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Confounding risk factors and preventative measures driving nephrolithiasis global makeup

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Abstract

Nephrolithiasis is increasing in developed and developing countries at an alarming rate. With the global spike in kidney stone diseases, it is crucial to determine what risk factors are influencing the current global landscape for kidney stones. Our aims for this review are: to identify and analyze the four categories of risk factors in contributing to the global scale of stone formation: lifestyle, genetics, diet, and environment; and discuss preventative measures for kidney stone formation. We also performed data search through the published scientific literature, *i.e.*, PubMed® and found that there is a significant link between lifestyle and obesity with cases of calcium stones. Food and Agriculture Organization of the United Nations and World Health Organization factor indicators for dietary intake and obesity, along with climate data were used to create the projected total risk world map model for nephrolithiasis risk. Complete global analyses of nephrolithiasis deplete of generalizations is nearly insurmountable due to limited sources of medical and demographic information, but we hope this review can provide further elucidation into confounding risk factors and preventative measures for global nephrolithiasis analysis.

Key words: Nephrolithiasis; Epidemiology; Risk factors; Global factors

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Core tip: We analyzed diet, lifestyle, genetics, and environment, four categorical risk factors that play major roles in the contribution of nephrolithiasis. Calcium stones and lifestyle factor obesity had a significant link; dietary factor of high protein and low intake of negative regulators increased the risk; and environmental factor of climate had a relatively high correlation to nephrolithiasis. Together, a model was formed to map a prevalence of nephrolithiasis of the world.

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INTRODUCTION

Kidney diseases affect hundreds of millions of people globally. The number of people affected by the disease continue to grow by each year, with 200 million people affected worldwide according to current estimations by the World Health Organization (WHO)^[1]. One of the most common forms of debilitating kidney disease is the formation of kidney stones known as nephrolithiasis. Kidney stones are an aggregation of crystalline structures that build up in the nephrons of the kidney. These crystalline structures impair the normal functioning of the kidney and often require costly interventions such as pharmacological treatment, laser and radio bombardment, and surgical interventions (if severe). Earlier, diseases like kidney stones had been restricted to developed countries; however, over the past decade there has been a global spread of chronic non-communicable diseases. As such, nephrolithiasis is on the rise in developed and developing countries at an alarming rate. With this global spike in kidney stone diseases, it is incredibly important to determine what risk factors are influencing the current global landscape for kidney stones. By understanding the root causes for the increase in prevalence of kidney stones, we can develop health interventions and recommendations to curb nephrolithiasis' global burden of disease.

Significant key risk factors that play the greatest role in kidney stone formation can be divided into 4 major categories: Dietary, genetic, environmental, and lifestyle. The main aim and scope of this study is to update the current knowledge on global prevalence, incidence, and risk of kidney stones. We have performed an extensive literature search to understand the development of the four different kidney stone types: Calcium (calcium oxalate and calcium phosphate), uric acid, struvite (magnesium ammonium phosphate), and cysteine. Throughout this literature search, we focused on our causes of stone formation to make a list of risk factors that play the largest role in the development of stones. Understanding these risk factors will allow us to create

a geographical model to map national and global areas of risk for kidney stones. Food and Agriculture Organization Corporate Statistical Database (FAOSTAT) and WHO data has been used to project the world map for nephrolithiasis.

There are 4 different types of kidney stones: Calcium stones, uric acid stones, struvite stones, and cysteine stones. These stones are comprised of different materials and have different causes. Calcium stones are the most common type of stone in most countries. Calcium phosphate stones are less common and are comprised of calcium and phosphate aggregation; however, these stones do account for a large percent of the economic burden because they are very difficult to treat^[2]. Brushite stones are an aggregation of calcium monohydrate phosphate, a slightly modified form of calcium phosphate. Precipitation of these crystals occurs at a lower urinary concentration level than normal calcium phosphate crystals, and once stones start to form, they become very difficult to treat due to the strength of ionic bonds. Calcium oxalate stones, the more common calcium stones, are comprised of oxalate calcium salts. Together, these account for 75%-80% of global stone prevalence in most countries^[3]. Uric acid stones are the third most common type of stone in the globe. They are the result of having supersaturated urea which can be caused by a multitude of factors. In addition, uric acid concentrations and aggregation also stimulates the crystallization of calcium oxalate *via* deposition of a crystalline overlay on a crystalline substrate^[4]. The uric acid crystal serves as a base allowing the formation of other stones based on the ionic make-up of the surrounding urine. The fourth most common type, struvite stones, are a result of bacterial imbalances which cause elevated levels of ammonia, decreased phosphate solubility, and carbonate imbalance in the body. All of which lead to precipitation of these phosphate rich struvite salts^[3]. Cysteine stones are the last type of stone. They are globally rare because they are a direct result of a genetic mutation that causes malabsorption in the renal tubal^[3].

LIFESTYLE

Age, race, demographic

Nephrolithiasis is a long-term disease that develops over time and is usually found much later in a patient's life. While people of young ages are not immune to or free from the development of kidney stones, ranging from ages 18 to 95, this disease is most commonly found in individuals 43 and older, with the highest incidence rate in people among ages 40 to 65^[5]. Additionally, stone development is more commonly found in male patients than female patients. A study focusing on the prevalence of stone development in the United States places the difference between men and women as high as 2 times^[6]; however, this is rapidly changing. Females ages 40 and older are now seeing a rise in stone development that has placed them much closer the incidence of men^[7].

Table 1 Summary of confounding risk factors (diet intake, obesity, and environment) for each country

Country	Diet ^[15]	Obesity ^[16]	Climate
United States	High in sugar and meat	Highly obese (30%-40%)	Varies, Southern states tend to have on average warmer temperatures than the north; though the eastern states tend to have more tropic conditions ^[17]
Scotland	High in sugar and meat	Highly obese (27.7%)	Temperate ^[18]
British Isles	High in sugar and meat	Highly obese (14%-27.7%)	Mild winter, warm summers
Australia	High in sugar, meat, and dairy	Highly obese (20%-30%)	Warmer climates
Malayan Peninsula	High in meat and fish	Moderate obesity (16.3%)	Equatorial climate
Spain	Moderate in sugar	Moderate obesity (15.6%)	Mediterranean climate ^[19]
	High in meat		
Germany	Very high in sugar	Moderate obesity (12.9%)	Temperate
Sweden	High in sugar	Moderate obesity (12%)	Very mild climate ^[20]
	Moderate in meat		
Italy	High in caffeine	Moderate obesity (9.8%)	Mediterranean climate
Pakistan	High in meat	Low obesity (3.4%)	Weather is extreme depending on the season
Japan	High in fish	Low obesity (3.1%)	Warm and humid
China	High in fish	Low obesity (2.9%)	Temperate, facing lead epidemic
India	High in meat and fish	Low obesity (0.7%)	Hot, tropical climate

There has been a higher amount of nephrolithiasis incidence in younger women, specifically calcium phosphate stones over the past years; however, the exact cause of increase is not well known^[8]. An explanation could be that women tend to have higher urine pH levels even after controlling for diet, possibly due to a differential rate of absorption of GI anions, which would also explain why they are more prone to calcium phosphate stone formation^[9]. Moreover, it is known that higher urine pH has more influence on the supersaturation of calcium phosphate than the compositions of calcium and phosphate^[10].

