Response to reviewer's comments – World Journal of Nephrology

Reviewer #1:

- Genes accused of elevated nephrolithiasis and description

  We agree with the reviewer that genes could play a role in elevating nephrolithiasis. However, we are trying to focus mainly on the environment, diet and life-style changes and the genes that may cause a direct predisposition with stone formation are distant for the present scope in an existing population. 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 (Zeng et al., Urolithiasis. 2018 Jun;46(3):271-278), SLC26A6 and NaDC-1 (J Am Soc Nephrol. 2013 Oct;24(10):1617-26) can play a physiological role in contributing to calcium stone formation because they play a major role in homeostasis to maintain physiological conditions. Other genetic factors may have an indirect correlation to nephrolithiasis by contributing to common comorbidities or risk factors to nephrolithiasis. One example is the deletion in the paternal chromosome 15 or by maternal uniparental disomy which causes Prader-Willi Syndrome may be indirectly correlated to nephrolithiasis due to hyperphagia disposition which usually leads to morbid obesity, one of the major lifestyle risk contributors to nephrolithiasis. Though research in correlating the two could be limited, there is a known case study of a Prader-Willi syndrome patient with a renal stone thought to be due to hyperphagia and elevated purine (Kiyo. 1998 Jan;44(1):37-9).

- Discuss correlates of pediatric nephrolithiasis more extensive and in a different sub category.

  We have touched on the pediatric effect of melamine on nephrolithiasis as an environmental contaminant within the environmental section of the manuscript. Since the manuscript is more focused on the four categorical risk factors: lifestyle, climate, diet, and genetics, but to include a subsection specifically for pediatric nephrolithiasis may be beyond the scope of the present manuscript. We agree, however, that pediatric nephrolithiasis is an important topic of discussion, and we have discussed more about the topic within the scope of our manuscript.

- Discuss more about the higher incidence of neph. in men vs. female, and why the incidence is more increasing in the females than in males in the recent years: e.g. working outdoor is a very significant issue; and struvite stones more prevalent in females.

  We agree with the reviewer's comment that there has been a higher amount of nephrolithiasis incidence in women, specifically calcium phosphate stones over the past years; however, the exact cause of increase is not well known. One can surmise that the countries increasing trend of obesity rates for women may also an increase in the prevalence in nephrolithiasis. 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, also explaining why they are more prone to calcium phosphate stone formation (Worcester et al. Am J Physiol Renal Physiol. 2018 Apr 1;314(4): F623-F629). Moreover, it is known that higher urine pH has more influence on the supersaturation of calcium phosphate than the compositions of calcium and phosphate Eur Urol. 1984;10(3):191-5. Struvites stones may have a

correlation with urinary tract infections with women, but the incidence of struvite stones is relatively low compared to other stones (Lieske et al. Clin J Am Soc Nephrol. 2014 Dec 5;9(12):2141-6.).

- Discuss about the medical problems (e.g. hyperparathyroidism, sarcoidosis, fat malabsorption and its correlates, cancers and so on)

  The reviewer has listed a number of possible comorbidities associated with kidney stones though we have already listed several comorbidities for discussion in the manuscript, including hypertension, type 2 diabetes, and chronic kidney disease.

- Your categorization of countries based on climate (table 1) is not accurate. For example, you reported Japan as a warm and Australia as temperate climate while the mean annual temperature in Japan is almost half of that in Australia (https://en.wikipedia.org/wiki/List_of_countries_by_average_yearly_temperature).

  We agree that the categorization of Australia and Japan for temperature is not accurate and we will rectify it in the manuscript. The reviewer has provided a Wikipedia link for the mean and annual temperature climates for Japan and Australia.

- Discuss the variations in the incidence of neph. in individual countries (e.g. higher in summers, white ethnicity, exposure to chemicals, sun exposure, and soon)

  We agree that nephrolithiasis needs to be further investigated in individual countries. However, the collection of data from a good number of individual countries is limited because the data is either inaccessible or non-existent . Nevertheless, there are countries that allow the public to have access to hospital data, allowing for meaningful analysis. A recent cohort questionnaire study of approximately 86,000 Southeastern United States men and women from 2002-2009, found that kidney stone risk was higher among whites (HR = 2.23, 95% CI 1.97-2.53) compared to blacks, and marginally higher among men compared to women (HR = 1.12, 95% CI 0.99-1.28). Interestingly, race was examined separately, males were significantly associated with incident stone risk among whites (HR = 1.45, 95% CI 1.20-1.75), but not among blacks (HR = 0.90, 95% CI 0.75-1.07; Hsi et al. Urology. 2018 Aug;118:36-42). As for seasonal or temperature based changes of we already included a multivariate study by Eisner et al. who examined the effects of ambient temperature on urinary composition in patients with nephrolithiasis, and found that increasing temperature correlated to increased concentration of urine calcium, super saturation of calcium oxalate, and super saturation of calcium phosphate (Eisner et al. BJU Int. 2012 Dec;110(11 Pt C):E1014-7). They also found that as seasons turn warmer (e.g. Winter to Spring or Spring to Fall) calcium phosphate supersaturation decreases.

- Discuss the role of supplementary vitamin D/calcium intake on the incidence (very important, discuss it in details)

  We agree and discussed the role of calcium intake supplementation within the manuscript, but we have not discussed the role of supplementary Vitamin D. We will add discussion for the supplementary Vitamin D which is commonly used for treating osteoporosis.

- Discuss the role of immigration to societies different than that of the native ones and the change in the incidence and role of ethnicity remained.

  We agree that the role of immigration should be discussed for it is a unique perspective in looking at the epidemiology of nephrolithiasis. Migration can potentially create an artificial trend on the prevalence of nephrolithiasis. Usually, migrants are either younger individuals looking for work or those with young families because they would need to be fit enough for labor. However, population pyramid data suggests that the age for immigrants are increasing each year (Migration Policy Institute (MPI) tabulation of data from the U.S. Census Bureau's 2016 American Community Survey. Data were accessed from Steven Ruggles, Katie Genadek, Ronald Goeken, Josiah Grover, and Matthew Sobek. Integrated Public Use Microdata Series: Version 6.0 [Machine-readable database]. Minneapolis: University of Minnesota, 2017). Meanwhile, no study has been done as to whether the aging immigrant population would affect the prevalence of nephrolithiasis.

- I propose to make global and national maps of each risk factors provided (e.g. diabetes mellitus, climate, economic level, ethnicity, alcohol consumption, and so on) and a map of the incidence of nephrolithiasis and discuss to correlate them together.

  We agree with the Reviewer and made changes to include the global maps categorizing the risk factors within the scope of our manuscript, which includes Obesity, Average Mean Temperature, and Protein intake.

Reviewer #2:

- However, one minor concern has been raised. Namely, no figures are found to indicate that lifestyle, diets, environment and additional factors including genetics are risk factors for nephrolithiasis. Therefore, the authors should add the representative figures to indicate risk factors for nephrolithiasis.

  We agree with the Reviewer and added additional representative figures for protein intake, obesity, and mean temperature. Genetics was not used for the world map projection, and therefore, we did not create a representative figure.

N.B. No other addressable comments were found from the other Reviewers (#3, #4 & #5).