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Dietary risk and protective factors of kidney stone formers in Switzerland

Legay Constance

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Department of Biomedical Sciences (DBS), UNIL
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Dietary risk and protective factors of kidney stone formers in Switzerland

Doctorate in medicine and sciences (MD-PhD)

Presented at the

Faculty of Biology and Medicine
of the University of Lausanne

by

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Jury

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Facteurs de risque et protecteurs dans l'alimentation chez les formeurs de calculs rénaux en Suisse

Doctorat en médecine et ès sciences (MD-PhD)

présenté à la

Faculté de biologie et de médecine
de l'Université de Lausanne

par

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pour Le Doyen
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Prof. Pedro Marques-Vidal

Remark

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"Let food be thy medicine and medicine be thy food."

Hippocrates

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On a final note, I would like to mention the exceptional and quite surreal events that unfolded during those three years. Just a few months after the beginning of the thesis, the whole world was hit by the COVID-19 pandemic, an extraordinary situation that lasted for nearly two years and forced us to reconsider many things in our lives and society and to adapt to a new normality.

I was lucky enough to not have been too impacted by this crisis and was able to carry on with my project, despite some aspects of the PhD life, such as conferences and courses, being canceled for the best part of those two years.

This situation revealed the importance of public health and epidemiology in particular. In my opinion, it highlighted the role and power of well-conducted public health policies for the health of the population and made epidemiology more relevant than ever.

Summary

Kidney stones represent an important public health concern. As well as acute symptoms and complications, kidney stones are also associated with chronic and metabolic diseases (chronic kidney disease, cardiovascular disease or diabetes). Kidney stones thus seem to reveal an underlying global pathophysiology rather than a transient urinary composition imbalance.

The role of diet in kidney stone disease has now been well established and dietary interventions have been identified to prevent kidney stone formation and recurrence. However, until now data about kidney stone formers in Switzerland was scarce. The aims of this thesis was thus to 1) review the dietary assessment methods used in kidney stone nutrition research, 2) explore the dietary data collected in the Swiss Kidney Stone Cohort (SKSC) to try identifying specificities in kidney stone formers' diet in Switzerland and 3) compare the dietary assessment methods used in the SKSC.

The systematic literature review highlighted the heterogeneity of the methods used, as well as the need for a more systematic description and validation of those methods, in order to produce interpretable and comparable results across studies. The description of kidney stone formers' diet and comparison with a group of non-stone formers identified differences between the two groups with stone formers reporting a lower intake of vegetables, tea, coffee, and alcoholic beverages, more specifically wine, but reporting a more frequent consumption of soft drinks than non-stone formers. These results are in agreement with the current literature and other aspects such as global dietary patterns would be interesting to investigate further. Finally, the agreement between 24-h dietary recalls and 24-h urine collections was better for the estimated intake of protein than for the estimated intakes of sodium, potassium and volume. This comparison also revealed the complexity of the notion of validity and its various facets. Careful consideration should be taken regarding the potential impact of individual characteristics (e.g. sex, BMI, linguistic region) on their performance.

In summary, the findings identified in this thesis contribute to a better understanding of the links between diet and kidney stone formation in Switzerland but still a lot remains to be understood regarding kidney stone pathophysiology. Only part of the data available in the SKSC has been exploited in this work and further research, combining metabolomics and genetic analysis, will allow gaining further insight.

Résumé

Les calculs rénaux représentent un problème de santé publique majeur. En plus de symptômes et complications aigus, les calculs rénaux sont aussi associés à des maladies chroniques et métaboliques (maladie rénale chronique, problèmes cardiovasculaires ou diabète). Les calculs rénaux semblent donc être des indicateurs d'une maladie globale plutôt qu'un déséquilibre transitoire dans la composition de l'urine.

Le rôle de l'alimentation dans la pathologie des calculs rénaux a maintenant été bien établi et des interventions diététiques ont été identifiées pour la prévention de la formation et la récurrence des calculs. Cependant, jusqu'à présent les données sur les formeurs de calculs rénaux en Suisse étaient limitées. Les objectifs de cette thèse étaient donc de : 1) passer en revue les méthodes employées en recherche médicale pour mesurer les apports alimentaires chez les formeurs de calculs, 2) explorer les données nutritionnelles collectées dans le cadre de la Swiss Kidney Stone Cohort (SKSC) pour tenter d'identifier des spécificités liées à l'alimentation des formeurs de calculs en Suisse et 3) comparer les méthodes utilisées dans la SKSC pour mesurer les apports alimentaires.

La revue systématique de la littérature a souligné l'hétérogénéité des méthodes employées ainsi que le besoin d'avoir une meilleure description et validation de ces méthodes afin d'obtenir des résultats interprétables et comparables entre les études. La description de l'alimentation des formeurs et la comparaison avec un groupe de non-formeurs a identifié des différences entre les deux groupes, les formeurs ont rapporté des quantités moins importantes de légumes, thé, café et boissons alcoolisées, le vin en particulier, mais ont rapporté une consommation plus fréquente de boissons sucrées que les non-formeurs. Ces résultats sont en accord avec la littérature et d'autres aspects comme l'impact global des habitudes alimentaires seraient également intéressants à développer. Finalement, la concordance entre les rappels et les récoltes d'urine de 24-h était meilleure pour l'estimation des apports en protéines que pour les apports en sodium, en potassium ou pour l'estimation de la quantité d'eau consommée en 24-h. Cette comparaison a également montré la complexité de la notion de validité et ses diverses approches. Une attention particulière devrait être portée sur l'impact potentiel de certaines caractéristiques personnelles (sexe, BMI, région linguistique) sur leur performance.

En résumé, les résultats identifiés dans cette thèse contribuent à une meilleure compréhension des liens entre alimentation et formation de calculs rénaux en Suisse mais beaucoup reste encore à découvrir concernant la physiopathologie des calculs rénaux. Seule une partie des données disponibles dans la SKSC ont été exploitées dans cette thèse et de futures recherches, combinant la métabolomique et la génétique, permettront une meilleure compréhension du lien entre alimentation et formation des calculs rénaux à l'avenir.

Glossary

Biosample	A biological specimen including, for example, blood, tissue, urine, etc. taken from a participant.
Diet	Foods and beverages usually consumed by a person or group.
Food	Substance consisting essentially of protein, carbohydrate, fat, and other nutrients used in the body of an organism to sustain growth and vital processes and to furnish energy.
menuCH	First national nutrition survey in Switzerland.
Nutrient	A substance or ingredient that promotes growth, provides energy, and maintains life. Macronutrients are consumed in relatively large quantities and include proteins, carbohydrates, fats, fibers and water. Micronutrients - vitamins and minerals - are consumed in relatively smaller quantities, but are essential to body processes.
Nutrition	Intake of foods and nutrients considered in relation to the body's dietary requirements.
Nutritional biomarker	A parameter that can be objectively measured and reflects biological consequence of dietary intake or dietary patterns and should indicate the nutritional status with respect to intake or metabolism of dietary constituents.
Self-report methods	Category of diet investigation methods based on data reported by the participants themselves.

List of abbreviations

24-HDR	24-Hour Dietary Recall
BMI	Body Mass Index
CI	Confidence Interval
CDC	Centers for Disease Control and Prevention
GD	GloboDiet®
FC	FoodCASE®
FFQ	Food Frequency Questionnaire
OR	Odds Ratio
SD	Standard Deviation
SE	Standard Error
SKSC	Swiss Kidney Stone Cohort
UK	United Kingdom
USA	United States of America

Table of content

1. Introduction

1.1. Kidney stones as a public health issue

1.1.1. Epidemiological situation

Kidney stones are one of the most frequent diseases of the urinary tract [1]. Their prevalence is estimated at 5-10 % in Europe, 7-13 % in North America and 1-19 % in Asia [2, 3], and global trends show that this prevalence has been increasing worldwide during the last decades [4]. Changes in nutritional habits or global warming with its related dehydration problems (both risk factors for kidney stone formation as we will discuss in more detail later in the introduction) were described as potential causes for this increase [2, 4].

Kidney stones are associated with high morbidity, potential complications include ureteral obstruction, urinary infection or even kidney failure [2, 5] , and with high costs [6, 7]. Passing a kidney stone can be completely asymptomatic or induce signs or symptoms such as macrohematuria or pain that can range from low-grade to very intense pain, typically manifesting as colic [2].

Furthermore, studies found associations between kidney stones and other conditions such as cardiovascular diseases with an increased risk of coronary heart disease (including myocardial infarction), obesity, type 2 diabetes, osteoporosis or chronic kidney disease [8-13]. Mechanisms linking kidney stones to chronic kidney disease involve the presence of crystals in the urinary tract (we will further develop this aspect in the next section). Indeed, some of those crystals have been identified as immunogenic, thus generating inflammation in the kidney tissue and contributing to interstitial nephritis and chronic kidney disease [14].

Another concern regarding kidney stone disease is that recurrence rates are high. A study conducted in the US identified numbers as high as 20 % at 5 years and nearly 40 % after 15

years for first-time stone formers [15]. Moreover, after each additional episode, the recurrence risk increases [16].

Kidney stones are thus a frequent disease with high recurrence rates, associated with high morbidity and linked to a constellation of chronic and metabolic diseases. These criteria establish kidney stones as a health problem for surveillance, as defined by the Centers for Disease Control and Prevention (CDC) [17]. In this context, understanding kidney stones' pathophysiology and identifying associated risk and protective factors is key to design interventions to control kidney stone disease. Furthermore, the recurrence aspect calls for effective preventive measures.

The pathophysiology of kidney stones is not fully elucidated to this day and some mechanisms leading to their formation still remain unknown [5]. Moreover, different types of kidney stones have been described and kidney stone disease constitute a heterogeneous group of individuals with various underlying pathophysiology. In the following section, we will summarize what has been discovered so far.

1.1.2. Pathophysiology and factors influencing the formation of kidney stones

To understand the pathophysiology of kidney stones, it is important to first introduce some notions regarding kidney physiology. The main roles of the kidneys are to maintain volume, acid-base and electrolytes balance in the body and to eliminate metabolic waste products. These functions are completed via blood filtration and production of urine. Several kidney structures are involved in the process of blood filtration and concentration of the urine filtrate via reabsorption, secretion and excretion mechanisms [18]. The final product, urine, is thus composed of water, metabolic waste products (e.g urea, uric acid or creatinine), various

electrolytes (e.g sodium, potassium, calcium, oxalate, and phosphate), proteins and other constituents depending on the metabolic and nutritional state of the organism [19].

Kidney stones are concretions of inorganic and organic crystals amalgamated with proteins that form in the upper urinary tract [5, 20]. Those crystals are formed by the crystallization of some of the urine solutes, for instance inorganic salts such as calcium oxalate and calcium phosphate or organic compounds such as uric acid. The crystallization process depends on several factors: the temperature, pH or the solute concentration, the more the urine is concentrated the higher the risk of crystallization of those solutes [21].

The concentration of crystals in the urine is a major factor for the initiation of kidney stone formation and the risk is strongly linked to urine supersaturation [22]. Increased concentrations of urinary calcium, oxalate, urate, and phosphorus and decreased concentrations of citrate (which acts as an inhibitor of stone formation by forming soluble complexes with calcium and thus reducing supersaturation of calcium salts [23]) and a low pH are thus favorable environments for kidney stone formation [5]. In that context, crystallization activity can be evaluated using the supersaturation ratio for a given salt as a proxy [22].

However, supersaturation does not always lead to stone formation, and several steps are involved in this process, from supersaturation to nucleation, crystal growth, crystal agglomeration and finally stone growth [22]. Even if the exact mechanisms are still not fully elucidated, it appears that different pathways can lead to stone formation [24]. Research identified the following: growth over Randall's plaque, growth over Bellini duct plugs, formation of microliths within inner medullary collecting ducts and formation in free solution within the calyces or renal collecting system [24].

Those different mechanisms lead to the formation of different types of kidney stones [24]. Indeed, several types of kidney stones have been identified [5]: calcium containing stones (which account for an estimated 80 % of stones) with calcium oxalate (the most frequent type)[25, 26] and calcium phosphate, uric acid (5-10% of stones), and less frequent types such as cystine or struvite (infection stones). Calcium oxalate stones seem to form primarily on Randall's plaque, whereas cystinuric stones were associated with microlith formation [24].

Causes of kidney stones are various and include metabolic, environmental and genetic factors [5, 27, 28]. The risk factors and mechanisms of formation differ according to the stone type [20]. For instance, hypercalciuria plays an important part in calcium stone formation whereas a low urine pH has a key role in uric acid stones [5, 20].

Genetics are also involved in the pathophysiology of kidney stones. If certain monogenic diseases related to the formation of kidney stones have been identified (e.g primary hyperoxalurias, hereditary hyperuricemias or 2,8-dihydroxyadeninuria), those diseases are rare and represent only 2% of stones in adults and 10% in children [29]. On the other hand, complex traits with polygenic involvement and interaction with other dietary and environmental factors (e.g climatic conditions, sun exposure…), are frequent in idiopathic stone formers [30].

Several studies identified the importance of diet on both the formation and management of kidney stones [31-34]. Some researchers even stated that nutritional exposure could be one of the most important factors involved in the increased frequency of nephrolithiasis in the population [28]. We will now see in more detail the impact of nutritional factors on kidney stone formation.

1.1.3. Nutrition and kidney stone formation

It is now well established in the scientific community that nutrition plays an important role in kidney stone formation [27, 28]. Studies showed that dietary intake has an impact on urine composition, especially on urine supersaturation [35]. For instance, investigators found that a diet rich in animal proteins increases the urinary excretion of calcium, urate, and oxalate and decreases the urinary excretion of citrate [36-38]. A study also showed that a low-calcium diet induced a reduction in urinary calcium and an increase in urinary oxalate excretion [39]. Another study found that increased dietary oxalate intake led to higher urinary oxalate excretion, especially if calcium intake was reduced [40].

The importance of diet on kidney stone formation was also shown in epidemiological studies. Studies conducted on large-scale American cohorts showed that a high dietary calcium intake decreased the risk of symptomatic kidney stones [31]. Also, low fluid intake, higher body mass index (BMI), low dietary calcium intake, higher intake of sugar sweetened beverages were all independently associated with higher risk of kidney stones [32].

The protective effects of a high fluid intake are now well established [27]. However, not all fluids seem to be equally beneficial for reducing the risk of kidney stones. Previous studies showed that tea [33, 41-45], coffee [33, 42-44, 46], and alcoholic beverages [33] such as beer [42, 44, 47, 48] or wine [42-44] were associated with a risk reduction. But other studies identified that the most important factor was total fluid intake, independently of the beverage category [49], or that alcohol was increasing the risk [50-52].

Vegetarian, Mediterranean and DASH-diets (diets overall characterized by a high intake of vegetables, fruits, whole grain, nuts, and legumes and a low/no intake of red meat) have also been identified as protective [28, 32, 34, 53-55]. Furthermore, recent systematic reviews and

meta-analysis looking at different diets (e.g low carbohydrates, vegetarian, vegan, low protein with or without high fibers) [56, 57], showed the complexity of evaluating the precise effects of those diets and encouraged further research in that domain. Those reviews concluded that normal calcium, low salt, high fluid and some well-conducted vegetarian or low carbohydrates diets could reduce the risk of kidney stones.

In conclusion, several dietary risk and protective factors for the formation of kidney stones have been described in the literature. Primary and secondary prevention based on efficient dietary recommendations has thus a major role to play to fight the rise in kidney stone prevalence [27]. Those findings lead to the development of guidelines in order to reduce both the risk and recurrence of kidney stones.

1.2. Current guidelines for the management and prevention of kidney stones

After a stone episode, a thorough investigation of the patient's medical and familial history should be performed to identify risk factors and the possible mechanisms for stone formation in their particular case [58]. Other tools to better characterize the risk profile of a given individual include evaluating their diet history using self-report methods such as 24-h dietary recalls (24-HDR) or food frequency questionnaires (FFQs) and conducting a metabolic evaluation with blood samples and 24-h urine collections [58]. 24-h urine collections can help identify specific urinary risk factors that can then be addressed with adequate dietary recommendations or drug treatments [58]. Also, analysis of the stone composition by x-ray crystallography or infrared spectroscopy when available can greatly help the diagnosis [58].

As previously mentioned, there is a high risk of recurrence after a stone episode and as dietary interventions can lower this risk, kidney stone formers usually receive dietary

recommendations in the context of their follow-up. Those recommendations can be categorized into general measures that can be applied to all stone formers or more specific measures that target specific urinary disorders.

A general measure is to increase the fluid intake to reach a urinary volume >2L/24-h, in order to dilute the urine and reduce the concentration of urine solutes [27, 59]. This fluid intake should ideally be distributed throughout the day and with a preference for neutral beverages such as fruit tea, herbal tea, kidney tea, bladder tea, tap water or mineral water with a low content of calcium, bicarbonate, and sulfate [27].

Specific recommendations can include low sodium, oxalate or protein dietary intakes or increased citrate intake, depending on the metabolic disorder identified in the patient. Regarding calcium intake, it is now recommended, even in calcium stone formers, to maintain a normal calcium intake (1000-1200 mg/day) [27, 59].

As we have seen, nutrition research based on fundamental, clinical and epidemiological studies, allowed to identify elements to prevent and manage kidney stones. However, current existing methods frequently used in nutritional epidemiology are subject to errors and biases which limit our ability to capture real dietary intake. We will now briefly describe those methods with their strengths and limitations.

1.3. Challenges in nutritional epidemiology

Nutritional epidemiology is subject to controversies, with some authors arguing that the methods used for the assessment of dietary intake are too imprecise to produce reliable data [60-62], and also challenges, for instance in terms of study design. Most of the scientific evidence in this domain comes from observational studies or short-term interventional studies, which do not represent well real life situations [63]. Indeed, long-term randomized

trials are difficult to conduct [63] due to the impossibility to blind the dietary interventions (except for supplements in the form of pills) or the difficulty to maintain long-term adherence to an attributed diet.

Yet research showed that the data collected, despite suffering from biases and errors, is still valuable and necessary, but that improvements in existing methods and development of new methods should be conducted [63-66].

We will now describe the different methods used in nutrition research, based on two main categories: self-report methods and objective nutritional biomarkers. We will also briefly discuss new emerging methods such as smartphone apps, connected tools or metabolomics.

1.3.1. Methods used in research

a. Self-report methods

Self-report methods are tools that are frequently used in nutrition research. These methods are based on participants' reports of their dietary consumption, either as a recall (e.g. FFQs or 24-HDR) or a real-time recording (e.g. food diaries) [67-71]. The main characteristics of each method are described in **Table 1** [67-71].