All ethnic groups were equally represented in the affected population. This is partly due to the fact that metabolic risk factors for nephrolithiasis seem to have very little variation when looking at differences in ethnic background^[11]. However, a recent cohort questionnaire study of approximately 42000 Southeastern United States white and black adult men and women from 2002-2009 found that, with adjustment for age, white adults had a greater risk for kidney stones compared to black adults with a hazard ratio of 2.23^[12]. When comparing men and women, risk was slightly higher with a hazard ratio of 1.12; however, white men were significantly associated for kidney stone incidence compared to white women with a hazard ratio of 1.45, though the correlation was not significant for men and women among blacks^[12].

Obesity

Obesity is one of the fastest growing epidemics in the world. It is a complex metabolic disorder that leads to serious, long term medical problems like cardiovascular disease, musculoskeletal disorders, and chronic kidney disease (CKD)^[7]. Recent publications have found a direct correlation between patients who are obese, overweight, and have higher body fat percentages to the development of nephrolithiasis^[13]. Calcium stones account for nearly 80% of kidney stone development

globally^[1] and have specifically been linked to obesity. Along with urinary calcium stone, obesity affects the overall excretion levels of uric acid, sodium, calcium, and citrate increasing the risk for developing uric acid stones^[14]. Increases in prevalence of both uric acid stones and calcium stones can be seen in obesity plagued countries over the past 10 years.

Recent estimates suggest that over 34% and 35% of men and women are classified as overweight respectively, and 10% and 14% of men and women are obese in the United States. Recent estimates of obesity rates according to WHO have shown that a majority of nations such as United States, Germany and Sweden were reported to have higher obesity rates than eastern countries. While Eastern countries such as Japan, China, and India were reported to have low prevalence rates of obesity (Table 1).

Childhood obesity rates have been increasing over the years as well. According to the WHO, for in children from age 0-5, the global obesity prevalence rate from 2005 to 2015 is 5.8% to 7.8% and is projected to increase to 9.1% by 2020^[21]. Moreover, a recent population based study which uses Israeli Defense Forces medical records found that the prevalence rate for having a history of nephrolithiasis before reaching 17 years old was 88.6 per 100000, more skewed toward those with BMI > 30 kg/m²^[22].

Through the FAOSTAT and the WHO data, we averaged the two data sets and attributed low, medium, and high obesity rates to each country by whether the percentage of those who are overweight and obese was greater than 30%, and/or by whether the obese population make up 40% of those who are obese and overweight (Figure 1).

Comorbidities

There is a continuing amount of evidence that ascertains co-existing conditions such as hypertension, diabetes, and CKD^[23-27] can increase the risk of kidney

