The Mediterranean lifestyle has traditionally been associated with a healthier life pattern, less prone to chronic illnesses, especially cardiovascular diseases. Among the different lifestyle variables, the concept of the Mediterranean diet (MedDiet) stands out as the healthiest aspect of the Mediterranean lifestyle. Moreover, although big differences in diet can be observed between the various countries on the Mediterranean coast, the Mediterranean lifestyle is also characterized by greater physical activity, mainly consisting of frequent walks encouraged by the warm and pleasant climate in comparison to central and northern Europe. So-called social support is also greater in the Mediterranean lifestyle with a closer and stronger family network and friends proving to be beneficial for health. However, there is great controversy about the Mediterranean siesta, mealtimes and sleep patterns. With regard to the MedDiet and despite the heterogeneity in the MedDiet definition, there is a commonly recognized pattern of consumption characterized by: a) high consumption of vegetables, fruits, cereals, legumes, nuts, and olive oil; b) moderate to high fish consumption; c) low consumption of red meats, and meat products; d) poultry and dairy products in moderate to small amounts and. There also seems to be a pattern of alcoholic and alcohol-free beverage consumption that varies depending on age. Environmental factors mainly contribute to this Mediterranean lifestyle, although genetic influences also interact. It is known that there are genetic variants that are associated with the intake of certain foodstuffs and among them the most relevant gene is the lactase gene (LCT) and its association with milk consumption. Thus, single nucleotide polymorphisms (SNPs) in the minichromosome maintenance complex component 6 (MCM6) gene are associated with differential transcriptional activation of the promoter of the neighboring lactase (LCT) gene and, thereby, influence lactase persistence (LP) in adulthood. The rs4988235 SNP, located at -13910 bp upstream from the LCT gene (-13910C>T) within intron 13 of the MCM6, has been the most studied SNP in relation to LP, milk intake and obesity-related diseases. Curiously, there is a north/south gradient in the prevalence of this gene variant, LP being less prevalent in the Mediterranean countries. Fruit, vegetable, sweets, sugared drinks, bitter drinks, etc. have been associated with variations in the different genes related to taste perception. There is increasingly detailed knowledge on the genes associated with the perception of sweet, bitter, sour, umami and salty tastes and their association with both food consumption, and the different health/disease phenotypes are being investigated. We have found associations between the perception of different tastes and the degree of adherence to the MedDiet. Moreover, diet itself may explain why certain gene variants are more prevalent in some countries than in others, as in the case of mutations in the MTHFR gene, which are more prevalent in Mediterranean countries than in northern Europe. In contrast, mutations in the APOE (E4 allele) are more frequent in northern Europe than in Mediterranean countries. To better understand these gene-diet interactions and their impact on the intermediate and final phenotypes of cardiovascular disease, we shall review several results from the PREDIMED (PREvención con DIeta MEDiterránea) study. We have detected interesting gene-diet interactions in which greater adherence to the MedDiet, or to some of its typical foods, is able to reverse the adverse effects that the risk alleles have on the specific phenotypes. Although in nutrigenetics, the interactions of SNP candidates with total liquid intake in the diet are less well known and difficult to study, there are classic examples in monogenic diseases that point to their importance. Outstanding among these examples is that of cystinuria, an autosomal recessive genetic disorder characterized by an impairment in the transport of cystine, ornithine, lysine, and arginine. Of these, only cystine is insoluble enough to cause stone formation. It can lead to significant morbidity in affected patients due to the often large and recurrent resulting kidney stones. Incidence of cystinuria in the Spanish Mediterranean population is high and has a specific genetic pattern. Mutations in the amino acid exchanger System b(0,+) are encoded by SLC5A1 and SLC7A9, predominantly underlie this disease. Our group showed a low prevalence of mutations in the SLC5A1 gene and a higher prevalence of mutations in the SLC7A9 gene, in contrast to that found in other countries. However, the wide variation of phenotypical traits suggests that further investigation into other genetic and/
or environmental factors should be carried out. Among the environmental factors, increased fluid intake and urine alkalinization are the most successful preventive recommendations. Cystinuria is not very frequent, but there are other genetic alterations that may result in stone formation and consequently nephrolithiasis, both of which can be improved with greater hydration. Likewise, some interactions between genes associated with vasopressin and liquid intake on blood pressure and other phenotypes of cardiovascular risk are becoming known.

Key words: Mediterranean, lifestyle, genetics, gene-diet interactions, cardiovascular.

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Water is life: an evolutionary perspective of hydration-related gene-environment interactions


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Since the time that archaic species left the water to live on land, the essential evolutionary demand was to provide the organism’s cells with an aqueous environment similar to the one that was left behind in the oceans. The importance of proper hydration continues to be manifested in modern humans that can survive weeks without food but only a few days without water. It was in 2004 when the Food and Nutrition Board at the Institute of Medicine of the National Academies released the Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate Report. In this report, we find a brief but comprehensive description about the importance of appropriate hydration to maintain health: “The largest single constituent of the human body, water, is essential for cellular homeostasis and life. It provides the solvent for biochemical reactions, is the medium for material transport, and has unique physical properties (high specific heat) to absorb metabolic heat. Water is essential to maintain vascular volume, to support the supply of nutrients to tissues, and to remove waste via the cardiovascular system and renal and hepatic clearance. Body water deficits challenge the ability of the body to maintain homeostasis during perturbations (e.g., sickness, physical exercise, or climatic stress) and can impact functions and health. Total water intake includes drinking water, water in other beverages, and water in food.” However, despite the paramount role of hydration we don’t have well-defined and soundly supported figures regarding daily water requirements for the general population. This is partially due to the many factors involved in defining the individual’s needs (i.e., age, sex, dietary habits, physical activity, climate, seasonality and geographical and cultural environment) and related mechanisms (i.e., thirst, genetic background).

Apart from the hydration-related functions outlined above, a major driver through human evolution has been the correct maintenance of osmolality and vascular volume in changing environments. This is prior to the out-of-Africa dispersion (included the initial hot and humid forest, followed by the hot and dry savannah) where members of the homo genus survived and thrived thanks to a highly efficient heat dissipation mechanism, achieved through evaporative heat loss (sweat). However, sweating leads to loss of water and salt, which triggers thirst, salt appetite and renal sodium conservation, essential for survival in that ancestral environment. The downside of this evolutionary adaptation is the current prevalence of hypertension and other common diseases, characteristic of the modern society exposed to such different environmental and behavioral conditions.

Despite the relevance of hydration in relation to human evolution, metabolic homeostasis and its potential involvement in most common chronic diseases, the field of gene-environment interactions and more specifically, the area of nutrigenetics, has focused exclusively on gene-(solid)nutrient interactions, with a blatant absence of gene-hydration interactions. Withstanding the fuzziness involved in collecting drinking information and the lack of practical biomarkers of hydration status, there is enough evidence to support that individuals in the general population can maintain homeostasis, and apparently good health, with reported water intakes that differ as much as one order of magnitude (i.e., between 400 and 4000 ml/day). This suggests different individual needs and susceptibilities (i.e., perspiration, urination or thirst) that could have a significant genetic component. For example, it is known that subjects in northern latitudes sweat more under similar environmental conditions than people in the tropics. Moreover, it is also known that the susceptibility to hypertension in blacks leaving in the US is higher than in US whites. Whereas no genome wide association studies have been reported related to hydration factors (i.e., thirst, water intake and water loss), there are a number of alleles at candidate genes related to blood pressure, renal function and arterial and cardiac contractility that were potentially advantageous in our ancestral African habitat.