Self-report methods are nevertheless subject to errors and biases [66-68, 72]. For instance, 24-h dietary recalls contain both random errors, due to day-to-day variation in the diet of individuals , and systematic errors [68], such as the consistent underreporting of certain foods and beverages (e.g. fats, sweets)[73]. Moreover, studies showed that total energy or protein intakes were poorly estimated with self-report methods [66, 73-75]. It is thus important to be aware of these limitations and use statistical models to correct for these biases when possible [72, 76].

Table 1. Main characteristics of self-report methods [67-71, 77]

Tool	Food record/diary	24-h dietary recall	Food frequency questionnaires
Category	Real-time recording; self-reported; short-term dietary assessment	Recall method; self-reported; short term dietary assessment	Recall method; self-reported; long term dietary assessment
Method description	Open-ended record of every food or beverage consumed in real-time, usually over 3-7 days With or without weighing of foods consumed	Detailed recall of foods and beverages consumed over one day (preferably the day before) Open-ended questionnaires, usually administered by trained interviewer	Frequency of foods and beverages consumption over a long period of time (month or year) Close-ended listings: either collective (e.g green leafy vegetables) or individual (e.g lettuce) Can be quantitative, semi-quantitative or non-quantitative
Strengths	Does not require recall Detailed dietary intake, also regarding food preparation	Detailed dietary intake, also regarding food preparation	Simple and cost effective Can be used to repeat dietary assessment over the years
	Captures average portion size of foods consumed by a person (if weighed) and meal patterns	Can be linked to food databases with specific information on recipe ingredients and product characteristics	Captures usual intake and foods and beverages more rarely consumed
Limitations	Costly and time-consuming Large respondent burden, high motivation and literacy required Rarely consumed foods and beverages are not well captured Need of multiple days to assess usual intake	Costly and time-consuming Risk of recall bias Rarely consumed foods and beverages are not well captured Need of multiple days to assess usual intake High burden for participants	Low accuracy with risk of recall bias Information collected only about food items in the questionnaire Little information or details on food preparation Should be developed and validated specifically for a given population or research question

b. Objective nutritional biomarkers

Objective nutritional biomarkers are measured in biological samples such as blood, urine or nails and can be used for one or several of the following purposes: to validate dietary instruments, as surrogate indicators of dietary intake or as measures of nutritional status for a nutrient [78, 79]. They can be classified into several categories: recovery, predictive or concentration biomarkers. The main characteristics of those different biomarkers are shown in **Table 2** [67-69, 78].

One advantage of those biomarkers is that they are objective measures and are thus supposed to be less prone to biases and errors, although some of them pose specific challenges from a laboratory measurement's perspective [78]. However, nutritional biomarkers also have limitations, due to the impact of individual metabolism or low recovery value for example [69, 80], and can still be subject to errors at different levels, from the quality of collection, sample storage or laboratory analyses [80].

Moreover, the clinical and public health relevance of selected nutritional biomarkers is not easy to assess when corresponding symptoms and signs are non-specific. Mild chronic deficiencies may therefore be hard to identify both at individual and at population level.

Table 2. Main characteristics of objective nutritional biomarkers [67-69, 78]

	Recovery biomarkers	Predictive biomarkers	Concentration biomarkers
Method description	Based on the knowledge of physiological balance between intake and output, estimate of absolute intake levels, usually dose-response relationship with intake	Sensitive to intake in a dose-response manner but overall lower recovery	Correlated with dietary intake but affected by metabolism and personal characteristics (e.g age, gender, smoking status, weight)
Identified biomarkers	24-h urinary nitrogen excretion: estimation of daily protein intake 24-h urinary sodium and potassium excretion: estimation daily sodium and potassium intake Doubly labeled water (DLW): estimation of total energy expenditure 24-h urine volume: estimation of fluid intake	24-h urinary fructose and sucrose as markers of sugar intake	Serum carotenoids: correlation with fruit and vegetable intake Fatty acids: measured in adipose tissue or vitamins in blood
Strengths	Not affected by inter-individual differences in metabolism	Could help mitigate error in self-report data	Can be used in studies of association with disease risk
Limitations	Only a few have been identified Multiple urine collections needed to estimate usual intakes	Only a few have been identified Lower recovery than recovery biomarkers	Cannot be considered surrogates for absolute intake

c. New methods

New digital technologies, such as online questionnaires or automated 24-h dietary recalls methods, can be used in combination to the traditional dietary assessment methods to facilitate data collection and improve participant's participation [81-84].

Moreover, new methods are also developed, such as smartphone applications that can estimate portion from pictures [84, 85] or connected tools such as water bottles with captors to estimate the liquid intake [84, 86]. However, evaluation of those new methods and their performance to estimate the dietary intake are still ongoing and it does not seem that such methods are routinely used in kidney stone research yet [87].

Finally, another promising approach is the development of metabolomics. Metabolomics aims at identifying metabolites in biological samples such as plasma or urine [88]. The hope is to identify signature metabolites for specific food and beverages and current approaches have already allowed to identify some markers of single food intake (e.g salmon, broccoli, raspberry, cruciferous vegetables) [89-91].

Another challenge is then to translate findings identified in research settings and apply them to the clinical practice to help improve individuals' health.

1.3.2. From research to translation into clinical recommendations

Once specific foods or beverages have been identified as protective or harmful, how can these findings be translated into clinical recommendations to improve health in a population? Dietary recommendations can for instance take the form of the Food Pyramid in Switzerland or the Dietary Guidelines for Americans in the USA [92].

An important concern is the high variability of diet depending on the country and the culture [93, 94]. If certain associations are found in a given setting, they might not be the same in another population, especially given the importance of global dietary patterns on health.

For example, research about diet and kidney stone formation was mainly conducted in countries such as the USA, UK, Italy, Spain or Japan [33, 34, 42, 53, 95-97]. But are the findings from those studies also applicable to the Swiss population? To answer this question, it was thus necessary to conduct research based on data specific to Switzerland to describe the dietary intake of kidney stone formers, identify if there are some diet specificities and look at the links between dietary intake and kidney stones.

We will now discuss what data was available in Switzerland before the launching of the Swiss Kidney Stone Cohort (SKSC), the first national cohort dedicated to the study of kidney stone formers.

1.4. Situation in Switzerland at the beginning of the study

The first Swiss national nutrition survey, menuCH, was conducted in 2014-2015 and assessed the dietary intake in the general adult population, using 24-h dietary recalls. The study identified some differences in food consumption across the different linguistic regions of Switzerland [98]. Results from the survey allowed to produce nutritional recommendations tailored to the Swiss population. Indeed, before that, nutritional recommendations were mainly based on national agriculture statistics or national surveys on single nutrition-related items [77].

However, menuCH was conducted in the general population and there was no specific data regarding kidney stone formers. Given the dearth of data regarding kidney stone formers' diet in Switzerland, it was thus important to collect nutritional data in this population to produce

evidence that can take into account cultural and regional specificities. In that context, the SKSC was launched in 2014 to study the epidemiology and pathogenesis of kidney stone disease in Switzerland.

1.5. Description of the SKSC and control group

1.5.1. The Swiss Kidney stone cohort (SKSC)

The SKSC is a multicentric cohort of kidney stone formers, recruited between May 2014 and March 2020, in five different centers located in the German and French-speaking parts of Switzerland (Berne, Zurich, Basel/Aarau, Lausanne, and Geneva) [99]. All centers followed the same harmonized study protocol. Both incident and recurrent adult (>18 y.o) stone formers were included in the cohort. The inclusion criteria were to have recurrent (>1) stone episodes or an incident episode with other risk factors such as first episode before 25 years old, positive family history, non-calcium oxalate stones, metabolic syndrome or osteoporosis [99]. The stone formers were followed-up in time, a first visit was conducted at ≥ 4 weeks post stone passage or intervention and after that, visits were scheduled at 3 months, one year, and then once a year during 3 years. After the 3 years, study nurses checked annually on participants by phone calls. Data collected at each visit included medical and stone history, physical examination data (e.g height, weight, waist-to-hip ratio, blood pressure, and pulse wave velocity), nutritional data (in the form of both 24-h dietary recalls and FFQs) as well as biological samples (blood, spot urine and 24-h urine collections).

1.5.2. Control group

A control group, composed of non-stone formers, was recruited from the general adult population in the Geneva, Zurich, Aarau and Lausanne centers. These participants had no kidney stone history and were free of stones, as ruled out by a native CT-scan of the abdomen.

Matching for sex and age with SKSC participants was done when possible. However, the control group includes more women and younger individuals than the SKSC. Participants to the control group were seen only for the first visit but their protocol was otherwise analogue to the SKSC (same data, urine and blood collection).

1.5.3. Dietary intake assessment

Regarding the dietary assessment, participants completed two consecutive 24 -h dietary recalls at each visit (a single 24-h recall was completed at the 3 months follow-up visit). Trained dietitians conducted the 24-h dietary recalls and recorded every food and beverage item consumed over the 48-h recall period, as described and quantified by the participants. The data was recorded with the help of a dedicated and validated software, GloboDiet® (GD, formerly EPIC-Soft®, version CH-2016.4.10, International Agency for Research on Cancer (IARC), Lyon, France, adapted to the Swiss food market) [100-102]. The multiple-pass method (recall process organized in standardized steps with probes from the interviewer) was used during the 24-h dietary recalls to help participants remember food and beverages consumed [98, 102]. In GD, food and beverages are classified into 18 precoded food groups and their subgroups, and specific descriptors allow a highly standardized description of foods and recipes [98, 102]. Furthermore, a picture book, also including typical Swiss recipes, helped participants to quantify the amounts of foods and beverages consumed [103].

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2. Aims, objectives and outline

2.1. Aims and objectives

This PhD thesis was centered on the nutritional epidemiology in Swiss kidney stone formers. The aims were to 1) evaluate how research had been conducted so far in this kidney stone nutrition research, 2) describe the diet of kidney stone formers in Switzerland, using data from the SKSC, and identify potential dietary specificities, and 3) conduct a methodologic evaluation of the two different dietary assessment methods (24-h dietary recalls and the 24- h urine collections) available in the SKSC and control group.

The thesis project was organized around the following three objectives:

Objective 1: To conduct a scoping review of methods used to evaluate dietary intake in kidney stone formers.

Objective 2: To describe kidney stone formers' diet at baseline, using the 24-h recalls, and compare it to the control group.

Objective 3: To compare selected data from 24-h dietary recalls with selected objective nutritional biomarkers, such as 24-h urinary volume (as an estimate of liquid intake), sodium (as an estimate of sodium intake), potassium (as an estimate of potassium intake) and urea excretions (as an estimate of protein intake) in kidney stone formers.

2.2. Thesis outline

The thesis is thus organized in several chapters, based on the three different objectives previously described (**Figure 1**).

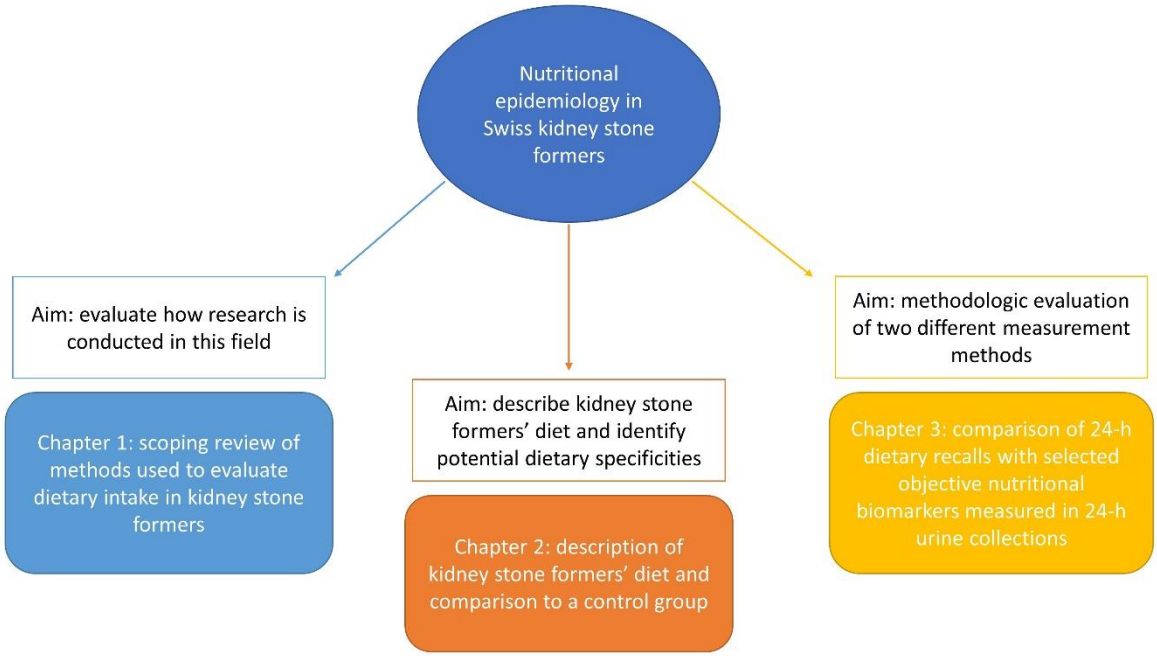

Figure 1. Overview of the thesis chapters

3. Scoping review of methods used to evaluate dietary intake in kidney stone formers

Title of the manuscript: Methods for the Dietary Assessment of Adult Kidney Stone Formers: A Scoping Review

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3.1. Abstract

Background Kidney stones are a frequent and potential severe condition, affecting 5-10% of the European population. Causes are multifactorial, diet in particular plays a major role in the formation and management of kidney stones. The aim of this scoping review is to assess the methods used to study the diet of adult kidney stone formers.

Methods We conducted a systematic search in Medline Ovid SP, Embase, Cinahl, Cochrane (CENTRAL), Web of Sciences databases on June 10th 2020. Self-report methods (such as food frequency questionnaires or 24-h dietary recalls), objective nutritional biomarkers and controlled diets were considered. We analyzed the selected publications based on the origin of participants, study design and dietary assessment methods used.

Results We screened 871 publications and included 162 publications. Most studies included participants from North America and Europe and were observational. Short and cost-effective tools such as food frequency questionnaires and other questionnaires were the most frequently used. Moreover, food diary was a frequently selected method to study the diet of kidney stone formers. New technologies (e.g online questionnaires, phone applications, connected tools) were rarely used.

Conclusion Accurate reporting of the methods used in nutritional studies is of key importance to interpret results and build evidence. Capturing long-term dietary intake is still a challenge for nutritional epidemiology. A combination of self-report methods with objective dietary biomarkers and new technologies probably represents the best way forward.

Keywords

Kidney stones – dietary assessment – nutritional epidemiology – scoping review

Supplementary Information Full search equations; Fig. 7 Number of publications per study with a FFQ; Table 1 Description of included studies

Acknowledgements We thank Thomas Brauchli for his help in the conception of the search equations and for conducting the systematic search in the databases.

Author contributions OB and MB had the idea for the article. OB, MB and CL worked on the methodology of the review. TK, AB and CL did the selection of the publications and data extraction. CL analyzed the data and drafted the original manuscript. All authors critically revised the work and approved the final manuscript.

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Declarations

Conflict of interest The authors declare they have no financial interests. OB is on the Editorial Board of the Journal of Nephrology.

Ethics approval Ethics approval was not required for this scoping review.

3.2. Introduction

Kidney stones are one of the most common diseases of the urinary tract, with a prevalence estimated at 5-10 % in Europe [1]. This prevalence has been increasing in the last decades, with changes in nutritional and lifestyle habits or global warming as possible causes [1, 2]. Many studies have explored the association between diet and kidney stones, establishing dietary risk and protective factors [3-6].

Kidney stones are of great concern for public health because of their associated morbidity and cost [1, 7]. Efficient preventive measures, including dietary recommendations, are thus becoming more and more important [8]. In this context, nutritional studies are of key importance to learn more about the impact of diet on kidney stones.

There are two main categories of dietary assessment methods. First, self-report methods are based on participants' reports of their dietary consumption. These methods are based on recall (e.g. food frequency questionnaires (FFQ), 24-h dietary recalls) or based on real-time recordings (e.g. food diaries) [9-13]. Second, objective nutritional biomarkers are measured in biological samples such as blood, urine or nails [9-14]. Each method has strengths and limitations and different tools explore different aspects of food consumption [9-13].

The aim of this scoping review [15] is to assess the methods used to study the diet of adult kidney stone formers and provide a better understanding of how researchers conducted nutritional studies. This may help guiding further research and improving the quality of evidence in this field [16].

3.3. Methods

The PRISMA-ScR checklist was used for reporting [17].

Search strategy

We identified key words and prepared search equations specific to a database with the help of a librarian (Thomas Brauchli). We first defined the target population using terms such as “urolithiasis, kidney stone, urine calculi”. We then introduced the concept of dietary assessment with terms such as “nutrition assessment, diet records, eating, fluid consumption”, indicating more specifically methods of interest “24h recall, food frequency questionnaire, online questionnaire, photo app”. We finally added terms to exclude animal and pediatric studies “not animals, not infant, child”.

A systematic search of Medline Ovid SP, Embase, Cinahl, Cochrane (CENTRAL), Web of Sciences databases was conducted on June 10th 2020 by TB using those search equations. We did not include a time limit and we considered only articles written in English (full equations in Supplementary material).

We added seven publications of interest by “hand-searching” [6, 18-23]. Furthermore, as the search equations did not include metabolomics, we conducted a focus search in PubMed with the terms “metabolomics” and “kidney stones” in January 2021. This search gave 16 results, two publications were selected and added to the review [24, 25].

Eligibility criteria

We selected publications that studied the diet of adult kidney stone formers. We were specifically interested in the dietary assessment methods and considered self-report methods (such as FFQs or 24-h dietary recalls), objective nutritional biomarkers and controlled diets (participants ingested a known amount of food and fluids) as this is another way of knowing the dietary intake of participants. Moreover, we added terms in the search equations to

identify new technologies such as online questionnaires, phone applications or connected tools.

We included only studies in adult (>18 years old) stone formers. We considered kidney stone formers with associated conditions, such as diabetes or obesity. We excluded studies focusing on struvite stones, as their formation differs significantly from the other stone types. We also excluded comments, editorials or letters.

Study selection

Two reviewers (AB and CL) did a first selection based on titles and abstracts using the online collaborative platform Rayyan (Rayyan Systems Inc.). When a disagreement occurred, discussion between the two reviewers was usually sufficient to reach a consensus. A third reviewer (OB) helped resolve the situations where an agreement could not be obtained.

After this first selection, two reviewers (TK and CL) screened the full-texts and extracted data from the publications. The final decision to include a publication was based upon agreement between the two reviewers (TK and CL).