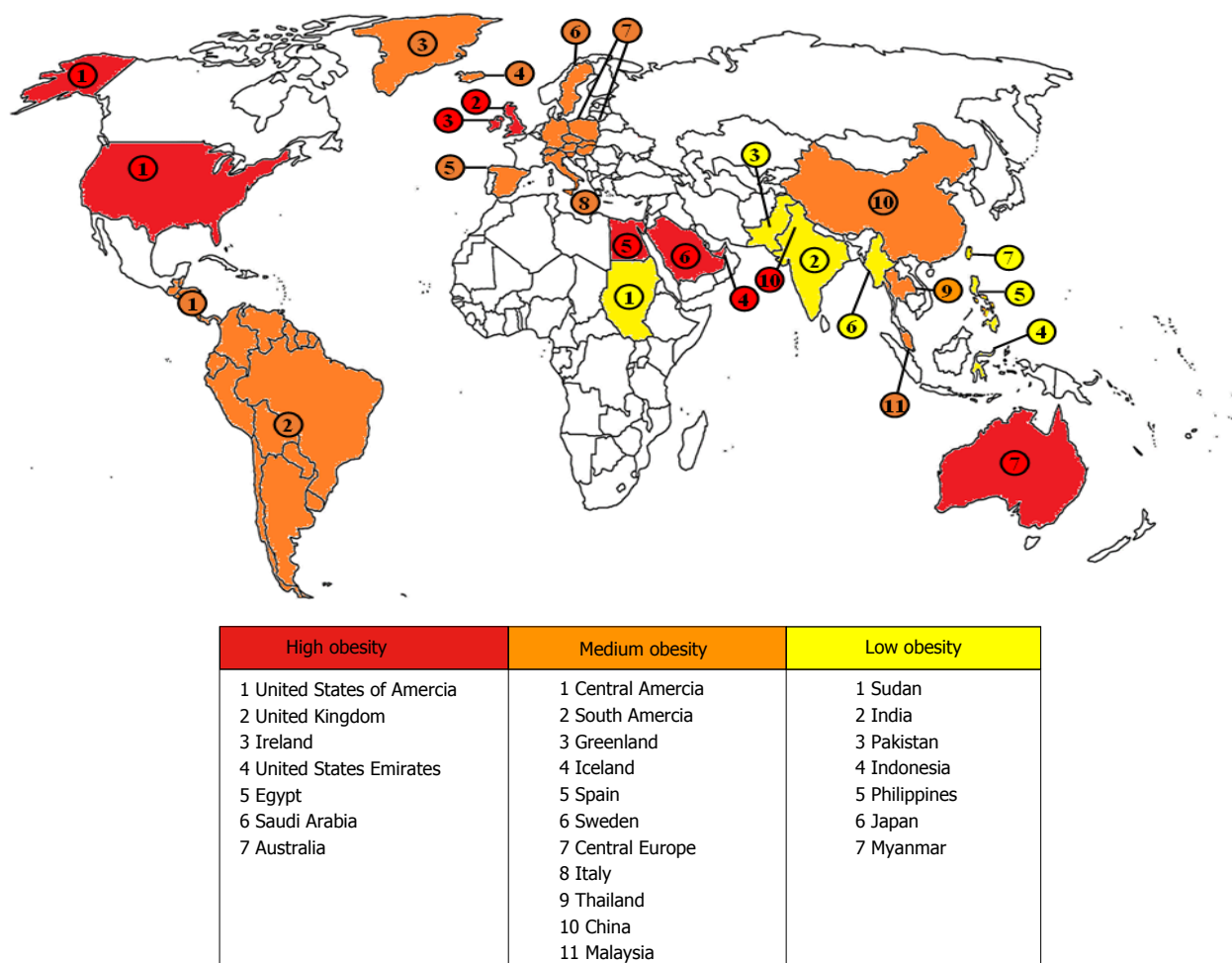


Figure 1 World map projection of obesity prevalence. Red countries are countries with high prevalence of obesity; orange countries have an either a greater than 40% of obese population of obese + overweight population; and yellow countries have lower prevalence of obesity. Obesity defined as measurement of body mass index ≥ 30 . Data retrieved from the Food and Agriculture Organization of the United Nations and the World Health Organization.

stone formation. Not only do these comorbidities force kidney stone formation into a more difficult prognosis, research shows their geographical location may affect their prevalence in comparison to other places in the world.

Type 2 diabetes is another metabolic syndrome that is consistently increasing globally, and with the overall stress that diabetes places on the kidneys, it has become the focus of interest for CKDs. In terms of nephrolithiasis, type 2 diabetes is a very important risk factor because the development of insulin resistance has a drastic effect on ammonia transport and production, altering urine pH significantly^[28]. The changing in urinary pH, as stated earlier, leads to an increase in concentration of uric acid, citrate, and sodium all of which increase uric acid stone formation and calcium stone formation.

Nephrolithiasis can lead to renal damage, which in turn, could lead to hypertension. Kidney stones can plague hypertensive patients disproportionately compared to normotensive individuals. Many patients who are hypertensive were shown to have increased 24-h output urinary Ca^{2+} ^[24]. The high levels of Ca^{2+}

of hypertensive patients put them at risk for possible development of nephrolithiasis. An individual with a history of nephrolithiasis is more likely to develop hypertension; however, whether hypertension increases the risk for nephrolithiasis is not well known^[24]. Hypertension prevalence in the United States and globally can also rise depending on where the person lives.

CKD, an incapacitating disease, affects 7% of those > 30 years old, translating to at least 70 million within developed countries worldwide and number may be higher given the unknown prevalence in underdeveloped countries^[27]. Since CKD is usually asymptomatic and diagnosing would rely on biomarkers which do not clearly differentiate between normal and disease, identifying CKD can be difficult. However, CKD can be an important predictor for cardiovascular related diseases and mortality before ESRD. Nephrolithiasis is a risk factor to CKD, and so patients with kidney stones are recommended to screen for subclinical CKD.

Physical activity

Physical activity frequency and intensity are lifestyle factors that are commonly recommended to treat

kidney stones. Levels of physical activity not only affect the severity of importation metabolic diseases such as obesity and diabetes, but they have a direct impact on the body's physiological waste excretion mechanisms. Physical activity encourages people to increase their water intake while simultaneously increasing the frequency of urine excretion. Both of these factors would likely reduce the risk of nephrolithiasis. A study found that women who had high risk of stone development based on age and weight were less likely to develop nephrolithiasis over time if they had moderate levels of physical activity compared to women with lower levels of physical activity^[29]. Conversely, high levels of physical activity and low levels of fluid intake perform the complete opposite physiological function, by decreasing urine pH and increasing urinary concentration of uric acid, Calcium, and oxalate causing higher rates of nephrolithiasis^[30]. Moreover, a self-reported survey from 1988-2002 states that physical activity within the United States amongst adults have actually increased, despite the increase in obesity rates, though the increase in sedentary lifestyle (automobile travel, less physically demanding occupations, etc.) may explain the discrepancy^[31].

Migration

One factor for nephrolithiasis prevalence that is not well known is migration. Migration can potentially create an artificial trend on the prevalence of nephrolithiasis for a country. According to the United Nations, Department of Economic and Social Affairs, high percentage of international migrants are 30-34 years old of both sexes, skewed toward the lower spectrum of the working ages (20-64), possibly because they would need to be fit enough for labor^[32]. Parks *et al.*^[33] states that the peak age for kidney stones for men is 30 while the women have a bimodal distribution of 35 and 55. While this may suggest that the risk of kidney stones overall for the countries receiving the migrants, various ethnical or cultural factors may play a role which may affect the risk differently. Meanwhile, it is not known as to whether the aging immigrant population would affect the prevalence of nephrolithiasis within a country.

DIET

Micronutrient consumption

The most important, overlooked risk factor for nephrolithiasis is the overall quality of a patient's diet. Dietary influences on the rates of nephrolithiasis have been well documented. There are 3 essential micronutrients that are required for the development of kidney stones: Sodium, oxalate, and calcium.

Sodium plays an important role in calcification and nephrolithiasis. Sodium has an effect on the absorption rate of cells in the proximal tubule in kidneys^[34]. Sodium levels affect the urea concentration and influence the degree of supersaturation of other minerals by attracting

surrounding water molecules. This, in turn, raises the concentration of all other dangerous crystalline salts in the urine like calcium oxalate, calcium phosphate, and uric acid crystals^[3].

Oxalate is an organic waste molecule that when in high levels can be very dangerous when found in foods. Oxalate easily binds with calcium in the kidneys to form calcium oxalate crystals. The aggregations of these crystals are calcium oxalate stones and they comprise the largest portion of global nephrolithiasis. Urinary oxalate levels are highly influenced by dietary intake of oxalate in foods. Foods high in oxalate are usually plant based; however, oxalate can also be formed through the metabolism of amino acids and the breakdown of vitamin C^[35]. Glycine and hydroxyproline account for the highest production of oxalate due to amino acid metabolism^[35].

