic testing have led to changes in lifestyle and nutrition behaviors both in the short and long-term.[73] The scientific-evidence to date indicates that the overall quality of a genomics-based weight loss intervention, not just provision of genetic information, will determine how successful the intervention will be in enhancing engagement, motivation, and ultimately adherence to sustained behavior changes that support weight management.

While studies have shown positive effects associated with genomics-based interventions and behavior change, it is worth noting that others have shown little to no effect on changes in behavior or weight outcomes in participants randomized to a genomics-based intervention compared to control interventions.[76] However, there are often limitations to these studies, in that these studies typically provide genetic information, yet fail to connect participants to personalized weight loss strategies, but rather deliver uniform interventions such as the evidence-based Diabetes Prevention Program (DPP) to both the intervention and control groups.[76] As recommended by the NIH Working Group, to advance the field of personalized weight loss, interventions must provide an individuals' genetic information along with dietary and lifestyle recommendations that are targeted to the individual based on their genetic information.[76]

The latest evidence-base around diet-related genes and health and weight outcomes, has allowed Nutrisystem® to apply a personalized approach to the clinically-tested Nutrisystem® weight loss program. Evidence supports that a personalized approach to weight loss can help to further enhance customer engagement and adherence to a healthier lifestyle, which will serve to optimize the Nutrisystem® program for each customer.

6. Nutrisystem's Clinically Tested Program

Nutrisystem's Clinically Tested Program

The Nutrisystem® program has relied upon the latest scientific evidence for weight management to design a weight loss program that is safe and effective. The foundation of the Nutrisystem® program is the provision of single-serving, portion-controlled meals and snacks. These portion-controlled foods, in combination with fresh grocery food add-ins, allow consumers to adopt a reduced calorie, high protein, and high fiber meal plan to support their weight loss efforts. Below is a summary of the evidence to support a portion-controlled, high protein, high fiber approach for weight loss, consistent with the Nutrisystem® program.

Portion Control and Weight Management

It has long been recognized in the scientific literature that provision of portion-controlled foods as a dietary intervention for weight loss is a more effective approach compared to conventional diets.[77] [78] In 2016, the culmination of the vast scientific literature in support of portion control for weight management led to the Academy of Nutrition and Dietetics recommendation that strong evidence exists for the use of portion-control and meal replacements or structured meal plans as part of a comprehensive weight-management program.[79]

While the acute effects that portion size has on food consumption has been well established in the scientific literature for some time, the effect that smaller portion sizes has on future food consumption is just now starting to be investigated. Recent studies in this area of portion control have shown that reducing the portion size of a food may "normalize" appropriate portion sizes and shift people to selecting and consuming smaller portions of similar foods in the future.[80]

With the ever-increasing portion sizes of meal occasions, both in and outside of the home, now more than ever it is important for those seeking to lose and manage their weight to be mindful of their portion sizes. Programs like Nutrisystem not only have the ability to reduce energy intake in the short-term through the provision of single-serving, portion-controlled foods, but over time can support changing consumers' perceptions of "normal" amounts of foods, helping to sustain their intake of appropriate portion sizes for weight management beyond their time on the Nutrisystem® program.

Protein and Weight Loss

Weight lost through an energy-restricted diet is often a result of both fat mass and fat-free mass (primarily as water and skeletal muscle). Over several decades, a common rule has stated that approximately one-quarter of the weight lost through energy restriction will be from fat-free mass; however, recent review of this dogma determined that a variety of factors will affect the actual proportion of weight lost as fat-free mass, one of those factors being dietary composition.[81]

The macronutrient profile of the diet is actively studied in weight loss research to identify the effects protein, carbohydrates and fats play on weight loss outcomes, including the effects these macronutrients have on changes in body composition. Protein intake has been proven to affect body composition changes associated with weight loss, by favoring fat loss and mitigating the loss of lean muscle mass.[82] [83] A 2012 meta-analysis compared energy-restricted, isocaloric, low-fat, high-protein diets with standard-protein, low-fat diets on weight loss, body composition, and resting energy expenditure, satiety and appetite, and cardiometabolic risk factors.[84] This review concluded that a low-fat, high-protein diet (< 30% energy from fat and 25 – 35% energy from protein) increases fat mass loss and mitigates the reductions in fat-free mass compared to low-fat, standard protein diets (< 30% energy from fat and 12 – 18% energy from protein).[84] In addition to the favorable outcomes associated with weight loss and body composition, both greater satiety and mitigation of the reduced resting energy expenditure that is often experienced due to weight loss were observed.[84] This analysis further adds evidence to earlier reviews concluding that higher protein compared to lower protein intake is associated with increases in satiety and thermogenesis, both factors that play an important role in supporting weight loss during an energy restricted diet.[85]