Data extraction

Data from a publication was extracted by only one reviewer (TK or CL) using a standardized extraction table in Microsoft Office Excel version 2016. The team (OB, MB, TK and CL) discussed together the items chosen for the extraction table. The extraction table was then first tested on a subset of publications and some items were added or clarified. The final extraction table included:

- data relative to the identification of the paper: title, author, journal, year of publication, country

- data relative to the design of the study: type of study, start and end dates, total study duration, name of the cohort and duration of follow-up if applicable, selection and matching criteria for case-control studies
- data relative to the participants: number of participants, number of patients/controls, age, sex (proportion male/female), BMI, ethnicity
- data relative to the method used: for self-report methods, details about duration and recurrence of record; for objective biomarkers, details about measured variables; elements of diet investigated; validation of the tool
- a short summary of the aims and principal results of the study

Data synthesis

We summarized the characteristics of the studies based on the origin of participants, study design and methods used. We described the methods in terms of number of publications. For the 24-h urine collections and other timed-urine samples, if the value of at least one of the sodium, potassium, urea, oxalate, citrate excretions or urinary volume was reported in a publication, we considered that a urinary biomarker was available. For spot urine, we considered pH in addition to the previously mentioned values. For the blood samples, if the value of at least one of the items glucose, lipid profile, micronutrients (vitamins and minerals), ferritin, albumin, urea or uric acid was given in the publication, we considered that a blood biomarker was available.

We then described in more details the characteristics of the 24-h urine collections. For this description, we worked in terms of studies and not publications. Thus, if at least one publication related to the same study described a 24-h urine collection, we considered that it was available in the study.

3.4. Results

We included 162 publications in this review. Several publications were related to the same study, this selection represents 122 independent studies (see **Table 1 in the Supplementary material**). **Fig. 1** shows the selection process for the included publications. In most publications, participants were recruited in North America (n=64 publications, 40%) and Europe (n=53 publications, 33%), whereas Asia (n=25 publications, 15%), South America (n=10 publications, 6%), the Middle East (n=7 publications, 4%) and Africa (n=3 publications, 2%) were less represented (**Fig. 2**).

The design was observational in 122 publications (75%) and interventional in 40 (25%). **Fig. 3a** shows the number of publications for the different types of observational studies. We split the design of observational studies into cross-sectional studies (n=48 publications, 39%), cohorts (n=39 publications, 32%) and case-control studies (n=35 publications, 29%). **Fig. 3b** represents the number of publications for the different types of interventional studies, split into randomized controlled trials (RCT) (n=11 publications, 27%) and other studies with an experimental setting but without randomization, labelled as quasi-experimental (n=29 publications, 73%).

Self-report dietary assessment methods were described in 155 publications (96%) (**Fig. 4)**. In this category, FFQs were the most frequently used (n=73 publications, 47%) and 24-h dietary recalls the least frequently used (n=8 publications, 5%). As shown in **Fig. 7** (Supplementary material), 30 publications using a FFQ were related to the Nurses' Health Study I, II and Health Professionals Follow-Up Studies.

There are different types of FFQs. Some FFQs look only at the frequency of consumption, whereas semi-quantitative FFQs look at the frequency as well as the portions consumed. For

FFQs without details about portions, it is still possible to obtain dietary intake by applying standard size portions [26]. However, semi-quantitative FFQs allow for a more precise estimation of the daily intakes. The authors described the FFQs as semi-quantitative in 53 publications (including the 30 publications related to the NHS and HPFS studies that used similar FFQs). In two publications, only the beverages were quantified. In one publication, another self-report method was used to obtain the quantities and combined with the FFQ to generate the intake and in 3 publications, the investigators reported the frequency of consumption and not the intake. Finally, in the other publications (n=14), we could not determine if the FFQ was semi-quantitative or if a standard size portion had been applied afterwards to generate the intake. This shows the importance of precisely describing the method used. It also calls for a standardization of the description of such method.

Food diaries were used in 47 publications (30%) and other questionnaires in 27 publications (17%). Food diaries were collected for a period of 7 days in 8 publications (17%), 4 days in 5 publications (11%), 3 days in 24 publications (51%) and 1 day in 5 publications (11%). Participants were placed under controlled diets in 25 publications (15%). Only a few studies (n= 4 publications, 2%) used regional or national food distribution data or household food purchases registries to study the diet.

The value for at least one urinary biomarker was indicated in 95 publications (59%), with 24-h urine collections for 85 publications (89%), other timed-urine for 6 publications (6%) and spot urine samples for 4 publications (4%). The three metabolomic studies included urine samples. The value for at least one blood biomarker was indicated in 45 publications (28%).

In the following sections, we considered the 24-h urine collections in terms of studies and not publications**. Fig. 5a** indicates the number of studies with and without 24-h urine collections

and **Fig. 5b** shows the repartition of the different types of collections performed: single collection and repeated consecutive or non-consecutive collections. Twenty-four hours urine collections were available in 81 studies (66%) and 41 studies (34%) did not have 24-h urine collections.

Most studies with 24-h urine had repeated collections: 11 studies (14 %) had repeated consecutive and 44 studies (54 %) had repeated non-consecutive collections. All 11 studies with repeated consecutive collections were performed during two consecutive days. In four studies, both repeated consecutive and repeated non-consecutive collections were done. Concerning the non-consecutive repeated collections, the time interval between the collections was not always reported and when reported, it was highly variable and depended on the study design. Finally, 31 studies (38%) had a single 24-h urine collection.

Fig. 6 shows the number of studies with results on 24-h urinary biomarkers. Excretion rate was reported for sodium (55 studies), potassium (42 studies), urea (24 studies), oxalate (60 studies), citrate (55 studies) and urinary volume (59 studies).

3.5. Discussion

To the best of our knowledge, this is the first scoping review addressing the methods used to evaluate the diet of kidney stone formers. We identified reviews on dietary assessment methods but those were not focused on kidney stone formers [16, 27, 28].

Short and self-addressed dietary assessment methods, such as FFQs or other questionnaires were preferred over methods that need more time or resources, such as 24-h dietary recalls. Previous reviews [16, 27, 28] also showed that FFQs were the most common choice to evaluate dietary intake and that 24-h dietary recalls were less often performed.

FFQs and other questionnaires consist of a pre-established and close-ended set of questions about food and beverage consumption [12] and are developed for a specific research question and a given population [12]. A questionnaire developed for a study can focus on certain aspects of the diet or be more general, depending on the aim of the study [11]. Validity of FFQs on different populations can thus be limited due to cultural specificities and their validity should be assessed before using them in a new setting [9, 29, 30]. Methods for the validation of FFQs are described in the literature [29, 31].

On the 73 publications that used FFQs, 54 (74%) specified that the FFQ was validated (of which 30 publications were linked to the same study and used the same FFQ) and 19 publications (26%) did not. Few details on the development and validation process were provided for other questionnaires. Overall, the description of the method used varied across studies. Details on the development of FFQs and other questionnaires, in particular for which population they were developed or their validity, were not available for all studies. This calls for the development of guidelines on how to prepare, validate and report FFQs in future studies.

Food diaries and 24-h dietary recalls seem to be rarely used to evaluate dietary intake in nutritional studies [16, 27] but are often used as references in validation studies [28]. We found that food diaries were used in nearly a third of the studies. Pragmatic aspects arising from 24-h urine collection performed in stone formers might favor this method. Indeed, when collected simultaneously, it is possible to compare nutritional data from the food diaries and urinary objective biomarkers measured in 24-h urine collections.

We included specific terms in the search equations for new technologies such as “online questionnaire* OR photo app* OR photo phone app* OR smart bottle*”. Several studies mentioned online questionnaires or web applications but overall, even in the more recent

papers, new technologies do not seem to be frequently used for the dietary assessment of kidney stone formers. As diet and its links to various health issues are increasingly studied nowadays, new technologies could help improve dietary assessment [32, 33]. It would be interesting to follow the use of those tools in kidney stone research in future reviews.

Twenty-four hour urine collections are used for the metabolic evaluation of kidney stone formers [8] and are often done in both clinical and research settings. In most studies included in our review, 24-h urine collections were available, but the type of collection varied (single, repeated consecutive or non-consecutive). It is important to check the quality and completeness of the collections before analyzing their composition and measuring objective nutritional biomarkers [34]. Several criteria exist to assess the quality of 24-h urine collections [35-37]. We observed that the criteria used to evaluate the quality and completeness of the 24-h urine collections varied across studies.

We considered 24-h urinary nitrogen, sodium, potassium, volume, oxalate and citrate as objective nutritional biomarkers. 24-h urinary nitrogen (referred as urea in our review), sodium and potassium are accurate proxies for the dietary intake of protein, sodium and potassium, respectively [38-41]. Urinary oxalate is mainly derived from endogenous metabolism [42, 43] but a previous study showed that dietary consumption could contribute up to 50 % of the urinary oxalate excretion [43]. Similarly, diet has an impact on citrate excretion [44] and dietary interventions can be used in case of hypocitraturia [45]. Finally, urinary volume was found to correlate with volume intake [46].

We found that oxalate and citrate excretions were frequently assessed, while urea was rarely reported [38]. Overall, the choice of biomarkers in 24-h urine collections is not standardized and still a matter of debate [47]. New urinary biomarkers are identified [44] and metabolomic

studies are promising. For instance, a study identified a urinary amino acid profile specific to kidney stone formers [25].

Overall, self-report methods, especially FFQs and other questionnaires, are widely used in research. Indeed, FFQs are a timesaving and cost-effective method that can be easily administered to a large number of participants [12]. Yet, as mentioned previously, these types of questionnaires cover only a set of pre-determined foods and beverages and should be validated before use [12]. On the other hand, food diaries or 24-h dietary recalls require more resources but can capture in detail foods and beverages consumed over a short period [9]. However, a single day diary or recall does not give a good representation of usual dietary intakes [9]. Moreover, all those self-report methods are subject to error and biases [9, 48], for instance when measuring protein or total energy intake [48, 49]. Some recommendations have been developed to correct for possible sources of errors when using those methods, for instance combining with objective biomarkers or using statistical methods to generate the usual intake [9, 48, 50]. The 24-h dietary recalls are considered the least biased of this category and the best instrument to measure dietary intake as well as look at associations between diet and health, but they need to be repeated several times to provide better insight on usual dietary intakes [10].

There are different types of objective nutritional biomarkers [9-12, 14]. Recovery biomarkers, such as 24 h urinary nitrogen, sodium or potassium, are directly related to dietary intake [9-11, 38-40]. However, investigators identified that 24-h urine values of sodium and potassium do not reflect well individual sodium and potassium intake, unless repeated collections are performed [41]. Other objective biomarkers such as predictive (e.g 24-h urinary fructose and sucrose) or concentration (e.g fatty acids measured in adipose tissues or vitamins in blood)

biomarkers are correlated with the intake but can be affected by individual metabolism [9, 11]. Objective biomarkers are thus an interesting tool to validate or measure more precisely the dietary intake [9, 11, 14] but, those markers still have limitations and for now, only a limited number are available. Recommendations for future research are to combine several methods, either two self-report methods such as FFQs and 24-h dietary recalls or self-report methods and objective biomarkers [10-12].

The metabolic evaluation of kidney stone formers in clinical practice is complex and includes medical and nutritional history to identify environmental, metabolic and genetic risk factors but also laboratory analyses (24-h urine and serum, stone composition) [8, 51-53]. Guidelines have been published regarding indications for the metabolic evaluation and recurrence prevention [53] depending on the population (high-risk or low-risk stone formers) and the type of stone.

Many studies were conducted in North America or in Europe and knowledge in this domain mostly comes from large American cohorts [54-56]. However, diet is highly variable across populations [9, 30, 57, 58] and it would be important to check if the same dietary recommendations are valid in other countries.

Furthermore, most studies had an observational design and among interventional studies, there were few RCTs. Interventional nutritional studies are more difficult to conduct as blinding and randomization are not always feasible. It is difficult to plan and maintain RCTs over long periods. RCTs also usually do not reflect real-life settings and have therefore limited external validity.

Finally, many studies in our review relied on punctual dietary assessment, with cross-sectional studies or single 24-h urine collections and did not evaluate diet longitudinally. This is a clear

limitation for usual food intake evaluation. Indeed, long-term diet is an important exposure for surveillance and epidemiology to study health-related outcomes [9].

We included various study designs to have an overview of the literature and considered many research questions and approaches. With the different methodologies in our selection, certain methods can be appropriate for a given purpose but not for another. Hence, we cannot draw a general conclusion concerning the different methods that would be applicable to all study designs. Moreover, we conducted a systematic search of the literature but it is possible that we missed some publications of interest.

3.6. Conclusion

Given the role of diet in kidney stone formation, it is important to know how research is conducted in this field to inform future studies. Self-report methods and especially FFQs are the most frequently used and knowledge in this field is mainly based on observational data and Western diets. Overall, we observed that there is heterogeneity in the methodology description.

We thus want to stress the importance of precisely reporting the methodology used to collect dietary data, as it is a key element to interpret the results and build evidence. In addition, it is important to evaluate the impact of different diets on stone formation and when possible try to implement longitudinal or interventional studies. Finally, the combination of self-report methods with objective dietary biomarkers, including blood and urine metabolomic analyses, as well as smartphone applications to take pictures of meals will represent the best way forward.

3.7. References

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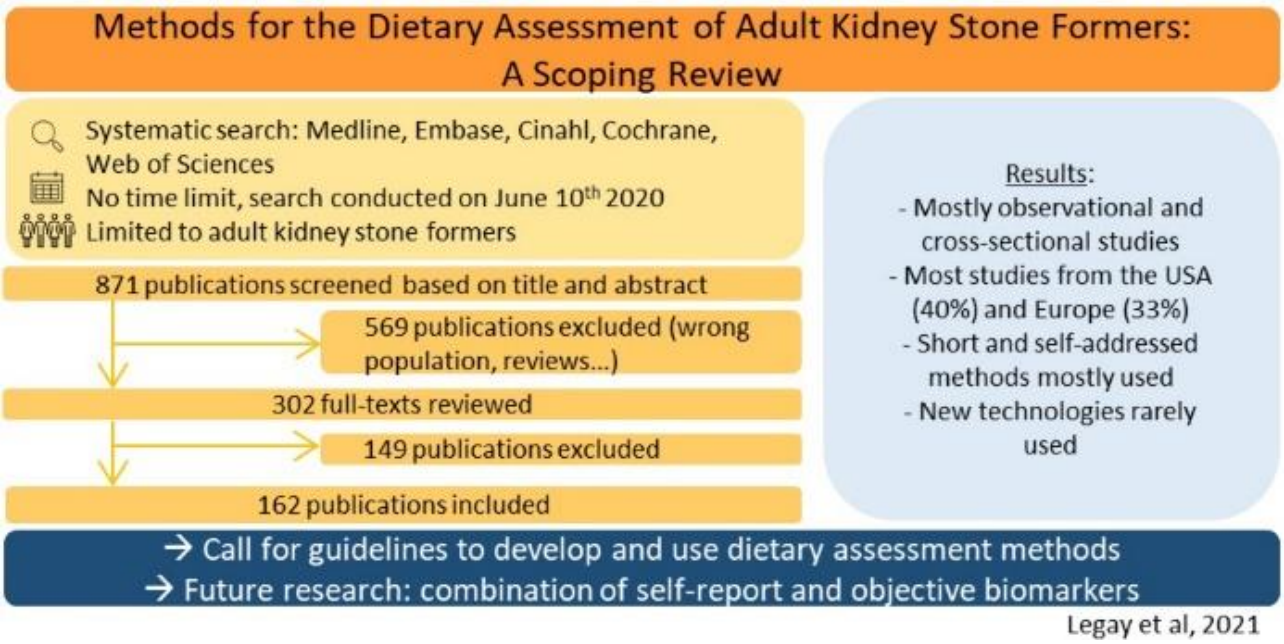
3.8. Figures


Methods for the Dietary Assessment of Adult Kidney Stone Formers: A Scoping Review
Systematic search: Medline, Embase, Cinahl, Cochrane, Web of Sciences
No time limit, search conducted on June 10th 2020
Limited to adult kidney stone formers
871 publications screened based on title and abstract
569 publications excluded (wrong population, reviews...)
302 full-texts reviewed
149 publications excluded
162 publications included
Results:
- Mostly observational and cross-sectional studies
- Most studies from the USA (40%) and Europe (33%)
- Short and self-addressed methods mostly used
- New technologies rarely used
→ Call for guidelines to develop and use dietary assessment methods
→ Future research: combination of self-report and objective biomarkers
Legay et al, 2021

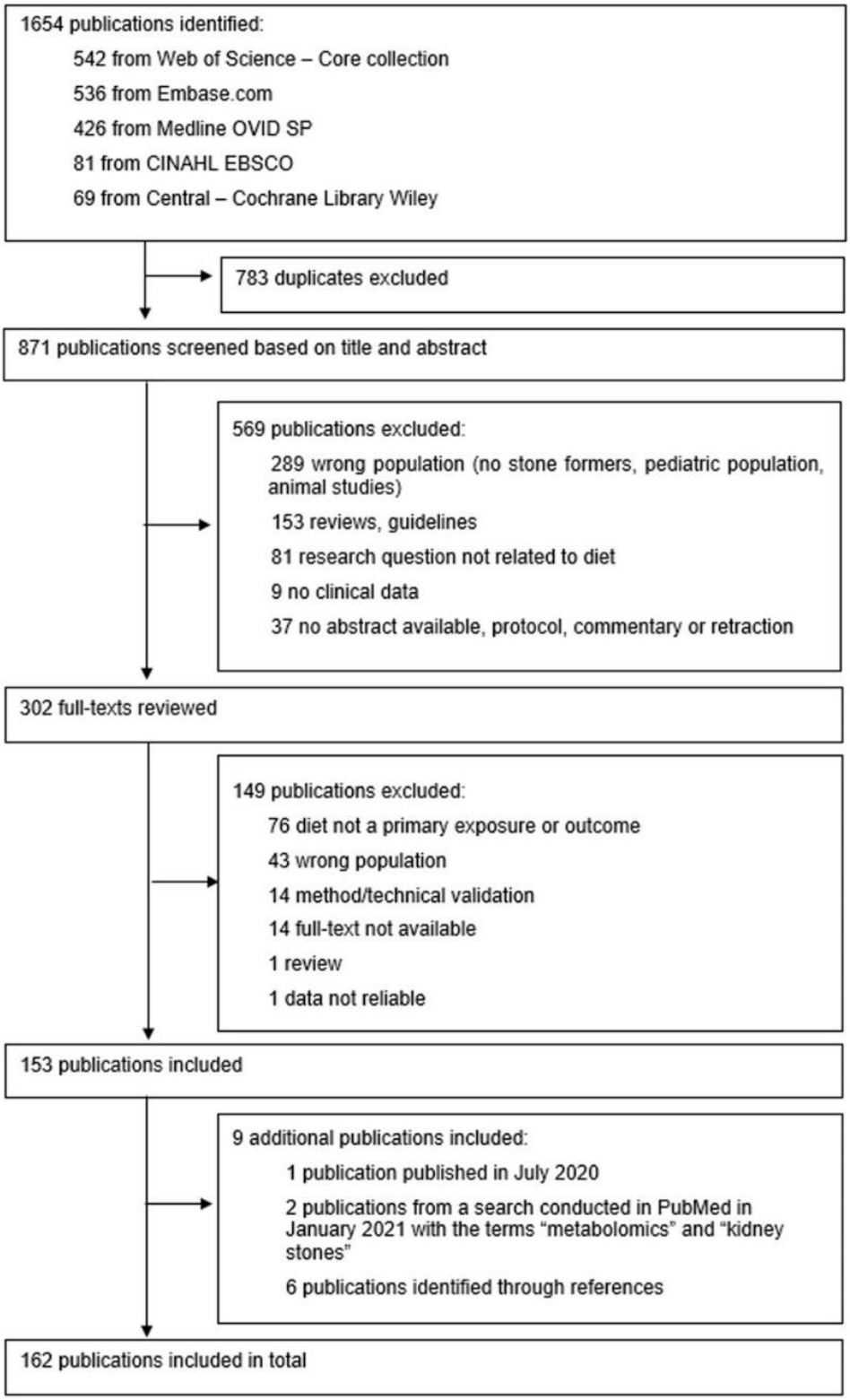


Fig. 1 Flow-chart representing the selection process of the publications included in the review