Calcium is the driving mineral that interacts with all stones. It is responsible for the formation of every type of stone. Calcium is a vital mineral used for musculoskeletal contraction and bone density support, so dietary levels of calcium are essential for a healthy patient. If dietary calcium levels are normal, the body absorbs less calcium in the small intestine and more in the distal tubule of the nephron; however, if there are low levels of calcium in the diet, the body will compensate by releasing more calcium into the blood from calcium storage locations like the bone. The calcium is absorbed in the small intestine and very little is absorbed in the kidney, leading to higher concentrations of calcium ions in the urine^[29]. With more calcium in the urine, there is a greater chance that these ions will bind to other dietary promoters of stones to form crystals that can aggregate to cause kidney stones^[36]. Calcium will bind to these stone forming molecules like oxalate and phosphate anywhere in the body, but they are easily excreted when they bind in the intestinal tracts, which can be improved by higher dietary levels^[5,37]. Some vitamins and minerals inhibit the development of stones. These minerals either compete with the harmful micronutrients creating less harmful salts and biological compounds or react with the harmful micronutrient neutralizing them. There are three known helpful, negative regulator micronutrients: Magnesium, citrate, and potassium.

Magnesium is a competitive inhibitor and binds to oxalate and excess phosphates much faster than calcium^[38]. The main reasons magnesium is an effective treatment is that it can easily be excreted *via* urinary excretion and has a minimal risk of developing into traditional stones^[39]. Higher urinary and intestinal concentrations of oxalate magnesium serve no threat to the individual; however, given the appropriate physiological conditions some calcium phosphate stones may be encouraged^[3]. There is an association with magnesium phosphate aggregation and formation of a calcium phosphate stone called brushite stone as well as struvite stones if urinary phosphate levels are high enough^[40]. Additionally, magnesium intake must also be monitored

carefully for patients who may be suffering from CKDs because the levels of filtration in the blood are reduced in CKD patients^[3].

Citrate is a common organic compound that when in normal concentrations has many anti-stone forming properties. Citrate blood levels have been shown to cause a significant decrease in individuals supplementing their diet with extra citrate medication^[41]. Citrate acts as a buffer regulating the urinary pH and calcium crystallization by means of increasing their solubility.

Similarly, Potassium is used as a regulator in calcium crystal formation. Potassium is inversely related to the development of kidney stones^[40]. Citrate and potassium are commonly used to increase urinary pH through oral potassium citrate supplementation, and has been shown to be 96% effective in treating patients with recurrent stone formation due to low blood citrate levels^[41]. Foods high in citrate have been shown to provide similar benefits to oral potassium citrate supplementation. A study looking into lemon juice as an alternative for potassium citrate to alter citrate concentrations found that it provided a 2.5 fold increase in original levels of urinary citrate whereas potassium citrate provided 3.5 fold increase^[42]. This dramatic increase in the urinary citrate levels has a direct effect on 2 major contributors of all stone formation, pH and ion concentration.

Animal protein

There is a common consensus that excessive animal protein consumption is one of the main dietary contributors to the development of stone disease^[43-45]. If excessive animal protein is consumed in the diet, the body will begin to metabolize the proteins. When the body metabolizes amino acids (two that cause most problems are proline and hydroxyproline) the body then converts these into harmful organic waste molecules like oxalate. Animal proteins have much higher concentrations of hydroxyproline and proline. The levels of these organic waste molecules in the blood will find their way into the kidney through normal filtration function. These increased levels of waste molecules in the urine are more likely to crystalize with surrounding calcium ions that have not been absorbed. Additionally, amino acid metabolism increases the acidity of the surroundings. The metabolism of animal proteins pose a double-sided threat to the development of nephrolithiasis by increasing two precursors: lowering the pH of the body and urine and increasing the blood concentrations of organic waste molecules that crystalize with ionic calcium. The result of these precursors leads to increased stone formation. All animal protein is not the same, with each different type carrying different concentrations of these high risk amino acids^[46]. Meat, Poultry, and Eggs are considered to be complete sources of essential amino acids because they contain adequate levels of the 20 essential amino acids; however, they also contain much higher levels of harmful amino acids that raise the pH and increase

urinary stress on the kidneys^[47,48]. Proteins from fish have fewer oxalate forming amino acids, a lower overall sulfur amino acid concentration, and a higher concentration of vitamin B6. Vitamin B6 is inversely correlated with the development of calcium oxalate stones^[49]. Animal protein intake also has an effect on the development of confounding metabolic diseases like obesity and type 2 diabetes^[50]. Countries where animal proteins intake accounts for a majority of their population's dietary energy intake have higher rates of type 2 diabetes than other countries. The link between diets high in animal protein and nephrolithiasis must be considered with caution because diets high in animal protein are also commonly associated with diets high in fat and sodium intake, but low in vitamin intake^[50].

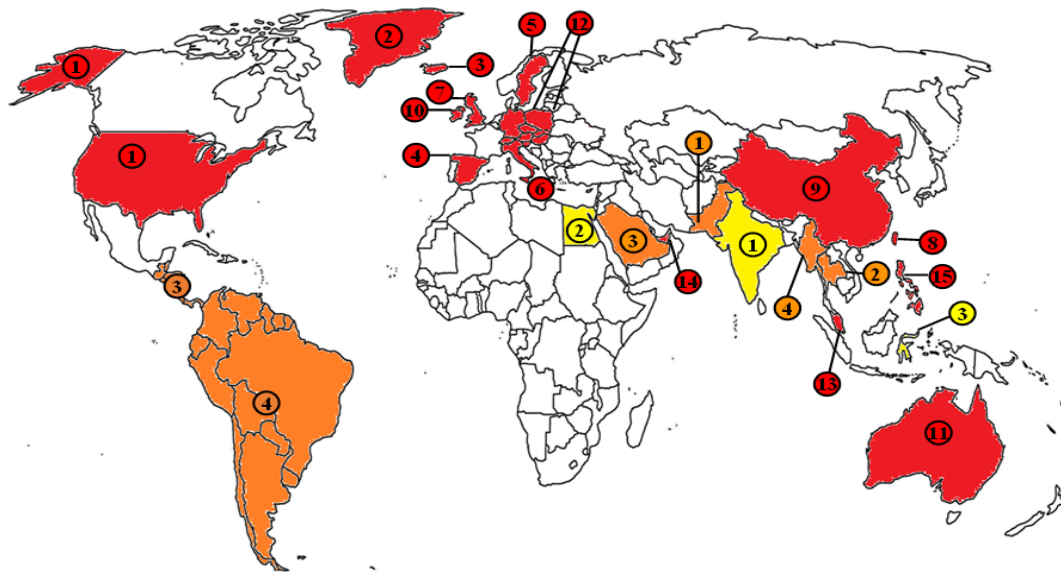
The protein intake world map was projected using the Food and Agricultural Organization of the United Nations database for 3-year averages of daily average protein supply per capita and daily average animal protein supply per capita (Figure 2). Total overall daily protein intake > 60 g for individual and whether the percentage of which comprises of animal proteins > 35% were used as indicator for animal protein intake magnitude of each country.