Protein is an important dietary component of the Nutrisystem® program, which is designed to deliver at least 25% of calories from protein. Based on the evidence that supports energy restricted, high protein diets for weight loss, the reduced-calorie, low-fat, high protein approach to the Nutrisystem® program helps support weight loss, while mitigating the reduction of lean muscle mass over time.

Fiber and Weight Loss

The fiber content of diet has been associated with weight management, with cohort studies observing that individuals consuming a high fiber diet weigh less compared to those consuming diets lower in fiber.[86] Controlled clinical trials on the effects of fiber on satiety and body weight have concluded mixed results. Both acute and long-term studies have demonstrated that fiber intake can have a significant effect on satiety and subsequent energy intake, both important factors for weight loss.[87] [88] One review on the effects of dietary fiber on hunger, satiety, energy intake, and body composition in healthy individuals reported that the addition of 14 grams fiber per day for more than 2 days was associated with a 10% decrease in energy intake and a weight loss of 4.18 pounds over 3.8 months, with individuals with obesity showing even greater reductions of energy intake and weight loss.[89] The changes in energy intake and body weight were observed both when the fiber came from naturally high fiber foods or from fiber supplements.[89] However, a 2013 meta-analysis assessing short-term fiber intake on satiety and food intake concluded that most isolated fibers do not induce satiety or reduce energy intake, resulting in the Academy of Nutrition and Dietetics position that additional long-term studies examining the impact of diets high in fiber on body weight are needed.[86]

While the scientific community continues to examine the role dietary fiber plays in energy intake and weight loss, the impact fiber has on overall health outcomes is well-established; yet, the standard American Diet often falls short in adequate intakes of dietary fiber.[86] The Nutrisystem® program is designed to deliver a minimum of 25 grams of fiber per day, exceeding the adequate intake recommendation from the Dietary Guidelines of 14 grams of fiber per 1,000 calories consumed.

Nutrisystem® Clinical Research

While the Nutrisystem® program is backed by the scientific evidence referenced above supporting a reduced calorie, portion-controlled, high protein, high fiber approach for weight loss, it is also critical to ensure the efficacy of the Nutrisystem® program for weight loss. As a leader in the health and wellness industry, Nutrisystem partners with academic institutions and independent third-party clinical research organizations to support clinical research that ensures the safety and efficacy of ours weight management programs.

The 2013 AHA/ACC/TOS Guidelines for the Management of Overweight and Obesity in Adults recommends that weight loss programs deliver a realistic and meaningful weight loss of 5% to 10% of initial body weight in the first 6 months, citing that this magnitude of weight loss may lead to clinically meaningful reductions in chronic disease risk factors.[90] A peer-reviewed study concluded that more participants on the Nutrisystem® program lost ≥ 5% of initial body weight in 16-weeks compared to participants on a do-it-yourself control diet (57.9% vs. 13.2%, p <

0.001).[91] Additionally, in an unpublished study, participants following the Nutrisystem® portion-controlled, structured program led to statistically significant decreases in body weight over a 4-week period (5.6% of initial body weight) relative to a self-directed Dietary Approaches to Stop Hypertension (DASH) diet (3.1% of initial body weight) in generally healthy overweight and obese men and women.

7. Discussion

Nutrisystem provides evidence-based health and wellness and weight management products for millions of customers. Consumer interest and popularity in genetic testing has rapidly grown and we believe consumers will benefit from a more personalized approach through genetic based recommendations. Our commitment to improve the science of weight loss is continually evolving and we strive to proactively refine our products and services as the scientific and technological landscapes advance. Nutrisystem seeks to develop partnerships with companies that equally value the efficacy, privacy and scientific advancement of the field of nutrigenetics and genetic testing technology to maintain Nutrisystem's leadership position in the space. These commitments reflect a culture of innovation to more rapidly accelerate and continually provide our customers with safe and effective health and wellness solutions. This personalized, holistic approach to weight management combined with the clinically-tested Nutrisystem program is only the first step in a commitment to innovate in the personalized nutrition space.

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