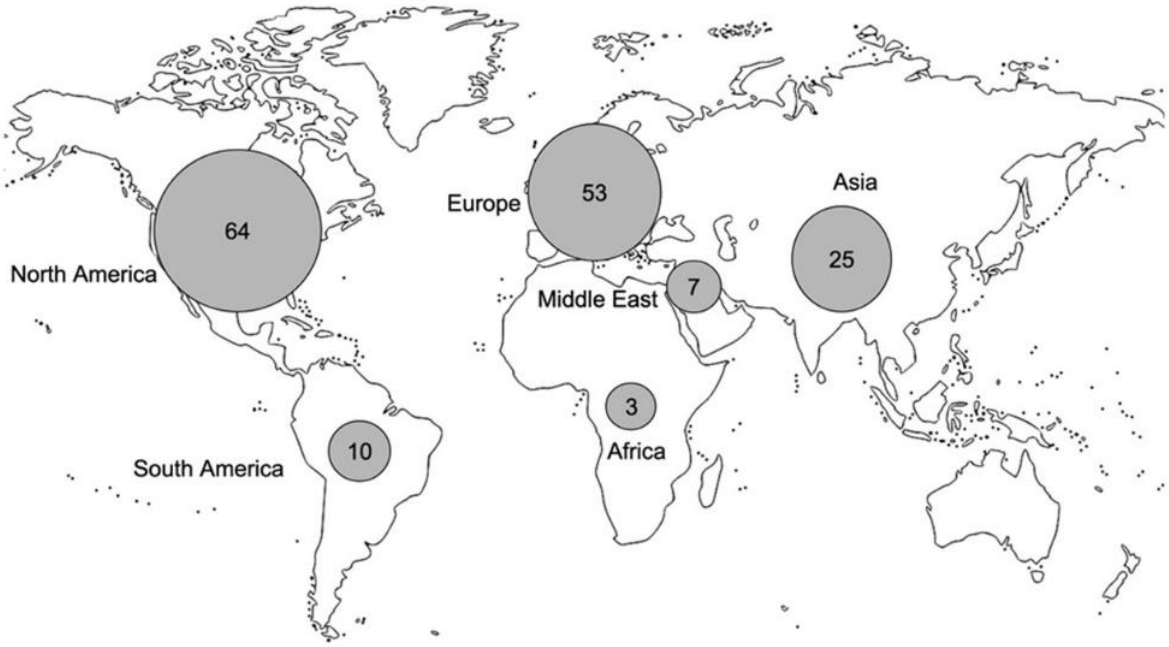


Fig. 2 Origin of the participants in the publications
North America region includes Canada, Puerto Rico and the USA
South America region includes Brazil
Europe region includes Austria, Bulgaria, Croatia, Czech Republic, Finland, France, Greece, Germany, Ireland, Italy, Macedonia, Poland, Romania, Serbia, Slovenia, Spain, Sweden and the UK
Middle East region includes Iran, Saudi Arabia and Turkey
Africa region includes Morocco and South Africa
Asia region includes China, India, Japan, Korea, Pakistan, Taiwan and Thailand

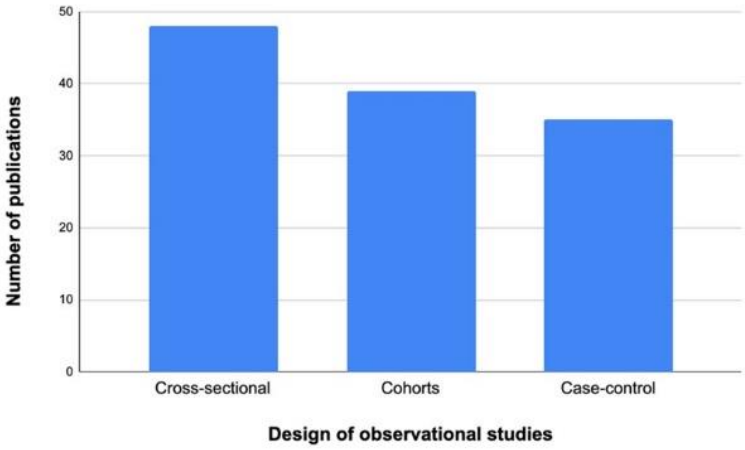


Fig. 3a Number of publications for each type of observational studies (n=122)

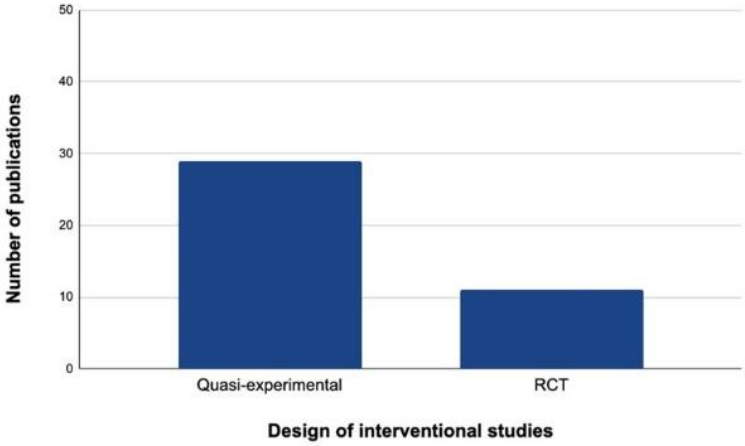


Fig. 3b Number of publications for each type of interventional studies (n=40)

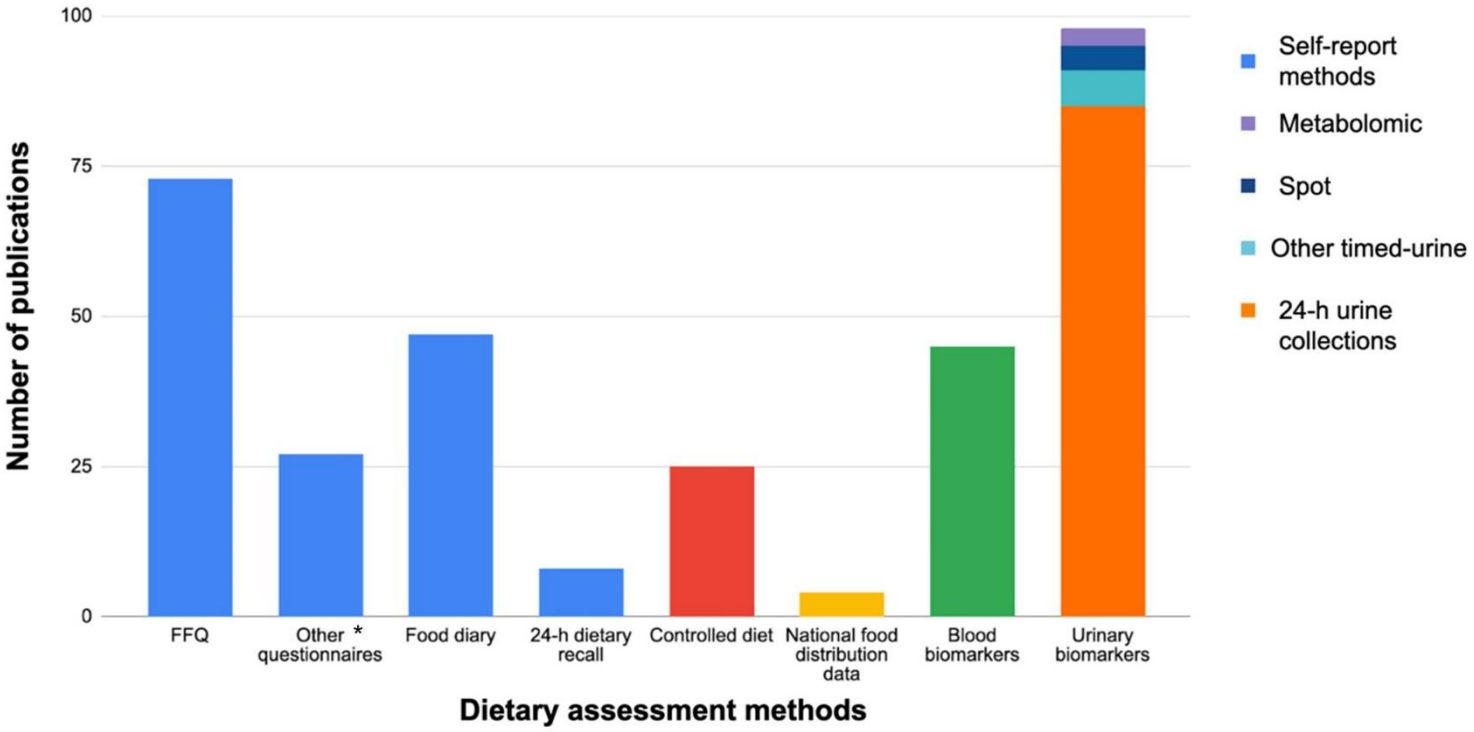


Fig. 4 Number of publications per dietary assessment method (n=162)
* other questionnaires include diet history and non-FFQ questionnaires

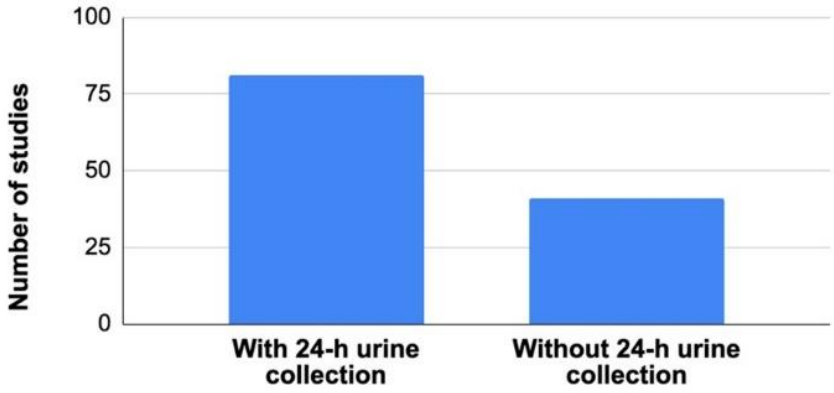


Fig. 5a Number of studies with or without 24-h urine collections available (n=122)

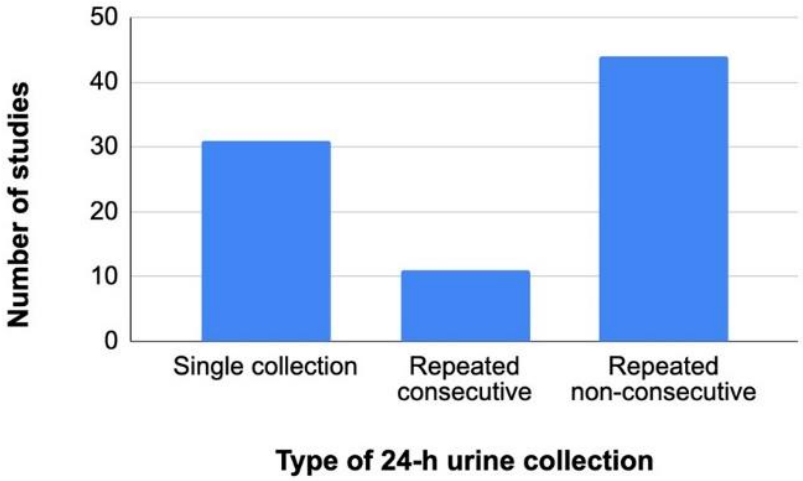


Fig. 5b Number of studies per type of 24-h urine collection (n=81)

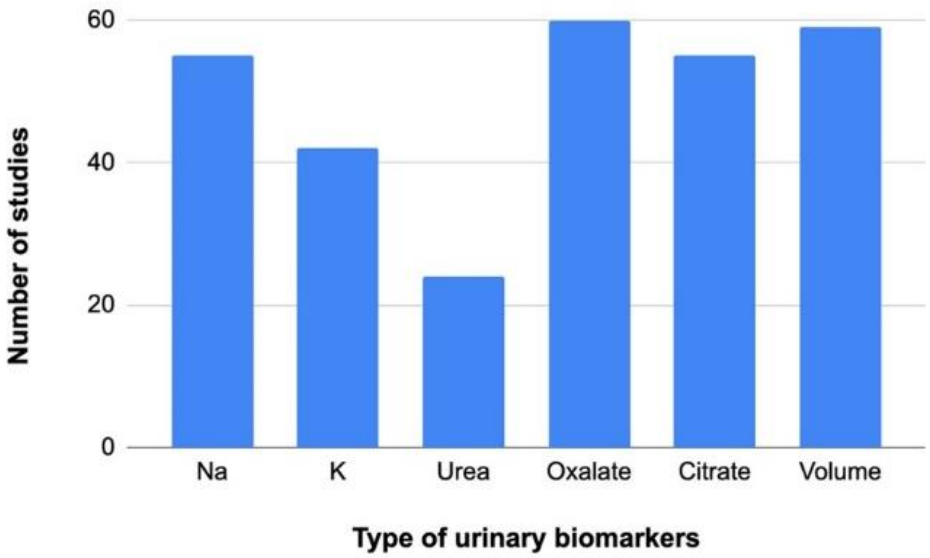


Fig. 6 Number of studies per type of urinary biomarkers measured in the 24-h urine collections (n=81)

The number of studies represents the studies in which the values of the biomarkers were reported in at least one publication based on this study

3.9. Supplementary material

Full search equations

Medline Ovid SP

(Urolithiasis/ OR exp Nephrolithiasis/ OR kidney lithiasis.ti,ab,kf. OR nephrolithiasis.ti,ab,kf. OR renal lithiasis.ti,ab,kf. OR renolithiasis.ti,ab,kf. OR ((kidney OR renal) adj2 (calcul* OR stone*)).ti,ab,kf. OR (urinary calcul* OR urinary lithiasis OR urinary stone* OR urinary tract calcul* OR urinary tract lithiasis OR urinary tract stone* OR urine calcul* OR urine lithiasis OR urine stone* OR uro-lithiasis OR urocalcul* OR urolith OR urolithiasis OR urolithogenesis OR urologic calcul* OR urological calcul*).ti,ab,kf.) AND (Nutrition Assessment/ OR Diet Records/ OR Mobile Applications/ OR ((diet* OR eating OR fluid consumption OR fluid intake OR food OR nutrient* OR nutrition*) adj3 (assess* OR behavio$r* OR biochemical analysis OR biochemistry OR diaries OR diary OR evaluat* OR habit$ OR measur* OR record*)).ti,ab,kf. OR ((biological marker* OR biomarker*).ti,ab,kf,sh. AND (diet* OR food OR nutrit*).ti,ab,kf,hw.) OR (24h recall OR 24hour recall OR 24-hour recall OR 24h urine collection OR 24hour urine collection OR 24-hour urine collection OR FFQ OR food frequency questionnaire OR online questionnaire* OR photo app* OR photo phone app* OR smart bottle*).ti,ab,kf.) AND English.lg. NOT (exp animals/ not humans/) NOT ((exp Infant/ OR exp Child/ OR Adolescent/) not exp Adult/) NOT (comment/ or editorial/ or letter/)

As of June 10th 2020, 426 references found.

Embase.com

('urolithiasis'/de OR 'nephrolithiasis'/de OR 'kidney lithiasis':ti,ab,kw OR 'nephrolithiasis':ti,ab,kw OR 'renal lithiasis':ti,ab,kw OR 'renolithiasis':ti,ab,kw OR ((kidney OR renal) NEAR/2 (calcul* OR stone*)):ti,ab,kw OR ('urinary calcul*' OR 'urinary lithiasis' OR 'urinary stone*' OR 'urinary tract calcul*' OR 'urinary tract lithiasis' OR 'urinary tract stone*' OR 'urine calcul*' OR 'urine lithiasis' OR 'urine stone*' OR 'uro-lithiasis' OR urocalcul* OR urolith OR urolithiasis OR urolithogenesis OR 'urologic calcul*' OR 'urological calcul*'):ti,ab,kw) AND ('nutritional assessment'/de OR 'food frequency questionnaire'/de OR 'mobile application'/exp OR ((diet* OR eating OR 'fluid consumption' OR 'fluid intake' OR food OR nutrient* OR nutrition*) NEAR/3 (assess* OR behavio$r* OR 'biochemical analysis' OR biochemistry OR diaries OR diary OR evaluat* OR habit$ OR measur* OR record*)):ti,ab,kw OR (('biological marker*' OR biomarker*):ti,ab,kw,de AND (diet* OR food OR nutrit*):ti,ab,kw,de) OR ('24h recall' OR '24hour recall' OR '24-hour recall' OR '24h urine collection' OR '24hour urine collection' OR '24-hour urine collection' OR FFQ OR 'food frequency questionnaire' OR 'online questionnaire*' OR 'photo app*' OR 'photo phone app*' OR 'smart bottle*'):ti,ab,kw) AND [english]/lim NOT ([animals]/lim NOT [humans]/lim) NOT ('juvenile'/exp NOT 'adult'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it)

As of June 10th 2020, 536 references found.