Sugars and sweeteners

The sugar and sweeteners in an individual's diet can play an important role in many metabolic disorders. Excess amounts of sugar intake lead to the overworking of the pancreas and can lead to an increase in heart disease, diabetes, and CKD^[51]. Both sugar and artificial sweeteners reduce water availability in urine if supersaturated with sugar in the blood, and would raise risk for the formation of all stone crystals which can aggregate to form stones^[51]. Different sugars have more of an effect on the biochemical content and concentrations of blood. Fructose metabolism raises the levels of uric acid in the blood. Not only does this cause a greater risk of uric acid kidney stones, but it also reduces nitric oxide levels which is important for insulin function and over a long period of time can induce insulin resistance. The lack in function of insulin in the blood leads to the development of type 2 diabetes, which increases the likelihood of stone formation.

Bacterial influences

With advancements in microbiology research, the scientific community has a much better understanding of the symbiotic relationship between microbial organism and normal physiological function. Different microbiomes in areas of the body work together to protect individuals from pathogenic invaders and in helping us metabolize foods our body normally could not. The gut microbiome is one of the most importance base of this very reason. *Oxalobacter formigenes* is a bacterium that is commonly found in the gut microbiome^[52]. These bacteria are capable of breaking down dietary oxalate before it can be absorbed *via* intestinal absorption^[53]. This bacterium



High protein intake	Moderate protein intake	Low protein intake
1 United States of America	1 Pakistan	1 India
2 Greenland	2 Thailand	2 Egypt
3 Iceland	3 Saudi Arabia	3 Indonesia
4 Spain	4 Myanmar	
5 Sweden		
6 Italy		
7 Scotland		
8 Japan		
9 China		
10 Ireland		
11 Northern Australia		
12 Central Europe		
13 Malaya		
14 United Arab Emirates		
15 Philippines		

Figure 2 World map projection of animal protein consumption. Protein retrieved from the Food and Agriculture Organization of the United Nations. High protein intake countries are red; moderate protein intake countries are orange; and low protein intake countries are yellow. Source: Food and Agriculture Organization of the United Nations, <http://www.fao.org/faostat/en/#country>. Reproduced with permission.

does not originate in the body at infancy. The bacteria is colonized through environmental exposure from foods^[53]. There is an indirect link between drastic changes in the GI microbiome and an increase in kidney stone formation^[52]. When one analyzes the urinary composition of individuals who have gone through bariatric surgery to control weight related problems, there is a dramatic spike in oxalate levels leading calcium oxalate formation^[52]. By breaking down oxalate before it can be absorbed into the blood stream, the bacteria prevent excess oxalate from accumulating in the urine which causes calcium oxalate crystal formation. By examining bacterial influences and sugar intakes of individuals and patients, it can lead to new findings between the link of an individual's diet and the risk of kidney stone formation.

Success of dietary interventions

Dietary interventions are commonly used to combat the formation of stone diseases by understanding the

levels of micronutrient regulators as well as protein intake. Recently dietary changes have been shown to have a direct effect on nephrolithiasis and stone formation^[54]. A recent push by dieticians to prevent the rise of chronic diseases due to cardiovascular disease is the implementation of the Dietary Approach to Stop Hypertension (DASH) diet, which was based off the Mediterranean diet. The implementation of this diet also has shown to be beneficial in preventing nephrolithiasis. The DASH diet consists of high dairy intake, low animal protein intake, and higher fruit and vegetable consumption^[55]. These diets show a significant increase in regulating micronutrients like magnesium, potassium, and citrate through the limitation of high risk foods resulting in overall decrease in stone erudition.