CINAHL EBSCO

(MH "Urolithiasis" OR TI "kidney lithiasis" OR AB "kidney lithiasis" OR TI nephrolithiasis OR AB nephrolithiasis OR TI "renal lithiasis" OR AB "renal lithiasis" OR TI renolithiasis OR AB renolithiasis OR ((TI kidney OR AB kidney OR TI renal OR AB renal) N2 (TI calcul* OR AB calcul* OR TI stone* OR AB stone*)) OR TI "urinary calcul*" OR AB "urinary calcul*" OR TI "urinary lithiasis" OR AB "urinary lithiasis" OR TI "urinary stone*" OR AB "urinary stone*" OR TI "urinary tract calcul*" OR AB "urinary tract calcul*" OR TI "urinary tract lithiasis" OR AB "urinary tract lithiasis" OR TI "urinary tract stone*" OR AB "urinary tract stone*" OR TI "urine calcul*" OR AB "urine calcul*" OR TI "urine lithiasis" OR AB "urine lithiasis" OR TI "urine stone*" OR AB "urine stone*" OR TI uro-lithiasis OR AB uro-lithiasis OR TI urocalcul* OR AB urocalcul* OR TI urolith OR AB urolith OR TI urolithiasis OR AB urolithiasis OR TI urolithogenesis OR AB urolithogenesis OR TI "urologic calcul*" OR AB "urologic calcul*" OR TI "urological calcul*" OR AB "urological calcul*")

AND

(MH "Nutritional Assessment" OR MH "Diet Records" OR MH "Mobile Applications" OR ((TI diet* OR AB diet* OR TI eating OR AB eating OR TI "fluid consumption" OR AB "fluid consumption" OR TI "fluid intake" OR AB "fluid intake" OR TI food OR AB food OR TI nutrient* OR AB nutrient* OR TI nutrition* OR AB nutrition*) N3 (TI assess* OR AB assess* OR TI behavio#r# OR AB behavior#r# OR TI "biochemical analysis" OR AB "biochemical analysis" OR TI biochemistry OR AB biochemistry OR TI diaries OR AB diaries OR TI diary OR AB diary OR TI evaluat* OR AB evaluat* OR TI habit* OR AB habit* OR TI measur* OR AB measur* OR TI record* OR AB record*)) OR ((TI "biological marker*" OR AB "biological marker*" OR TI biomarker* OR AB biomarker*) AND (TI diet* OR AB diet* OR TI food OR AB food OR TI nutrit* OR AB nutrit*)) OR (TI "24h recall" OR AB "24h recall" OR TI "24hour recall" OR AB "24hour recall" OR TI "24-hour recall" OR AB "24-hour recall" OR TI "24h urine collection" OR AB "24h urine collection" OR TI "24hour urine collection" OR AB "24hour urine collection" OR TI "24-hour urine collection" OR AB "24-hour urine collection" OR TI FFQ OR AB FFQ OR TI "food frequency questionnaire" OR AB "food frequency questionnaire" OR TI "online questionnaire*" OR AB "online questionnaire*" OR TI "photo app*" OR AB "photo app*" OR TI "photo phone app*" OR AB "photo phone app*" OR TI "smart bottle*" OR AB "smart bottle*"))

NOT (((MH "Child+") OR (MH "Adolescence+")) NOT (MH "Adult+"))

As of June 10th 2020, 81 references found.

Central - Cochrane Library Wiley

(urolithiasis OR "kidney lithiasis" OR nephrolithiasis OR "renal lithiasis" OR renolithiasis OR ((kidney OR renal) NEAR/2 (calcul* OR stone*)) OR "urinary calcul*" OR "urinary lithiasis" OR "urinary stone*" OR "urinary tract calcul*" OR "urinary tract lithiasis" OR "urinary tract stone*" OR "urine calcul*" OR "urine lithiasis" OR "urine stone*" OR uro-lithiasis OR urocalcul* OR urolith OR urolithiasis OR urolithogenesis OR "urologic calcul*" OR "urological calcul*") AND (((diet* OR eating OR "fluid consumption" OR "fluid intake" OR food OR nutrient* OR nutrition*) NEAR/3 (assess* OR behavior* OR behaviour* OR "biochemical analysis" OR biochemistry OR diaries OR diary OR evaluat* OR habit OR habits OR measur* OR record*)) OR (("biological marker*" OR biomarker*) AND (diet* OR food OR nutrit*)) OR ("24h recall" OR "24hour recall" OR "24-hour recall" OR "24h urine

collection" OR "24hour urine collection" OR "24-hour urine collection" OR FFQ OR "food frequency questionnaire" OR "mobile application*" OR "online questionnaire*" OR "photo app*" OR "photo phone app*" OR "smart bottle*"))

As of June 10th 2020, 69 references found.

Web of Science – Core collection*

(urolithiasis OR "kidney lithiasis" OR nephrolithiasis OR "renal lithiasis" OR renolithiasis OR ((kidney OR renal) NEAR/2 (calcul* OR stone*)) OR "urinary calcul*" OR "urinary lithiasis" OR "urinary stone*" OR "urinary tract calcul*" OR "urinary tract lithiasis" OR "urinary tract stone*" OR "urine calcul*" OR "urine lithiasis" OR "urine stone*" OR uro-lithiasis OR urocalcul* OR urolith OR urolithiasis OR urolithogenesis OR "urologic calcul*" OR "urological calcul*") AND (((diet* OR eating OR "fluid consumption" OR "fluid intake" OR food OR nutrient* OR nutrition*) NEAR/3 (assess* OR behavior* OR behaviour* OR "biochemical analysis" OR biochemistry OR diaries OR diary OR evaluat* OR habit OR habits OR measur* OR record*)) OR (("biological marker*" OR biomarker*) AND (diet* OR food OR nutrit*)) OR ("24h recall" OR "24hour recall" OR "24-hour recall" OR "24h urine collection" OR "24hour urine collection" OR "24-hour urine collection" OR FFQ OR "food frequency questionnaire" OR "mobile application*" OR "online questionnaire*" OR "photo app*" OR "photo phone app*" OR "smart bottle*")) NOT ((Child* OR Adolescen*) NOT adult))

As of June 10th 2020, 542 references found.

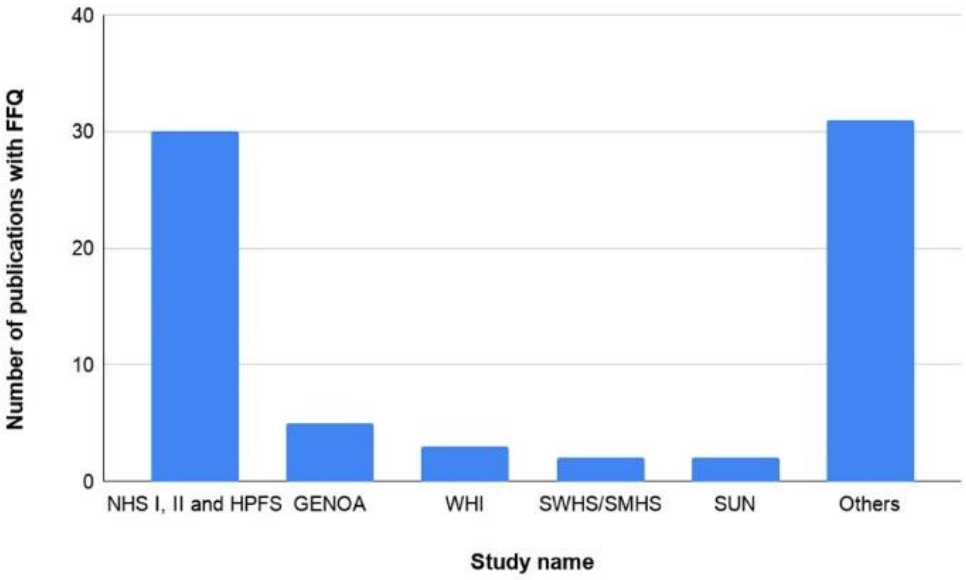


Fig.7 Number of publications per study with a FFQ (n=73)

NHS I and II: Nurses' Health Study I and II
HPFS: Health Professionals Follow-Up Study
GENOA: The Genetic Epidemiology Network of Arteriopathy cohort
WHI: The Women's Health Initiative Observational Study
SWHS/SMHS: Shanghai Women's Health Study and Shanghai Men's Health Study
SUN: The Seguimiento Universidad de Navarra

Table 1 Description of included studies

Study Name	Number of publications	Observational design	Interventional design	References
Studies with multiple publications	48	47	1	
NHS I and II, HPFS *	30	30	0	[1-30]
GENOA †	5	5	0	[31-35]
WHI ‡	3	3	0	[36-38]
SUN §	2	2	0	[39, 40]
SWHS and SMHS ¶	2	2	0	[41, 42]
Bonn Urolithiasis Follow-up Study	2	1	1	[43, 44]
Naya et al.	2	2	0	[45, 46]
Damasio et al.	2	2	0	[47, 48]
Studies with a single publication	114	75	39	[49-162]
Total	162	122	40	

* Nurses' Health Study I and II, Health Professionals Follow-Up Study
† The Genetic Epidemiology Network of Arteriopathy cohort
‡ The Women's Health Initiative Observational Study
§ The Seguimiento Universidad de Navarra
¶ Shanghai Women's Health Study and Shanghai Men's Health Study

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4. Description of kidney stone formers' diet and comparison to a control group

Title of the manuscript: Differences in the food consumption between kidney stone formers and non-formers in the Swiss Kidney Stone Cohort

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4.1. Abstract

Objective: Diet has a major influence on the formation and management of kidney stones. However, kidney stone formers' diet is difficult to capture in a large population. Our objective was to describe the dietary intake of kidney stone formers in Switzerland and to compare it to non-stone formers.

Methods: We used data from the Swiss Kidney Stone Cohort (n=261), a multicentric cohort of recurrent or incident kidney stone formers with additional risk factors, and a control group of CT-scan proven non-stone formers (n=197). Dieticians conducted two consecutive 24-h dietary recalls, using structured interviews and validated software (GloboDiet). We took the mean consumption per participant of the two 24-h dietary recalls to describe the dietary intake and used two-part models to compare the two groups.

Results: The dietary intake was overall similar between stone and non-stone formers. However, we identified that kidney stone formers had a higher probability of consuming cakes and biscuits (odds ratio, OR[95% CI] =1.56[1.03; 2.37]) and soft drinks (OR=1.66[1.08; 2.55]). Kidney stone formers had a lower probability of consuming nuts and seeds (OR =0.53[0.35; 0.82]), fresh cheese (OR=0.54[0.30; 0.96]), teas (OR=0.50[0.3; 0.84]), and alcoholic beverages (OR=0.35[0.23; 0.54]), especially wine (OR=0.42[0.27; 0.65]). Furthermore, among consumers, stone formers reported smaller quantities of vegetables (β coeff[95% CI]= - 0.23[- 0.41; - 0.06]), coffee (β coeff= - 0.21[- 0.37; - 0.05]), teas (β coeff= - 0.52[- 0.92; - 0.11]) and alcoholic beverages (β coeff= - 0.34[- 0.63; - 0.06]).

Conclusion: Stone formers reported lower intakes of vegetables, tea, coffee, and alcoholic beverages, more specifically wine, but reported drinking more frequently soft drinks than non-stone formers. For the other food groups, stone formers and non-formers reported similar

dietary intakes. Further research is needed to better understand the links between diet and kidney stone formation and develop dietary recommendations adapted to the local settings and cultural habits.

Keywords Kidney stones – dietary assessment – nutritional epidemiology

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4.2. Introduction

Diet plays a key role in both the formation and management of kidney stones. Previous studies in the US [1-4], UK [5, 6], and Spain [7, 8] identified dietary protective and risk factors linked to the development of kidney stones. Current dietary guidelines to prevent kidney stones include a sufficient fluid intake to reach a urinary volume >2L/24-h in order to dilute the urine and reduce the concentration of urinary lithogenic components [9, 10]. Low sodium, oxalate and protein dietary intakes with a normal calcium intake (1000-1200 mg/day) and a high fruits and vegetables intake can also decrease the risk of kidney stone formation [9, 10]. The human diet is multidimensional, complex, and highly variable [11] and cultural factors influence food choices [12]. It is thus important to explore further the associations between dietary factors and the risk of kidney stones to deepen our understanding of the role of diet in nephrolithiasis pathophysiology.

Kidney stones are associated with high morbidity (potential complications include ureteral obstruction or kidney failure) and high costs [13, 14]. Kidney stone prevalence reaches 5-10 % in Europe and has been increasing worldwide during the last decades [13, 15, 16]. Primary and secondary prevention based on efficient dietary recommendations has a major role to play to fight this public health problem [9, 17].

The Swiss Kidney Stone Cohort (SKSC) has been launched in 2014 to study the epidemiology and pathogenesis of kidney stone disease in Switzerland [18]. The first Swiss national nutrition survey, menuCH, conducted in 2014-2015, assessed dietary intake in the Swiss general adult population via 24-hour dietary recalls [19]. Given the paucity of data on the diet of kidney stone formers in Switzerland so far, it was of great interest to collect high quality nutritional data specific to kidney stone formers. Here, we described the food consumption of kidney

stone formers from the SKSC at baseline and compared it to a group of non-kidney stone formers.

4.3. Materials and methods

Study Population

The SKSC is a multicentric cohort of kidney stone formers covering five centers in the German and French-speaking parts of Switzerland (Berne, Zurich, Basel/Aarau, Lausanne, and Geneva) [18]. The cohort includes both incident and recurrent stone formers, recruited from the nephrology outpatient clinics. Inclusion criteria were to have recurrent (>1) stone episodes or an incident episode with other risk factors such as first episode before 25 years old, positive family history, non-calcium oxalate stones, gastrointestinal disorders, metabolic syndrome,osteoporosis, chronic urinary tract infection or chronic renal failure. Participants under 18 years old were not included in the cohort. The same harmonized protocol was used across all centers. Participants were recruited between May 2014 and March 2020.

The SKSC contains a unique set of data, with detailed anthropometric measures, nutritional data, and biological samples. After a baseline examination (≥ 4 weeks post stone passage or intervention), follow-up visits were conducted at 3 months, one year, and then once a year during 3 years. After the 3 years, study nurses checked annually on participants by phone calls. Data collected at each visit included medical and stone history, physical exam, 24-h dietary recalls, 24-h urine collections, and blood samples.

A control group of non-stone formers was recruited in the general adult population, by advertisement (in Geneva, Zurich, Aarau and Lausanne centers). Controls, unlike kidney stones formers, were seen only for a baseline visit, yet we used the same standard operating procedures for dietary intake and questionnaire data, as well as for urine and blood sample

collections. These participants had no kidney stone history and were free of stones, as ruled out by a native CT-scan of the abdomen. Matching for sex and age with SKSC participants was done when possible but in the final sample, the control group includes more women and younger individuals than the SKSC.

Dietary Intake Assessment

At each visit, participants completed two consecutive 24-h dietary recalls (except at the 3 months follow-up visit where only a single 24-h recall was completed), in which participants described and quantified every food and beverage item consumed over the 48-h recall period. Trained dieticians conducted the interviews, using a dedicated and validated software to collect the data, GloboDiet® (GD, formerly EPIC-Soft®, version CH-2016.4.10, International Agency for Research on Cancer (IARC), Lyon, France, adapted to the Swiss food market) [20-22]. Interviews were distributed over weekdays and weekends and throughout the year, depending on participants' availability and moment of inclusion in the study. For stone formers, 127 interviews (49%) were done during weekdays only, 100 (38%) during weekends only and 34 (13%) were a mix of weekdays and weekends. For non-stone formers, 84 interviews (43%) were done during weekdays only, 93 (47%) during weekends only and 20 (10%) were a mix of weekdays and weekends.

As previously described [19, 22], the 24-h dietary recalls were multiple-pass (recall process organized in standardized steps with probes from the interviewer to help participants remember food and beverages consumed) and automated. We categorized foods or beverages into 19 main food groups (e.g. vegetables, cereals, meat, fish and seafood, non-alcoholic beverages), based on food groups precoded by GD. These food groups are further divided into several subgroups. Specific descriptors allow a highly standardized description of

foods and recipes [19, 20]. Furthermore, a picture book, also including typical Swiss recipes, helped participants to quantify the amounts of foods and beverages consumed [23]. Macronutrients (energy, protein, carbohydrates and fat) intakes were calculated by GD for each interview.

Vegetables are an important source of oxalate in the diet. As oxalate plays a major role in the physiopathology of kidney stones, we were interested in detailing the consumption of vegetables depending on their oxalate content. We categorized vegetables based on their oxalate content using the table from the Harvard T.H Chan School of Public Health as the reference [24]. Based on this reference table, we associated an oxalate content category to 51 out of the 104 vegetables available in GD (49%). There are seven different oxalate content categories: very high (n=8 vegetables), high (n=3 vegetables), moderate (n=11 vegetables), low (n=3 vegetables), very low (n=11 vegetables), little/none (n=15 vegetables), unknown (for the vegetables that could not be associated with an oxalate content category (n=53 vegetables).

For beverages, we used the Food and Agriculture Organization of the United Nations (FAO) database [25] for the density of the different liquids. As the density of most beverages was close to 1, we applied a general conversion factor of 1g=1ml for the non-alcoholic and alcoholic beverages.

Statistical Analysis

To compare characteristics of stone and non-stone formers, we used the chi-square test for categorical variables and the two-sample t-test for continuous variables.

Whenever participants did not consume a given food or beverage during the two baseline recalls, they were labelled as non-consumers (and attributed a consumption value of zero) for this specific food or beverage group.

For each participant, we calculated the mean consumption of the two consecutive 24-h dietary recalls from baseline to describe the dietary intake, by macronutrients, food groups, and subgroups, in the stone and non-stone formers groups. We generated mean consumed quantities considering all the participants, both consumers and non-consumers.

We also compared the dietary intake between stone formers and non-stone formers. Some of the food groups had a large proportion of non-consumers and presented a skewed distribution. As linear regression models do not fit well such data, we therefore used two-part models [26] to compare the dietary intakes between the two groups. The two-part model estimates separately 1) the association of the kidney stone status (stone formers coded as 1 and non-formers as 0), taken as the independent variable of interest, with the probability of consumption (consumers coded as 1 and non-consumers coded as 0), as the dependent variable of interest, in a logistic regression model and 2) the association of kidney stone status with the quantities reported by consumers, taken as the dependent variable of interest, in a linear regression model. In both models, we included as covariables age, sex, body mass index (BMI), linguistic region (French- or German-speaking part of Switzerland), mean energy intake, and education level (coded as low [secondary school], middle [high school, apprenticeship] and high [university degree]). We used a log-transformation of the dependent variable (mean consumed quantity) to better approximate a symmetric and normal distribution of the residuals. Furthermore, we decided that a minimum of 50 consumers and non-consumers (logistic regression) and 50 consumers (linear regression) in a food group was needed to have

enough information in the data to run the regression model. We considered two-sided p-value <0.05 as statistically significant in our analyses.