ENVIRONMENT

Temperature and humidity

Surrounding geographical environments have a varying

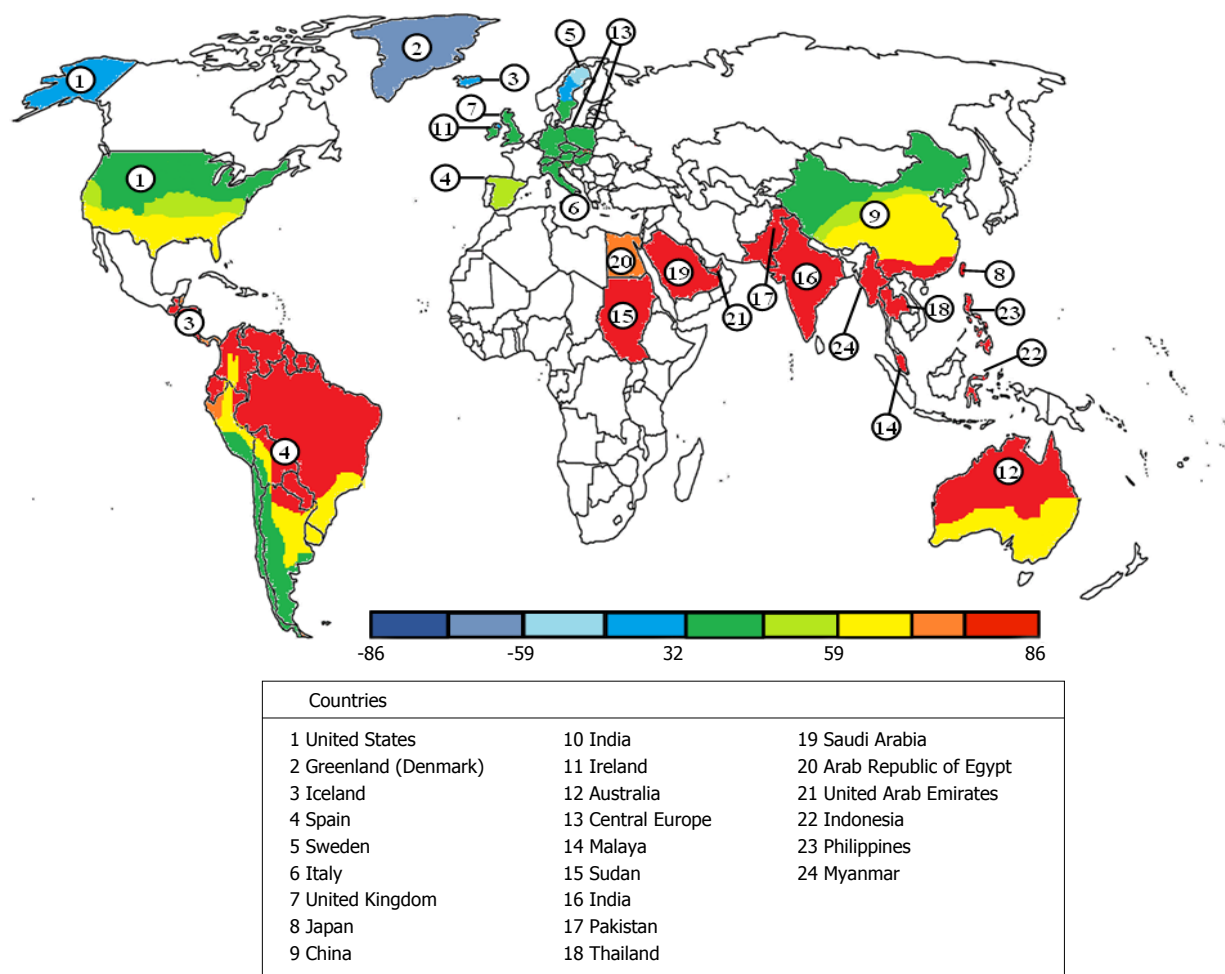


Figure 3 World map annual temperature projection. Annual mean temperature (°F) data estimate of countries. Color spectrum correlates to estimated annual temperature. Data retrieved from: The Nelson Institute Center for Sustainability and the Global Environment, University of Wisconsin-Madison.

effect on metabolic and physiological function, and this is especially true in the formation of stone disease. The urinary system dramatically changes based on the temperature and aridity of an individual's surrounding environment^[3]. Urinary ion concentrations are altered by the temperature of the patient by reducing urinary volume excretion^[56]. A multivariate study using 599 patient data, showing the effects of both seasonal and temporal change in urinary composition, found that urinary calcium, urinary oxalate, and uric acid^[57]. The longer a patient is exposed to higher temperature environments, the more at risk these individuals are for developing stones. When examining the relationship between humidity and urinary ion concentration through different seasons of the year, however, the study did not find significant correlations^[57]. An observational study focusing on the rise in stone prevalence as they relate to average mean temperature in the United States alone shows a correlation between areas with a temperature greater than 10 °C over the course of a year, with higher prevalence of stone formation in these populations^[13]. This suggests that temperature may play as a significant indicator for predicting nephrolithiasis prevalence. We created a projected

world map indicating different mean temperature for each country (Figure 3).

Urban heat islands and urbanization

Temperature change due to global warming is important to consider when looking at the long term rise in nephrolithiasis; however, we are seeing a much more rapid increase in the prevalence of stone disease in urban, high density locations known as "urban heat islands"^[58]. Urban environments are 1-3 degrees higher ambient temperature annually than rural areas but temperatures can be as high as 12 degrees higher during high heat months such as the summer season^[59]. The ambient temperature changes due to these heat islands is much more apparently affecting urban populations to a much larger degree than global warming, increasing rates of nephrolithiasis in urban populations globally. Exposure to higher temperatures is associated with a greater risk for stone development in males; however, the association with higher temperatures and stone development in females is less significant which brings into question the overall affect that temperatures have on prevalence of nephrolithiasis when adjusted for age, race, and gender^[60].

Exposure to harmful chemicals

Heavy metals are common environmental and occupational toxins that can have detrimental effects on physiological function in many body systems, including kidney function. Even minute exposure to metals that are not biologically needed by the body lead to serious diseases like lung disease, cardiovascular disease, certain types of cancer, and renal failure^[39]. Heavy metals induce calcium stone aggregation due to their similar charge and ease of substitution with other bioavailable ions in the urine^[61]. Cadmium is a heavy metal used in construction and manufacturing, usually to prevent the corrosion of steel. The metal is considered highly toxic and there is no biological use for cadmium in organisms. Cadmium is a competitive inhibitor to calcium, in turn can increase urinary calcium concentration. Acute chronic exposure to cadmium causes severe renal damage as a result of tubular protein-urea^[62]. Lead is the most common heavy metal contaminate and it can be found in almost all products^[63]. The widespread use of lead in manufacturing, paint, gasoline, and construction have ceased in modern developed countries due to a general consensus on the harmful effects of lead on people's health; however, it is still commonly used in developing countries despite global warnings of health impacts on populations^[63]. Exposure to low levels of lead can have drastic effects on kidney function. One of such effect is the increased formation of uric acid. This increase in uric acid and subsequent decrease in kidney reabsorption of nutrients can contribute to the development of nephrolithiasis.

Melamine exposure and contamination

Melamine is an industrial additive that is commonly found in plastics and cleaning supplies^[64]. It is a molecule high in nitrogen content that manufacturers add to dilute food products in an attempt to increase levels of protein content by deceiving protein tests that measure for nitrogen levels^[64]. An addition of this chemical to food products even in trace amounts has been known to cause renal damage and kidney failure. Though melamine toxicity cases are not frequent and consistent, the outbreak can have a devastating epidemiological impact. In 2008, a reported 294000 infants and young children affected by melamine in China were sent to the emergency room^[65]. Among those cases, 51900 were hospitalized, and among the 2085 children screened, 348 children had kidney stones; however, the method of detection did not account for smaller urinary stones and the actual number may be underrepresented^[65].

In 2004 and 2007, a discovery of melamine in animal food products exported by China in the past has led to widespread animal death due to renal failure with calcification in the kidneys^[66]. Interestingly, pet food in the United States during the 2007 outbreak shows similar melamine levels as the contaminated infant milk products in China. Pet food has also shown cyanuric acid, a chlorine-stabilizing agent used in swimming

pools^[64]. Melamine's role in altering renal reabsorption rates and the overall development of melamine crystal formation are under investigation, but this compound is known to cause serious problems and must be taken into careful consideration^[67].

ADDITIONAL FACTORS TO CONSIDER

Genetics

A familial history of kidney stone disease is one of the strongest causes of penetration for kidney stone formation. The overall impact of genetic disorders contributing to the development of nephrolithiasis in patients is astonishingly high. Roughly 10% of individuals affected by nephrolithiasis can attribute some aspect of their condition directly to a heritable disease^[68]. An autosomal recessive genetic disease Cystineuria, is directly responsible for 1% of all kidney stones^[69]. This disease leads to the development of cysteine stones, which are highly infectious and affect people of all ages. This disorder is commonly found in children and account for roughly 25% of childhood nephrolithiasis^[70]. Hypercitraturia in family members with nephrolithiasis may also be the result of inheriting a genetic disease from stone-forming families, in addition to environmental factors. Many diseases such as Hypertension or Diabetes can form potential higher risks for kidney disease by passing it on through future familial generations.