As the education level was missing in 53 participants (11.5%) and BMI in 3 participants (0.6%), we used multiple imputations by chained equations. Ten complete datasets were generated using a regression model for the BMI and an ordered logit model for the education level. All variables included in the two-part models were used as potential predictors.

Finally, we compared the macronutrients' intake to the values obtained in menuCH [19], using a t-test with a normal approximation. This comparison was done as a quality check regarding the data collection and to evaluate if the intake was similar between the two studies.

The analyses are based on a database extraction done in December 2020 and were performed with Stata 16 (Stata Corporation, College Station, TX, USA). To produce the figures, we used the package ggplot2 (Wickham, 2016) from the software R, version 4.1.1 (R Core Team, 2021).

4.4. Results

There were 261 participants in the SKSC and 197 participants in the non-kidney stone formers group that had complete data to be analyzed (**Table 1**). The two groups differed in their proportion of men and women, mean age, education level, and BMI, as well as the protein intake in women.

The mean consumed quantities (in grams) for the different food groups and subgroups are shown in **Table 2**. This description allows evaluating which food groups are consumed in large or small quantities and thus identifying central elements of the diet. Legumes, nuts and seeds, dietetic and sports food and savory snacks had a low mean consumption in both stone and non-stone formers, whereas vegetables, fruits, dairy products, cereals, meat, and beverages were consumed in large quantities.

Table 3 shows the number of consumers for the different food groups, representing the participants who consumed at least once an item from a given food group during the two 24-h dietary recalls. Kidney stone status was significantly associated with the probability of consuming nuts and seeds, fresh cheese, cakes and biscuits, soft drinks, teas as well as alcoholic beverages and wine (**Table 3**). Kidney stone formers had a higher probability of consuming cakes and biscuits (odds ratio (OR) 95% confidence interval [95% CI] =1.56[1.03; 2.37]) and soft drinks (OR[95% CI] =1.66[1.08; 2.55]). However, they had a lower probability of consuming nuts and seeds (OR[95% CI] =0.53[0.35; 0.82]), fresh cheese (OR[95% CI] =0.54[0.30; 0.96]), teas (OR[95% CI] =0.50[0.3; 0.84]) and alcoholic beverages (OR[95% CI] =0.35[0.23; 0.54]), the latter through a lower consumption of wine (OR[95% CI] =0.42[0.27; 0.65]), but not of beer.

Among consumers, stone formers reported smaller amounts of vegetables (β coeff[95% CI]= -0.23[- 0.41; - 0.06]), coffee (β coeff[95% CI] = -0.21[- 0.37; - 0.05]), teas (β coeff[95% CI] = -0.52[- 0.92; - 0.11]) and alcoholic beverages (β coeff[95% CI] = - 0.34[- 0.63; - 0.06]) than non-formers (**Table 3**). Quantities reported by the consumers for other food groups were not statistically different between stone and non-stone formers (**Table 3**).

The mean consumed quantities for the different vegetables, based on their oxalate content category, are shown in **Figure 1**. The low categories (none/little, very low, and low) represent 37% of the total consumption for the stone formers and 36% for the non-stone formers, the moderate category represents 32% of the total consumption in both groups and the high categories (high and very high) represent 9% of the total consumption for the stone formers and 13% for non-stone formers.

There were both qualitative and quantitative differences in the consumption of beverages. **Figure 2** shows the percentage of consumers by beverage category for the stone formers and non-stone formers. Water and coffee were the most often consumed beverages. There were more stone formers reporting the consumption of soft drinks and more non-stone formers reporting the consumption of tea and wine. Mean consumed quantities for non-alcoholic and alcoholic beverages are reported in **Figure 3**. Both non-stone and stone formers had a high mean fluid intake over 2000 ml, however non-stone formers reported higher quantities of tea, coffee, and alcoholic beverages (especially wine) than stone formers.

Daily energy intake was slightly higher in menuCH (mean ± standard error: 2185 ± 16.6 kcal), than in stone formers (2015 ± 40.7 kcal, $p<0.001$) and non-stone formers (2065 ± 44.8 kcal, $p=0.01$). The protein intake was higher in menuCH (82.7 ± 0.7 g/day) than in stone formers (76 ± 1.7 g/day, $p<0.001$) but similar to that of non-stone formers (80 ± 2.3 g/day $p=0.27$). The carbohydrates intake was higher in menuCH (230.4 ± 2.1 g/day) than in stone formers (215 ± 5.2 g/day, $p<0.01$) and non-stone formers (208 ± 5.5 g/day, $p<0.001$). Finally, the mean fat intake was similar in menuCH (89.7 ± 1.2 g/day) than in stone formers (88 ± 2.1 g/day, $p=0.48$) and non-stone formers (90 ± 2.5 g/day, $p=0.91$).

4.5. Discussion

Overall, in our sample, the diets of kidney stone formers and non-formers were similar but we mainly identified some differences in the consumption of vegetables and beverages between the two groups. We found that kidney stone formers consumed smaller amounts of vegetables, coffee, tea, and alcoholic beverages than non-stone formers and reported more frequently the consumption of soft drinks and cakes and biscuits. In contrast, non-stone

formers reported more frequently the consumption of nuts and seeds, fresh cheese, tea, and wine compared to stone formers.

An important strength of this study is the collection of two 24-h dietary recalls for both groups. Indeed 24-h dietary recalls are considered the least biased tool in the category of self-reported dietary assessment methods [27]. Moreover, the use of the software GloboDiet® (GD), which has been validated in European dietary surveys [20, 21, 28, 29], allows for a precise and standardized characterization of dietary intake. Finally, the quality controls applied in GD and the possibility for multi-languages use [22, 29] make it a reliable tool in the multicentric setting of the SKSC.

Yet, like all self-report methods, 24-h dietary recalls are subject to errors and biases [27, 30-32] and have been shown to poorly estimate total energy intake [27, 31, 33]. 24-h dietary recalls contain both random errors, due to day-to-day variation in the diet of individuals, and systematic errors [27], such as the consistent underreporting of certain foods and beverages (e.g. fats, sweets) [33]. Random errors induce a greater variance in the measures and can lead to inaccurate usual intake distributions. However, regarding the mean intake, a study identified that single recalls or the average of two 24-h dietary recalls estimated correctly population estimates of mean intakes and were not inferior to estimates using other more sophisticated models for this specific purpose [34]. In our study, as we worked with the mean consumption and not the usual intake, results should thus be less impacted by such errors. Finally, as 24-h dietary recalls focus on a single day (usually the previous day), the magnitude of systematic errors is less important than with other methods [32].

Furthermore, the SKSC included both incident and recurrent stone formers. In the context of a stone event, after metabolic evaluation and during their follow-up, kidney stone formers

usually receive dietary recommendations. These recommendations can be general, such as increasing their liquid intake or avoiding high oxalate content foods and beverages [9, 35]. Recommendations can also specifically target urinary risk factors (e.g. hypercalciuria or hypocitraturia) identified after a metabolic evaluation with an analysis of 24-h urine composition [9, 35]. It is thus possible that some recurrent stone formers had already modified their diet at the baseline visit, while others did not.

The results of this study are consistent with the literature. We found that non-stone formers consumed more vegetables than stone formers. The impact of vegetable consumption on stone formation is complex. Studies showed a protective effect of vegetables on the risk of kidney stones [36-42] but some types of vegetables, such as leafy greens, were identified as risk factors [43, 44]. Indeed, leafy greens have a high content of oxalates and can thus increase the risk of oxalate-based stones, the most common stone type [9, 45]. As intestinal absorption of oxalate can be influenced by the presence of calcium, it is also interesting to note that we observed no statistically significant difference in the quantities of dairy products (one of the major source of calcium in the diet) reported by the consumers.

Vegetables interact with other elements of the diet and their impact on kidney stone formation needs to be considered in the context of the whole diet. Some studies identified that diets such as the Mediterranean, DASH, or vegetarian diets (characterized by a high intake of vegetables, fruits, nuts, and legumes and a low/no intake of red meat) were associated with a reduced risk of kidney stones [2, 5, 8, 35, 46, 47].

Moreover, vegetables are an important source of various elements, such as fibers, potassium, phytates, citrate, or oxalates among others. However, depending on their combination and balance with other foods and beverages, these elements might have a different impact on the

risk. For instance, the impact of high fiber diets was inconsistent: studies identified high fiber diets as protective [6, 39], without effect [48], or at increased risk [49] for kidney stone formation. Fibers can decrease the urinary excretion of oxalate and calcium by binding minerals and fats in the gastrointestinal tract [17] but if a fiber-rich diet is associated with a low calcium intake, the result can thus be a lowered urinary calcium excretion and higher oxalate concentration [35]. Another example is green tea. Tea is known to contain oxalates, which could put tea in the "at-risk" category but overall, due to components such as antioxidants and other phytochemicals, green tea has been shown to be protective against kidney stone formation [17]. Finally, investigators also highlighted the importance of the balance between different components of the diet, showing that a higher animal protein-to-potassium (mainly derived from vegetables and fruits) ratio was associated with a higher risk [50].

Insufficient fluid intake is one of the most important risk factors for kidney stone formation [9]. Some beverages seem to be protective while others increase the risk but these effects are still debated [9]. Previous studies showed that tea [6, 42, 51-54], coffee [6, 51-53, 55], and alcoholic beverages [6] such as beer [49, 51, 53, 56] or wine [51-53] were associated with a decreased risk. However, studies also identified that total fluid intake was the main protective factor, independently of the beverage category [43], or that alcohol was increasing the risk [57-59]. Overall, it seems that urine dilution is key but different beverages may have properties leading to either a decreased or an increased risk.

As mentioned, stone formers were not naive when they entered the cohort and may have received and already implemented some dietary recommendations. In that context, interpretation of the low consumption of tea and other oxalate containing food should be

exerted with caution. In addition, we still identified qualitative and quantitative differences for beverages between non-formers and formers, despite the fact that increasing volume intake is one of the main dietary recommendation for kidney stone prevention. This could reveal a difficulty to implement these recommendations in the day-to-day life.

Finally, regarding the comparison of macronutrients' intake with menuCH, there were some statistically significant differences in energy intake, protein intake and carbohydrates intake between menuCH and the SKSC. However, the scales and ranges of the energy and macronutrients intakes are similar between the two studies.

This study is the first to describe the diet of kidney stone formers in Switzerland, where the diets in the French and German-speaking regions are known to substantially differ [19]. As kidney stones are becoming more prevalent, it is of key importance to better understand the dietary characteristics of kidney stone formers in order to build dietary recommendations that take the local settings and cultural habits into account. This description of the food intake is thus a first step towards understanding kidney stone formers diet' specificities and can inform future studies. Yet, as mentioned before, self-report methods are prone to errors and biases. Therefore, future research combining objective nutritional biomarkers such as sodium, potassium, or urea excretion in 24-h urine collections and data collected with self-report methods will help evaluate the impact of diet on kidney stone formation in Switzerland.

4.6. Practical implications

This study helps define points of action in the prophylaxis of kidney stones in Switzerland. We found that stone formers consumed fewer vegetables and had a tendency to drink more soft drinks and less tea/coffee and alcoholic beverages. As recommended in the existing literature [9, 10, 35] and in accordance with the present results, health professionals should

encourage stone formers to eat a diet rich in vegetables, dairy products and limited in meat and salt. Additionally, a high intake of beverages (with a preference for water and non-sweetened beverages) is indicated to dilute the urine and limit its saturation in lithogenic components.

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4.8. Tables

Table 1. Characteristics of the participants with two 24-h dietary recalls at baseline

		SKSC (n= 261)	Non-kidney stone formers (n=197)	p-value*
Women, n (%)		93 (36%)	90 (46%)	0.03
Age (years), mean [min,max]	All	47.3 [19,79]	43.4 [20,81]	<0.01
	Men	48.2 [20,79]	45.7 [22,81]	0.15
	Women	45.6 [19,73]	40.6 [20,62]	<0.01
German speaking part, n (%)		148 (57%)	109 (55%)	0.77
Education level 53 missing (33 SKSC, 20 non-formers)	Low	27 (12%)	3 (2%)	<0.01
	Middle	131 (57%)	72 (40%)	
	High	70 (31%)	102 (58%)	
BMI (kg/m^2), mean (SD) 3 missing (2 SKSC, 1 non-formers)	All	26.6 (4.7)	25.2 (4.4)	<0.01
	Men	26.7 (4.5)	26 (3.8)	0.15
	Women	26.2 (5.2)	24.2 (4.9)	<0.01
Total calorie intake (kcal/24h), mean (SD) †	All	2015 (658)	2065 (629)	0.41
	Men	2203 (628)	2274 (648)	0.38
	Women	1674 (572)	1817 (508)	0.08
Total protein intake (g/24h), mean (SD) †	All	76 (28)	80 (33)	0.22
	Men	84 (28)	88 (37)	0.34
	Women	62 (23)	70 (25)	0.03
Total carbohydrates intake (g/24h), mean (SD) †	All	215 (84)	208 (77)	0.38
	Men	235 (86)	229 (82)	0.55
	Women	178 (66)	184 (63)	0.58
Total fat intake (g/24h), mean (SD) †	All	88 (34)	90 (35)	0.50
	Men	95 (33)	98 (39)	0.45
	Women	76 (33)	81 (29)	0.28

* the two groups were compared using the chi-square test for categorical variables and the two sample t-test for continuous variables

† calculated using the mean intake of the two 24-h dietary recalls for each participant

Table 2. Description of mean food consumption for all participants (consumers and non-consumers), by sex

	Mean consumption, g (SE) *			
	Men		Women	
	Stone formers (n=168)	Non-stone formers (n=107)	Stone formers (n=93)	Non-stone formers (n=90)
Potatoes	45(5)	49(7)	45(6)	39(6)
Vegetables	138(8)	188(19)	154(11)	214(15)
Legumes (pulses)	4(2)	9(3)	4(2)	3(1)
Fruits	148(11)	133(13)	139(12)	168(17)
Nuts and seeds	6(1)	10(2)	5(1)	10(2)
Dairy products (all subgroups †)	241(15)	263(19)	195(19)	228(19)
Milk	100(12)	114(16)	70(13)	66(11)
Substitute milks (soy, coconut)	12(5)	14(5)	11(8)	31(11)
Yogurt	47(6)	41(7)	47(8)	57(12)
Fresh cheese	14(4)	17(5)	8(3)	16(4)
Cheese	43(3)	51(5)	35(4)	37(4)
Cereals	261(12)	255(12)	175(10)	182(10)
Meat	119(7)	115(9)	78(7)	81(8)
Fish and seafood	34(4)	26(4)	26(5)	29(4)
Eggs	19(2)	23(3)	15(2)	20(3)
Oils and fat	19(1)	22(2)	21(2)	20(2)
Sugar, chocolate and sweets	36(3)	38(4)	32(4)	31(3)
Cakes and biscuits	49(6)	41(6)	32(6)	29(5)
Non-alcoholic beverages (ml) (all subgroups †)	2269(66)	2125(82)	2008(71)	2133(98)
Juices	75(11)	80(16)	75(16)	66(12)
Soft drinks	211(27)	158(26)	145(29)	126(34)
Coffee	233(20)	296(26)	229(22)	233(22)
Tea	36(9)	114(30)	45(14)	156(29)
Infusions	114(22)	100(30)	207(36)	179(36)
Water (tap and bottled)	1583(72)	1360(86)	1298(74)	1369(100)
Alcoholic beverages (ml) (all subgroups †)	152(19)	277(40)	43(11)	116(17)
Wine	61(9)	107(17)	21(7)	77(15)
Beer	85(14)	159(37)	20(8)	32(9)
Spirits	3(2)	0.3(0.3)	0.07(0.05)	0.2(0.2)
Spices and sauces	39(3)	34(3)	33(4)	30(3)
Soups	39(8)	33(9)	44(10)	50(12)
Dietetic and sports food	5(2)	10(6)	0.3(0.15)	3(1)
Savory snacks	11(2)	12(3)	14(3)	10(3)

* calculated using the mean intake of the two 24-h dietary recalls for each participant, standard error (SE)

† including subgroups not detailed in this table

Table 3. Influence of the kidney stone status on the probability of consumption and differences in the mean dietary consumption between kidney stone formers and non-formers

		Step 1 (consumption yes/no)			Step 2 (consumed quantities among consumers)		
		Logistic regression*			Linear regression*		
	Consumers, n (%)	**OR**	**95% CI**	**p-value**	**Coeff** †	**95% CI**	**p-value**
Potatoes	217(47.4)	1.06	0.70;1.59	0.79	-0.08	-0.28;0.13	0.46
Vegetables	436(95.2)	NA‡	NA	NA	-0.23	-0.41;-0.06	**0.009**
Legumes (pulses)	46(10)	NA	NA	NA	NA	NA	NA
Fruits	354(77.3)	0.87	0.53;1.45	0.60	0.008	-0.18;0.2	0.94
Nuts and seeds	158(34.5)	0.53	0.35;0.82	**0.004**	-0.26	-0.67;0.16	0.22
Dairy products	446(97.4)	NA	NA	NA	-0.09	-0.26;0.09	0.34
Milk	268(58.5)	0.93	0.61;1.4	0.71	-0.12	-0.44;0.2	0.45
Substitute milks	47(10.3)	NA	NA	NA	NA	NA	NA
Yogurt	186(40.6)	1.07	0.71;1.61	0.75	-0.06	-0.3;0.18	0.61
Fresh cheese	65(14.2)	0.54	0.30;0.96	**0.036**	0.45	-0.14;1.03	0.13
Cheese	373(81.4)	0.76	0.45;1.28	0.31	-0.02	-0.21;0.18	0.88
Cereals	455(99.3)	NA	NA	NA	0.05	-0.06;0.16	0.35
Meat	405(88.4)	0.52	0.26;1.02	0.06	-0.02	-0.19;0.15	0.83
Fish and seafood	187(40.8)	0.92	0.61;1.4	0.70	0.20	-0.05;0.45	0.11
Eggs	225(49.1)	0.82	0.55;1.23	0.35	0.04	-0.22;0.30	0.77
Oils and fat	430(93.9)	NA	NA	NA	-0.04	-0.22;0.13	0.64
Sugar, chocolate, sweets	391(85.4)	1.09	0.6;1.97	0.78	-0.008	-0.23;0.21	0.94
Cakes and biscuits	251(54.8)	1.56	1.03;2.37	**0.038**	0.07	-0.16;0.30	0.56
Non-alcoholic beverages (ml)	458(100)	NA	NA	NA	0.04	-0.04;0.12	0.34
Juices	233(50.9)	1.33	0.89;1.99	0.17	-0.08	-0.55;0.38	0.72
Soft drinks	183(40)	1.66	1.08;2.55	**0.02**	-0.27	-0.57;0.03	0.075
Coffee	344(75.1)	0.83	0.52;1.33	0.44	-0.21	-0.37;-0.05	**0.011**
Tea	95(20.7)	0.50	0.3;0.84	**<0.01**	-0.52	-0.92;-0.11	**0.012**
Infusions	135(29.5)	1.24	0.79;1.95	0.35	0.01	-0.21;0.41	0.53
Water (tap and bottled)	443(96.7)	NA	NA	NA	0.11	-0.04;0.26	0.17
Alcoholic beverages (ml)	218(47.6)	0.35	0.23;0.54	**<0.001**	-0.34	-0.63;-0.06	**0.02**
Wine	153(33.4)	0.42	0.27;0.65	**<0.001**	-0.29	-0.59;0.006	0.05
Beer	95(20.7)	0.74	0.45;1.21	0.23	-0.18	-0.47;0.12	0.24
Spirits	15(3.3)	NA	NA	NA	NA	NA	NA
Spices and sauces	442(96.5)	NA	NA	NA	0.18	-0.12;0.48	0.23
Soups	116(25.3)	0.92	0.58;1.46	0.74	0.26	-0.37;0.88	0.42
Dietetic and sports food	48(10.5)	NA	NA	NA	NA	NA	NA
Savory snacks	115(25.1)	0.93	0.58;1.48	0.75	0.001	-0.39;0.39	0.1

* kidney stone formers coded as 1 and non-formers as 0. Models were adjusted for age, sex, body mass index, linguistic region, mean energy intake, and education level

† the dependent variable (mean consumption) has been log-transformed

‡ NA in the logistic regression: less than 50 participants in the consumers or non-consumers group; NA in the linear regression: less than 50 participants in the consumers group

4.9. Figures

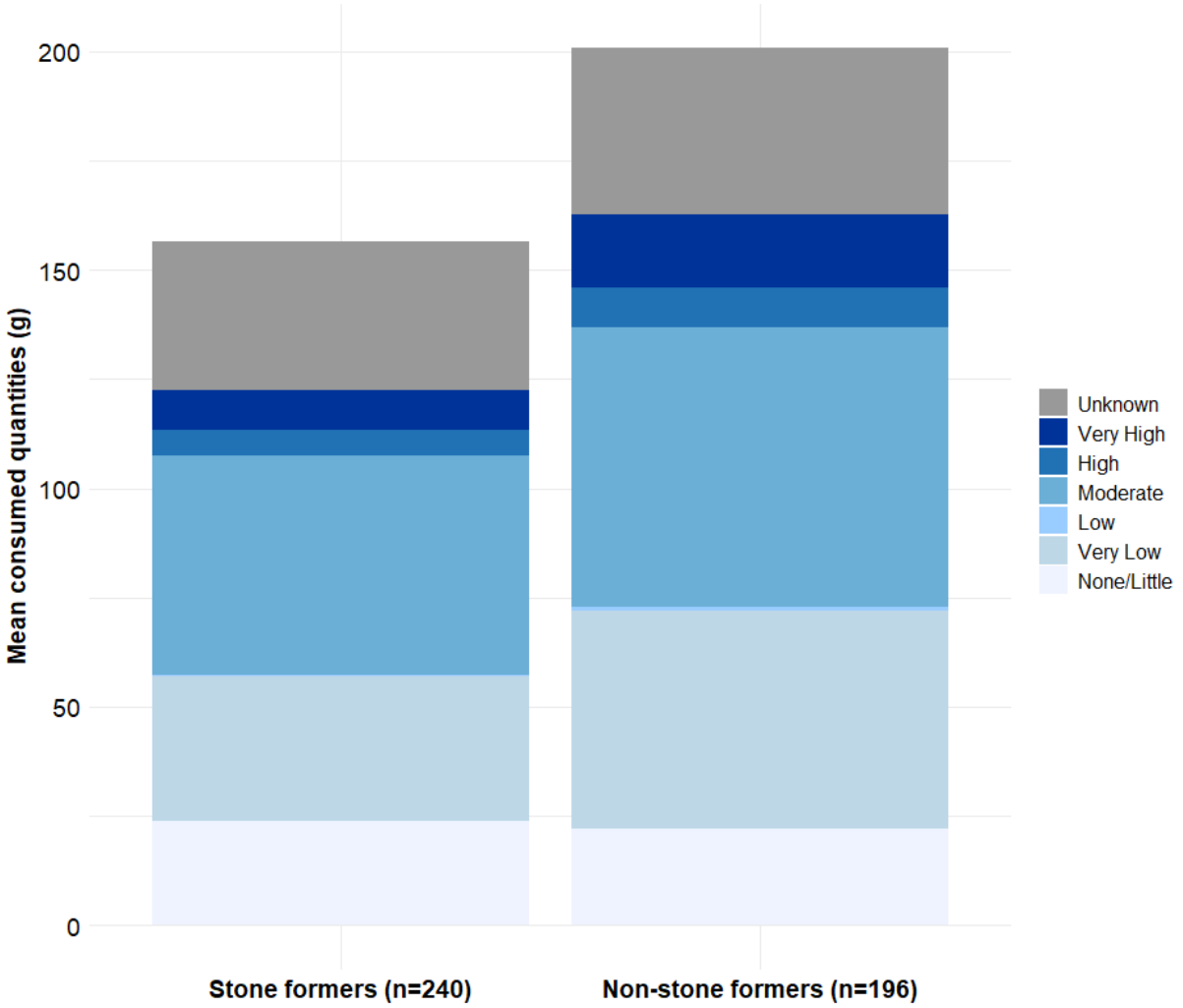

Figure 1 Mean consumed quantities of vegetables, among consumers, by oxalate-content categories

None/Little (n=15 vegetables), Very Low (n=11 vegetables), Low (n=3 vegetables), Moderate (n=11 vegetables), High (n=3 vegetables), Very High (n=8 vegetables) and Unknown (for the vegetables that could not be associated with an oxalate content category (n=53 vegetables)

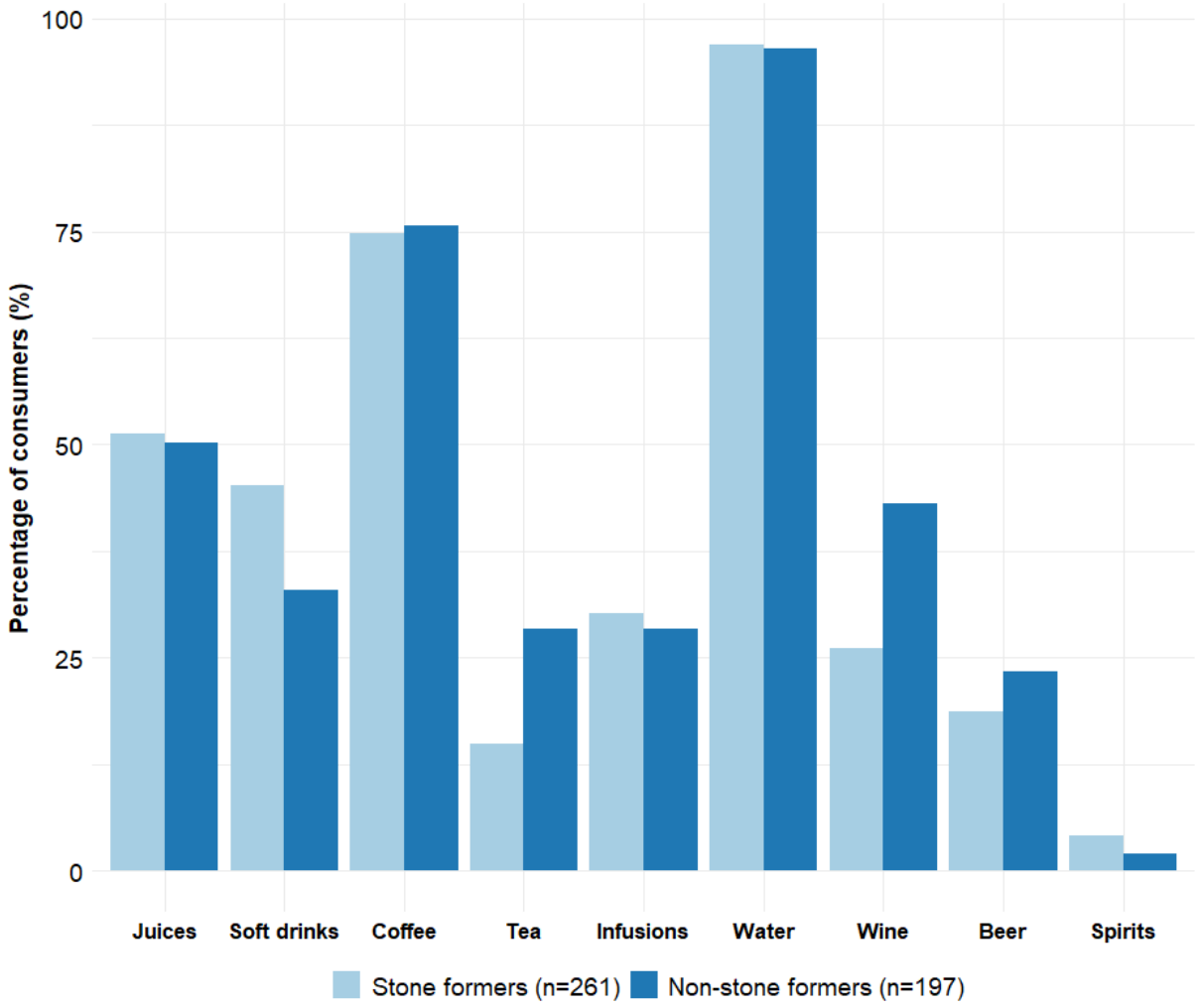

Figure 2 Percentage of consumers in the stone and non-stone formers groups, by beverage category

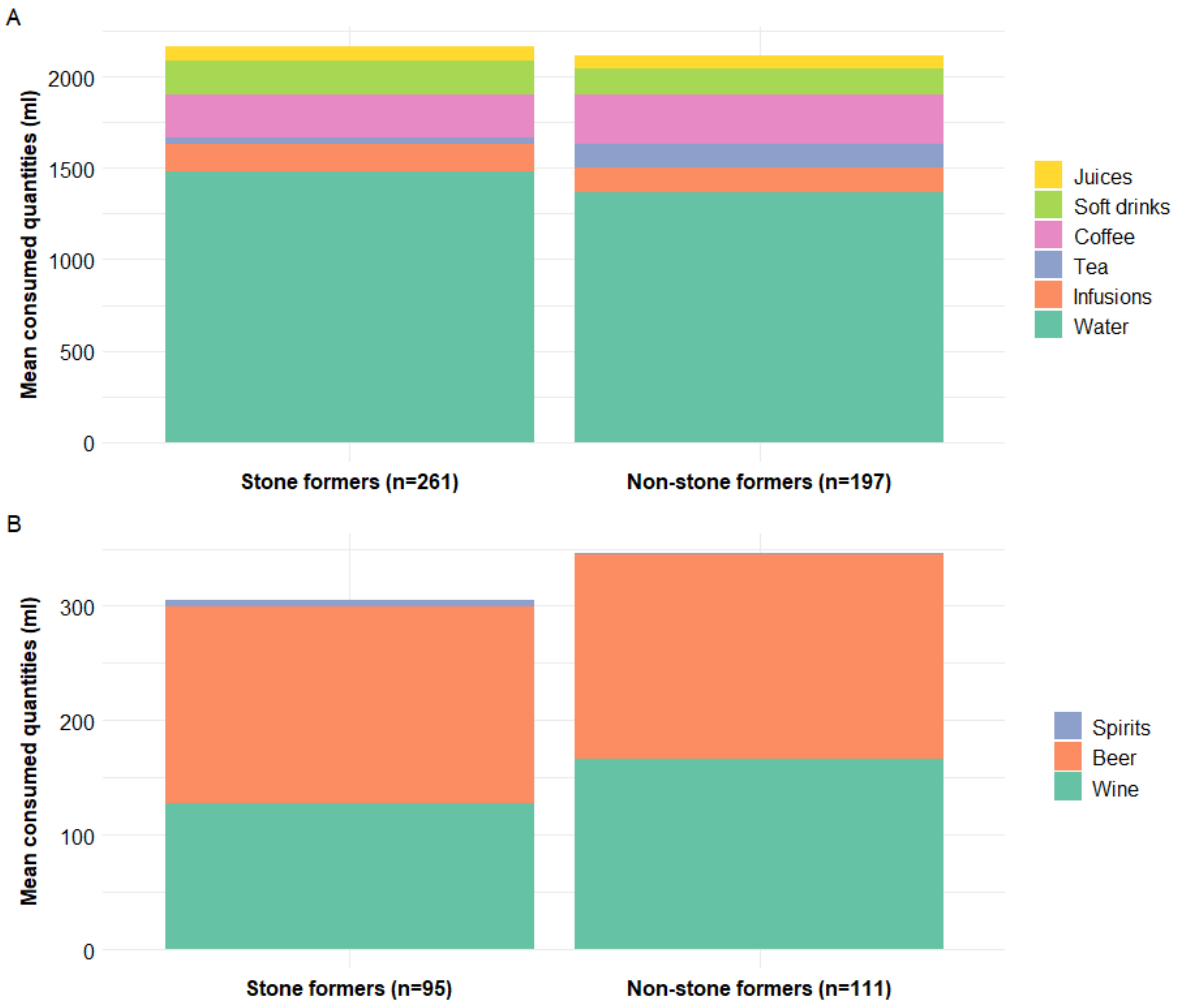

Figure 3 Mean consumed quantities of non-alcoholic (A) and alcoholic (B) beverages, among consumers

5. Comparison of 24-h dietary recalls with selected objective nutritional biomarkers measured in 24-h urine collections

5.1. Introduction

The question of the validity of dietary assessment methods used in nutritional research is of key importance [1]. Indeed, if nutritional research allowed a better understanding of associations between diet and health [2-4], these methods are subject to criticism and controversies. For some investigators, such methods should not be used [5, 6], while others recognize their importance for research despite inherent errors and biases [7, 8].

In this context, several studies evaluated the validity and compared the performance of those methods [9-21]. Results from those studies confirmed that dietary assessment methods have biases and errors but overall, researchers concluded that they are still useful, valid, and allow conducting important research in nutritional epidemiology [7, 8, 22-24].

Furthermore, no definitive gold standard method has been identified. Indeed, if objective nutritional biomarkers are usually considered the method of reference, only few have been identified and there is still the possibility of various errors from collection to laboratory analysis and influence of individual metabolism [25]. Finally, validation studies showed an important heterogeneity in the facets of validity that were analyzed and the dietary assessment methods that were compared (self-report methods vs other self-report methods, self-report methods vs objective biomarkers).

To evaluate the dietary assessment conducted in the Swiss Kidney Stone Cohort (SKSC) and control group, we compared the dietary estimates of sodium, potassium, protein and volume intakes obtained from 24-h dietary recalls and 24-h urine collections during the first visit. We used several statistical tests to explore different facets of validity, as well as the relationship between the two dietary assessment methods within each of the following strata: kidney stone status, sex, linguistic region and BMI.

5.2. Methods

We worked with the estimates of sodium, potassium, protein and volume intakes derived from the two dietary assessment methods available in the SKSC and control group: 24-h dietary recalls and 24-h urine collections. We selected those specific elements of the diet as they were previously described as objective nutritional biomarkers in urine samples [9, 26-29].

24-h dietary recalls

In the 24-h dietary recalls, participants described every food and beverage consumed over the 48-h recall period. An internal validation process was conducted on a regular basis across the different centers in order to check that dieticians were performing 24h recall interviews the same way. Macronutrients estimates were directly available in GloboDiet ® (GD), but to obtain the micronutrient composition of the different foods and beverages, the data had first to be linked to the Swiss Food Composition Database. This linkage was done using the software FoodCASE ® (FC) [30], and each proposal was validated by a senior dietician. Of note, macronutrients composition was also obtained from the Swiss Food Composition Database.

We thus obtained the composition in sodium, potassium and other micronutrients for each food and beverage described in the 24-h dietary recalls. We could then generate the total intake of sodium and potassium per recall for each participant. Regarding protein intake, we used both the estimate available in GD and the value obtained after the linkage to the Swiss Food Composition Database that we will refer to as FoodCASE (FC) estimate. Finally, for the volume intake, we also had two variables capturing two different ways of handling water intake: the beverage intake (non-alcoholic and alcoholic groups) in GD and a variable

estimating the water content from each food and beverage derived from the Swiss Food Composition Database, which we will also refer to as FC estimate.

24-h urine collections

The participants collected two consecutive 24-h urine collections under their normal living conditions (at home or at work). They were given two separate containers, one with a preservative (Thymol) for the first 24-h collection and another one, without any additive (native), for the second 24-h collection. The participants were instructed to discard the first morning urine at the start of the first 24-h collection, and then begin collecting all urine specimens using the container with the preservative. The first urine on the next morning was added to the first container. After that, following urines were collected using the second container, without additive, for the second 24-h collection. The last specimen was collected the next morning at the same time that the second collection started. The two containers were then brought to the center at the end of the second 24-h collection. Participants were asked to indicate beginning and ending time of each collection as well as potential missing urines. The duration of collection was calculated based on the self-reported time of start and end of collection period.

Several criteria have been described to evaluate the completeness of 24-h urine collections [31-33], from recovery of para-aminobenzoic acid (PABA), to time and volume intervals or 24- h creatinine excretion per kilogram of body weight. However, no criteria or combination of criteria was found to be more accurate than the others in comparison to PABA recovery and no specific criterion was identified as more accurate to identify incomplete 24-h urine collections [33]. Based on the literature [33] and the distribution in our sample, we decided to keep in our final sample the 24-h urine collections collected in the duration range of 20-28-h,

a volume range of 300-6000 ml and a with a creatinine excretion (µmol/24-h/kg) within the 1st and 99th percentiles of the distribution.

Urinary volume as well as sodium, potassium and urea concentrations (expressed in mmol/l) were measured in each 24-h urine collection. As the tolerated collection duration range was 20-28-h, we decided to first normalize the volume of all collections for 24-h (assuming a linear relationship) before generating excreted quantities. Regarding sodium and potassium excretions, we used the normalized volume for 24-h and the molecular weight of the elements, 23 g/mol for sodium and 39 g/mol for potassium, to convert concentrations to excreted quantities in mg. To estimate the protein intake, we used the urea excretion measured in the 24-h urine collections. First, we divided the urea concentration by 0.357 to obtain the value of urea nitrogen instead of the whole molecule of urea [34]. We then multiplied this value by the normalized volume to obtain the excreted quantity of urea nitrogen. Finally, to generate the protein intake estimate, we proceeded as follows [35]: urinary nitrogen excretion = urine urea nitrogen + non-urea nitrogen, with the assumption that non-urea nitrogen excretion is relatively constant at 30 mg/kg per day. Furthermore, each gram of nitrogen is derived from 6.25 g of protein. Thus, the formula we used was: estimated protein intake (g/d) = 6.25*(urine urea nitrogen (g/d) + (30 mg/kg/d * weight (kg)).