There is also a possible heritability for urinary osmolality and volume, which could implicate genetic regulation of thirst^[71], while studies have considered urine volume as a risk factor for stone disease. Nephrolithiasis found in adults will most likely be a strong indicator for kidney stone formation in their children and carried on in future familial diseases. Individuals will have to be aware of the possibility of the reoccurrence of stone formation.

Genes which potentially affect the predisposition only influences the risk factors of nephrolithiasis; such as comorbidities or phenotypical symptoms which may increase the risk of nephrolithiasis in the longer run. Several genes which code for TRPV5^[72], SLC26A6 and NaDC-1^[73] can play a physiological role in contributing to calcium stone formation because they play a major role in homeostasis in maintaining physiological conditions. Other genetic factors may have an indirect correlation to nephrolithiasis by contributing to common comorbidities or risk factors to nephrolithiasis.

Reoccurrence of stone formation and family history

While there is no direct genetic predisposition of nephrolithiasis, there is in fact a correlation to family history of stone formation and nephrolithiasis. Nephrolithiasis offspring can possibly carry several urinary metabolic risks predisposing to stone formation that are similar to their parents. Kidney stones develop about 3 times more frequently for individuals with positive family history^[74]. A correlation has been expressed between

Table 2 Prescription medications and treatment of condition with contributions to nephrolithiasis

Medication	Treatment of condition	Function
Acetazolamide	Glaucoma	Diuretic used to prevent and reduce the symptoms of altitude sickness
Vitamin D supplements	Osteoporosis	Mineralization in bone and calcium reabsorption
Vitamin K	Excessive bleeding	Assists blood clots, bones, heart disease
Calcium supplements	Osteoporosis	Assists calcium building, bones, cardiovascular
Warfarin	Blood clotting	Reduce blood pressure/vitamin K inhibitor
Lithium chloride	Mental illness	Psychiatric medication

family history of kidney stones and the onset of nephrolithiasis in patients. Patients are 2 times more likely to develop stone disease, with some studies showing relative risk rates as high as 2.5^[37]. This is one of the strongest associations with the development of stones disease. If a patient develops nephrolithiasis, there is a 50% chance that they will develop another stone within the next 5 years. These cases of recurrence are equally spread out amongst the different type of kidney stones^[3]. Moreover, descendants with nephrolithiasis display urinary metabolic disorders associated with kidney stones^[75]. These abnormalities may also be observed in the parents or predecessors. Although the reoccurrence of stone formation and family history can be observed through genetics, diseases occurring simultaneously with kidney stone formation pose a risk as well.

Medications

Available medications may work well for a patient's kidney stone treatment; however, some medications can not only have adverse side effects but can also contribute to alleviating or worsening potential onset of nephrolithiasis. Medications that pertain to this possibility include acetazolamide, vitamin K, vitamin D, Ca²⁺ supplements, beta blockers such as warfarin, and lithium chloride.

Acetazolamide, a carbonic anhydrase inhibitor, is commonly used to combat glaucoma^[76]. It can cause renal tubular acidosis which can result in calcium phosphate calculi^[77]. Vitamin K is used to counteract excessive bleeding. Vitamin K deficiency could be considered as a main cause of osteoporosis, atherosclerosis and other calcium deposit issues throughout the body.

An individual taking Ca²⁺ supplements may use it to supplement calcium deficiency. Calcium supplements are widely available for the general population. A study of thirty-two healthy navy privates have shown that taking calcium supplements can result in a reduction in urinary oxalates and an elevation in urinary citrate^[78]. Vitamin D supplements, fat-soluble vitamins, are commonly prescribed to treat osteoporosis because of its role in calcium regulation. 50% of woman with osteoporosis are found to have inadequate vitamin D levels^[79], while its deficiency is also associated with other comorbidities such as cardiovascular disorders, cancer, and kidney disorders. Moreover, a study of 456 idiopathic stone

formers have shown that 31% among them were vitamin D deficient^[80], raising up the question of its role in calcium stone formation. The summary of the medications are shown above (Table 2).

Warfarin is used to treat blood clots. It can cause renal damage in patients with CKD and is also associated with progression of renal disease. The mechanism leading to renal damage is hemorrhage and red blood cell tubular casts. Individuals are usually prescribed lithium chloride and used as an anti-depressant. Chronic intake of high lithium amounts causes renal damage. However, lithium chloride acts as an anomaly. There is accumulating evidence from animal studies that indicates that low lithium administration may benefit in kidney disease prevention caused by oxidative stress or inflammation^[81]. The availability of these medications worldwide is not always in abundance, however for patients and individuals taking them, they must be wary of the possibility of kidney stone formation and nephrolithiasis regardless of their living environment.

GLOBAL INTERCOUNTRY COMPARISON

Analysis of United States (Northern/Southern)

Lifestyle and diet are highly influential factors for kidney stone formation in the United States, especially lifestyle, in comparison to the world (Figure 4).

The United States is primarily divided by its latitude and longitude between northern, southern, western, and eastern regions. Most obviously seen, the effects of a state's geographical location on kidney stone formation can be easily discerned between the Northern and Southern states in America (Figure 5). In all, while prevalence in stone formation is elevated from the west to the east side of the United States, formation is also more pronounced from the north to the south side of the United States^[82]. Therefore, Alabama, Mississippi, Tennessee, North Carolina, and other Southern states are considered in the "stone belt"^[13]. This incidence can be attributed to the temperature of Southern region and states as well as the dietary intake of residents inhabiting these States. Men who usually live in southern most latitudes are 60% more likely to report a history of stones than those living in the northern most latitudes^[13].

Analysis of Japan/Iceland

The ambient temperature of these 2 island countries is

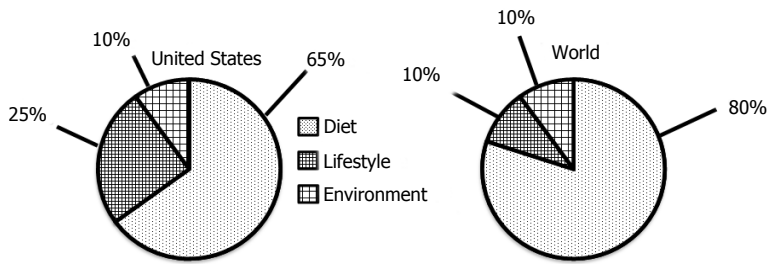
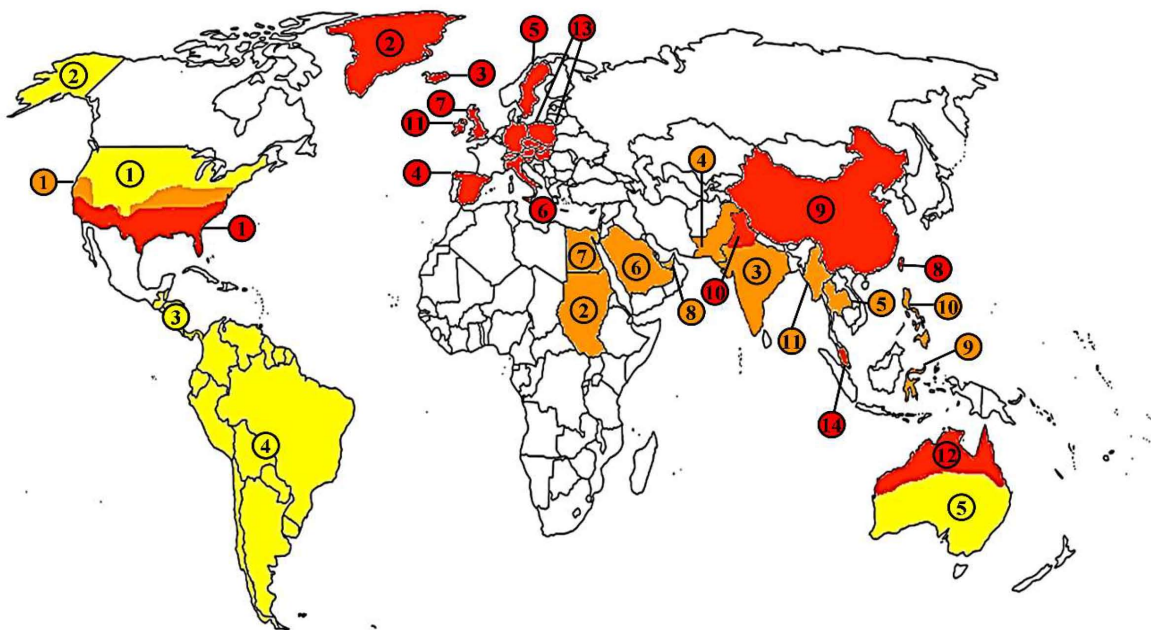


Figure 4 Proposed risk factor percentage distribution for diet, lifestyle and environment. Percentage was determined upon literature review. Lifestyle and diet were the more influential factors for the United States than the world. The environment percentage was about the same for both the United States and the rest of the world.



High prevalence	Moderate prevalence	Low prevalence
1 United States (South)	1 United States of America (Northeast/West)	1 North America
2 Greenland	2 Sudan	2 Alaska
3 Iceland	3 India	3 Central America
4 Spain	4 Pakistan	4 South America
5 Sweden	5 Thailand	5 Southern Australia
6 Italy	6 Saudi Arabia	
7 Scotland	7 Arab Republic of Egypt	
8 Japan	8 United Arab Emirates	
9 China	9 Indonesia	
10 Northern India	10 Philippines	
11 Ireland	11 Myanmar	
12 Northern Australia		
13 Central Europe		
14 Parts of the Malayan, Peninsul		

Figure 5 Projected world map of magnitude of nephrolithiasis prevalence. Magnitude of nephrolithiasis in each country using conglomeration of risk factor indicators dietary intake, obesity, and climate. Degree of prevalence is color coded in red (high prevalence), orange (moderate prevalence), and yellow (low prevalence). High prevalence information obtained through Romero *et al*^[82].

distinctly different, with Iceland ranging from 0 °C-10 °C and Japan 10 °C-20 °C. One would then expect that Iceland would have a lower prevalence of kidney stone; however, Iceland actually has much higher rates of kidney stones. Iceland rates of stone prevalence are

very similar to western rates of stone prevalence^[48]. This is partly due to the fact that Iceland has a much higher degree of risk for nephrolithiasis due to the average diet and lifestyle risk factors that affect the majority of the country. In a comparison between the two countries,

almost all risk factors for developing kidney stones can be seen in the Icelandic population whereas very few can be found in the Japanese population. According to data from the Food and Agricultural Organization of the United Nations and WHO, an Icelandic diet is calorie dense and consists mainly of animal protein and sugars. They account for roughly 30% of caloric intake per day for someone living in Iceland^[16]. On the contrary, Japan has a much smaller overall consumption of animal protein and sugars, as they only account for 15%^[16]. This dietary difference between the two countries is enough to cause such a dramatic difference in the prevalence of nephrolithiasis in these countries.

Analysis of Australia (Northern/Southern)

Australian rates of kidney stones have had a measured increase over the past decade, similar to that of western countries as they have a similar diet to that of industrialized western countries. Individuals in developed countries like Australia and the United States are more likely to develop nephrolithiasis because they are at a much greater risk of developing metabolic diseases that increase risk. Over 60% of Australians are overweight and obese, with little amounts of physical activity^[16]. Average ambient temperature within the country ranges based on geographical location. The northern part of the country has a harsher hot climate when compared to the southern part of the country.

CONCLUSION

The overall consensus of experts and researchers in this field is that there is no salient contributing factor to the development of nephrolithiasis, but rather it is a combination of risk factors that can cause this disease. Different countries and their populations have different risk factors that they are exposed to over the course of their lifetime. The creation of a model that will fit the current global epidemic of nephrolithiasis is bound to have different degrees of accuracy. It is important to note that these risk factors are an indirect causal relationship, meaning that not all risk factors are necessary for the development of the disease; however, the few that have been listed are well understood or play the largest role in shaping the etiology of the disease.

It is difficult to accurately determine dietary differences within a country because it is nearly impossible to monitor dietary fluctuations and changes by region based on current publicly available data. One can extrapolate the idea the diets of rural individuals will have diets that are very different than individuals living in an urban area due to factors like access to different types of technology and food sources; however, this cannot be quantified nor easily estimated. Certain lifestyle factors like obesity, type 2 diabetes, and metabolic disorders that play a role in the formation of different stones are monitored closer by countries and

international health organizations than other lifestyle contributors like physical activity. While these other factors play an important role in shaping the global nephrolithiasis breakdown, an accurate quantification of factors would be required to enhance the global understanding of kidney stone risk factors.

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