Statistical Analysis

We worked with the mean estimates for participants with two 24-h urine collections (n=363) and used the single value available for the participants with only one collection (n=14). We used several tests to evaluate the different facets of validity [36].

We first looked at the cross-classification of participants with the two methods, according to tertiles of the distribution. We generated the percentage of participants classified in the same,

adjacent or opposite tertiles depending on the method. This test looks at the agreement at the individual level [36]. Interpretation criteria previously described propose to consider a percentage of >50% in the same tertile and <10% in opposite tertile as a good outcome.

We used Pearson's correlation coefficients to look at the strength and direction of association between the two methods at the individual level. Interpretation criteria are that a correlation coefficient ≥0.50 represents a good outcome, between 0.20 and 0.49 an acceptable outcome whereas a coefficient <0.20 is a poor outcome [36].

We also evaluated the mean absolute and percent differences. We used paired t-tests to compare the mean absolute difference between the two methods (the reference value was the 24-h urine collection estimate) and we considered a p-value <0.05 as statistically significant in our analyses. For the mean percent difference, we subtracted the value obtained with the 24-h urine collection to the value obtained with the 24-h dietary recalls that we divided by the value obtained with the 24-h urine collection and multiplied by 100 for each participant. We then took the mean of those individual values. A mean percent difference >10% was considered as a poor outcome [36].

Finally, we were interested in comparing the values in different subgroups of our sample. Differences regarding the performance of dietary assessment methods according to sex and BMI have been previously described [12-14, 17]. Furthermore, our sample is composed of two different groups, stone formers (including both incident and recurrent formers) and non-stone formers. As recurrent stone formers might have already been in contact with dietitians and given dietary advice, we hypothesized that there could be differences between formers and non-formers. Another subgroup was based on the linguistic region. Indeed, a previous study [37] identified important differences in the dietary intake across different regions in

Switzerland and we wanted to investigate if it could translate into differences in the performance of the dietary assessment methods. To compare the values obtained in those subgroups, we used $\chi 2$ and t-tests when indicated and performed a test of significance for the difference between two correlations based on dependent groups, using the package cocor in R [38].

5.3. Results

The final sample is composed of 740 urine collections from 377 participants. There were 363 participants with 2 consecutive 24-h urine collections and 14 participants with a single collection after applying the selection criteria (**Table 1**). The number of participants in each subgroup is detailed in **Table 1**.

As shown in **Table 2**, sodium and potassium mean estimated intakes (mg/24-h) were 20%-30% lower in 24-h dietary recalls than in 24-h urine collections. Moreover, volume intakes estimated with 24-h dietary recalls were at least 25% higher than in the 24-h urine collections. Important differences (up to nearly 780 ml depending on the subgroup) were observed concerning the volume intakes between GloboDiet (Volume GD) and FoodCASE (Volume FC) estimates. Mean protein intakes were similar between the GloboDiet (Protein GD), FoodCASE (Protein FC) and 24-h urine estimates.

The results from the cross-classification according to tertiles of the distribution (**Table 3**) showed that sodium intake had a poor outcome with less than 50% of the participants classified in the same tertile and more than 10% of the participants classified in the opposite tertile, whereas potassium intake had a good outcome, overall as well as in most of the observed strata. For the protein and volume intakes, the outcome was also good, with similar results for the two variables available. The comparison between subgroups indicated

statistically significant differences in the proportion of participants in the tertiles for the volume GD and volume FC between linguistic regions. A greater proportion of participants were classified in the same tertile in the German-speaking subgroup than in the French-speaking subgroup.

Correlation coefficients were ≥0.50 (good outcome) for protein and volume intakes and between 0.2-0.49 (acceptable outcome) for the sodium and potassium intakes (**Table 4**). The differences between the subgroups were significant for protein depending on the kidney stone status and for volume FC depending on the linguistic region. Protein intake was better correlated between 24-h dietary recalls and 24-h urine collections for non-formers than for formers and volume FC was better correlated for German-speaking than for French-speaking participants.

Table 5 shows the mean absolute and relative differences between 24-h dietary recalls and 24-h urine collections (used as the reference method). Mean absolute differences were significantly different from zero and mean relative difference were >10% (poor outcome) for sodium, potassium and volume intakes. For protein intake, the mean absolute difference between the two methods was not significantly different from zero (except for the subgroup with BMI <25 kg/m^2) and the mean relative difference was <10%, which would be considered as a good outcome. Differences between the BMI subgroups were significant for sodium intake, with bigger differences in participants with a BMI>25 kg/m^2. Furthermore, non-formers had bigger differences in potassium intake than formers. Significant differences were also observed for the protein intake depending on the BMI category and for the volume intake depending on the sex, with bigger differences in men than women.

5.4. Discussion

We compared the two dietary assessment methods available in the SKSC, 24-h dietary recalls and objective nutritional biomarkers measured in 24-h urine collections, using several statistical tests to evaluate different facets of validity. Overall, we identified that agreement between 24-h dietary recalls and 24-h urine collections estimates was better for protein intake than for sodium, potassium or volume intakes.

Difficulties in accurately capturing elements of the diet (sodium intake in particular) with current dietary assessment methods were also identified in previous studies [12-14, 17, 20, 27]. Studies comparing self-report methods to 24-h urine collections found that sodium was underreported in self-reported methods compared to urine measurements [12, 13, 17, 27] and that the reporting accuracy for sodium intake was statistically significantly different between the methods [20]. Regarding potassium intake, some studies found that the intake was well captured [13] or that the accuracy was not different between the methods [20] but other identified that potassium was underestimated [17] or overestimated [39, 40] with self-reported methods. Finally, protein intake was usually well captured [20], with stronger correlations for protein density than for absolute protein according to a study [14] but underestimation in self-reported methods was also described [17].

In our sample, sodium intake was the element of the diet that showed the least agreement between the two methods. Estimated sodium intake was about 20% lower using 24-h dietary recalls than using 24-h urine collections, with a mean difference around 1200 mg/24-h between the two estimates. Previous studies identified that estimated sodium intake with 24- h dietary recalls were on average 22% less than with the 24-h urine collections [40] and that mean sodium intake was underestimated by about 600 mg/24-h in 24-hour diet recalls

compared to 24-h urine collections [27]. This suggests that it is challenging to capture dietary sodium intake using 24- h dietary recalls. It is well-known that dietary sodium intake substantially varies between days within the same person [40, 41] and that multiple 24-h urine collections are needed to adequately capture usual dietary sodium intake of a given person [41, 42].

Investigators using data similar to ours, 24- h dietary recalls collected with EPIC-Soft® (now known as GloboDiet®) and 24-h urine collections, showed that a questionnaire-based salt adjustment could improve the reporting accuracy [12]. Conclusions of this study were that further development of this type of questionnaire as well as the inclusion of elements to better describe the salt content during the 24-h dietary recalls would be useful to improve dietary sodium intake [12]. These observations represent interesting suggestions for future nutrition studies.

Estimated potassium intake was about 30% higher using 24-h urine than using 24-h dietary recall. Mixed results have been previously obtained with studies finding good agreement between the two methods [13, 20] and other identifying underreporting [17] or over reporting [39, 40] with self-reported methods. This result highlights the difficulty of estimating dietary potassium intake using 24-h dietary recalls. Of particular interest, the two dietary assessment methods better agreed among kidney stone formers than among non-formers. One possible explanation could be that some kidney stone formers have already received dietary counseling regarding elements of the diet to prevent stone formation, for example an increased vegetable consumption (one of the main source of potassium in the diet). This could induce a desirability bias, with those participants being more attentive when reporting certain elements of the diet, including vegetables.

We also observed different outcomes depending on the statistical test that was used. For instance, for the potassium intake, the two methods showed a good agreement for the cross-classification but the correlation coefficient was <0.5. Regarding the volume intake, both cross-classification and correlation coefficient had a good outcome but we identified important mean absolute and relative differences between the estimates obtained with the two methods. Regarding the important differences observed between the two variables available from the 24-h dietary recalls, volume GD and volume FC, it is important to keep in mind that those two variables do not represent the same way to capture water intake. Volume GD is the self-reported beverage intake, including both alcoholic and non-alcoholic beverages, whereas volume FC is based on the water content of every food and beverage as given in the Swiss Food Composition Database.

Those statistical tests illustrate different facets of validity, for instance the agreement or the strength and direction of the association between the two methods. As we have seen, the outcome can be favorable for a given test but considered as poor for another test. In this context, as described in a previous review [36], combining several tests when evaluating the validity could help gain a better insight into those different facets of validity.

Moreover, we found that personal characteristics such as the kidney stone status, sex, linguistic region or BMI can have an impact on the agreement and association between the two methods. Previous studies identified that the reporting accuracy was lower at higher BMI for men but was highest for obese women depending on the country studied [12] or that misreporting for sodium, potassium and protein intake tended to be more severe for dietitians in a study comparing dietitians versus non-dietitians [20]. Higher nutrition knowledge and

health consciousness were mentioned as potential reasons for the differences that were observed [20].

In our sample, different exposures to dietary advice between recurrent and incident stone formers as well as non-stone formers and differences in dietary awareness depending on the subgroups could also exist and may bias the reporting of foods and beverages consumed. Also, differences in practical feasibility for the 24-h urine collections according to the subgroups (e.g women, overweight people) could also influence the quality of the collection and thus also impact the agreement and association between the two methods.

As mentioned, several factors can influence the quality of 24-h urine collections (e.g indications given to the participants regarding the collection procedure, their understanding of such indications, other personal characteristics) and errors can also appear after the collection, for example during the storage of samples or laboratory measurements. Moreover, no definitive criterion has been identified to assess the completeness of those collections [33]. 24-h urine collections are nonetheless usually chosen as the reference method in studies [12, 13, 17], including the present analysis. It is thus important to keep in mind the limitations of the estimates provided by objective nutritional biomarkers and that such objective biomarkers, like the self-report methods, are not immune to biases and errors.

Overall, further improvement to current dietary assessment methods as well as development of new methods (new biomarkers, metabolomics, new technologies with phone apps…) are necessary to strengthen the accuracy of dietary assessment and long-term diet and health association studies.

5.5. Conclusions

In our sample, the agreement between 24-h dietary recalls and 24-h urine collections was better for protein intake estimates than for sodium, potassium and volume intake estimates. This comparison highlighted the complexity of the notion of validity by illustrating its various facets and showed the potential impact of individual characteristics (e.g. sex, BMI, linguistic region) on the performance of the dietary assessment methods. Overall, this analysis confirms that accurately capturing certain elements of the diet can be challenging and that further research is necessary to improve dietary assessment methodology.

5.6. References

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35. APPENDIX 3. METHODOLOGICAL ASPECTS OF EVALUATING EQUATIONS TO PREDICT GFR AND CALCULATIONS USING 24-HOUR URINE SAMPLES. Available from: https://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_ckd/p10_appendix3.htm.

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5.7. Tables

Table 1. Characteristics of 24-h urine collections and participants

	Characteristics	
24-h urine collections	All collections	774
	Time collection <20-h, N	9
	Time collection >28-h, N	7
	Normalized volume <300ml, N	0
	Normalized volume >6000ml, N	6
	Creatinine excretion <61.15 µmol/24-h/kg (1st percentile), N	7
	Creatinine excretion >334.9 µmol/24-h/kg (99th percentile), N	15
	Collections excluded based on time collection, normalized volume and creatinine excretion criteria, N *	34
	Final sample, N	740
	Participants with two 24-h urine collections, N	363
	Participants with one 24-h urine collections, N	14
	Mean collection time, minutes (SD)	1430 (41)
	Mean normalized volume, ml (SD)	2014 (834)
	Mean creatinine excretion, µmol/24-h/kg (SD)	163 (48.7)
Participants	All participants	377
	Mean age, years (SD)	45.6 (13.2)
Kidney stone status	Formers, N	190 (50.4%)
	Non-formers, N	187 (49.6%)
Sex	Men, N	224 (59.4%)
	Women, N	153 (40.6%)
Linguistic region	French-speaking, N	155 (41.1%)
	German-speaking, N	222 (58.9%)
BMI(kg/m^2)	<25, N	195 (51.7%)
	>=25, N	182 (48.3%)

* some collections combined several excluding criteria

Table 2. Mean estimated intakes for 24-h dietary recalls and 24-h urine collections, by subgroups

Variable	Subgroup		24-h recalls estimate, mean (SD)	24-h urine estimate, mean (SD)
Sodium (mg/24-h)		All	2864 (1235)	4076 (1598)
	Kidney stone status	Formers	2876 (1305)	4083 (1615)
		Non-formers	2851 (1162)	4070 (1584)
	Sex	Men	3159 (1267)	4472 (1657)
		Women	2432 (1049)	3497 (1310)
	Linguistic region	French-speaking	2900 (1252)	3927 (1489)
		German-speaking	2839 (1224)	4180 (1665)
	BMI	BMI <25	2873 (1148)	3748 (1442)
		BMI >=25	2854 (1324)	4428 (1684)
Potassium (mg/24-h)		All	2151 (788)	3322 (1270)
	Kidney stone status	Formers	2040 (739)	3008 (1073)
		Non-formers	2263 (821)	3642 (1373)
	Sex	Men	2236 (799)	3424 (1168)
		Women	2026 (756)	3174 (1396)
	Linguistic region	French-speaking	2278 (716)	3473 (1122)
		German-speaking	2062 (824)	3217 (1356)
	BMI	BMI <25	2151 (790)	3290 (1355)
		BMI >=25	2151 (788)	3357 (1174)
Protein GD (g/24-h)		All	77.8 (30.9)	76.7 (24)
	Kidney stone status	Formers	76 (27.8)	74.7 (24.4)
		Non-formers	79.7 (33.7)	78.7 (23.6)
	Sex	Men	85 (32.6)	84.8 (24.3)
		Women	67.3 (24.7)	65 (18)
	Linguistic region	French-speaking	79 (25.5)	77.6 (22.4)
		German-speaking	77 (34.2)	76.1 (25.1)
	BMI	BMI <25	76 (28.6)	71.9 (23.2)
		BMI >=25	79.7 (33.1)	81.9 (23.9)
Protein FC (g/24-h)		All	78.4 (29)	
	Kidney stone status	Formers	76.7 (28.1)	
		Non-formers	80.2 (29.9)	
	Sex	Men	85 (29.5)	
		Women	68.7 (25.3)	
	Linguistic region	French-speaking	81 (28)	
		German-speaking	76.6 (29.6)	
	BMI	BMI <25	76.7 (28.2)	
		BMI >=25	80.2 (29.9)	
Volume GD (ml/24-h)		All	2312 (888)	2015 (790)
	Kidney stone status	Formers	2304 (892)	1929 (804)
		Non-formers	2320 (886)	2102 (767)
	Sex	Men	2432 (944)	1998 (805)
		Women	2136 (769)	2040 (769)
	Linguistic region	French-speaking	2153 (834)	1949 (775)
		German-speaking	2423 (910)	2061 (798)
	BMI	BMI <25	2270 (836)	2041 (767)
		BMI >=25	2357 (941)	1987 (814)
Volume FC (ml/24-h)		All	3064 (955)	
	Kidney stone status	Formers	3031 (976)	

	Non-formers	3097 (934)
Sex	Men	3196 (999)
	Women	2871 (853)
Linguistic region	French-speaking	2911 (839)
	German-speaking	3171 (1016)
BMI	BMI <25	3030 (923)
	BMI >=25	3100 (989)

Table 3. Cross-classification according to tertiles of the distribution and comparison between subgroups

Variable	Subgroup		Same tertile	Adjacent tertile	Opposite tertile	p-value*
Sodium (mg/24-h)		All	43%	44%	13%	
	Kidney stone status	Formers	44%	45%	11%	0.61
		Non-formers	43%	43%	14%	
	Sex	Men	38%	46%	16%	0.96
		Women	39%	46%	15%	
	Linguistic region	French-speaking	41%	50%	9%	0.14
		German-speaking	43%	42%	15%	
	BMI	BMI <25	45%	43%	12%	0.33
		BMI >=25	38%	51%	12%	
Potassium (mg/24-h)		All	**53%**	**38%**	**9%**	
	Kidney stone status	Formers	48%	40%	12%	0.16
		Non-formers	**56%**	**36%**	**7%**	
	Sex	Men	**52%**	**39%**	**9%**	0.78
		Women	**51%**	**42%**	**7%**	
	Linguistic region	French-speaking	51%	39%	10%	0.5
		German-speaking	**57%**	**35%**	**8%**	
	BMI	BMI <25	**51%**	**40%**	**9%**	0.95
		BMI >=25	**52%**	**38%**	**9%**	
Protein GD (g/24-h)		All	49%	44%	7%	
	Kidney stone status	Formers	47%	45%	8%	0.4
		Non-formers	**51%**	**44%**	**5%**	
	Sex	Men	**50%**	**42%**	**8%**	0.25
		Women	45%	42%	13%	
	Linguistic region	French-speaking	48%	44%	8%	0.96
		German-speaking	**50%**	**42%**	**8%**	
	BMI	BMI <25	**52%**	**41%**	**7%**	0.91
		BMI >=25	**52%**	**40%**	**8%**	
Protein FC (g/24-h)		All	**50%**	**44%**	**7%**	
	Kidney stone status	Formers	47%	45%	8%	0.3
		Non-formers	**55%**	**40%**	**6%**	
	Sex	Men	**55%**	**38%**	**7%**	0.13
		Women	45%	44%	10%	
	Linguistic region	French-speaking	49%	46%	5%	0.16
		German-speaking	**51%**	**40%**	**9%**	
	BMI	BMI <25	**54%**	**38%**	**8%**	0.82
		BMI >=25	**56%**	**35%**	**9%**	
Volume GD (ml/24-h)		All	**52%**	**39%**	**8%**	
	Kidney stone status	Formers	**53%**	**40%**	**7%**	0.63
		Non-formers	51%	39%	10%	
	Sex	Men	52%	38%	10%	0.91
		Women	**53%**	**39%**	**8%**	
	Linguistic region	French-speaking	43%	46%	11%	**0.01**

		German-speaking	**59%**	**33%**	**7%**	
	BMI	BMI <25	**53%**	**37%**	**9%**	0.54
		BMI >=25	49%	43%	8%	
Volume FC (ml/24-h)		All	**56%**	**37%**	**7%**	
	Kidney stone status	Formers	**54%**	**40%**	**6%**	0.57
		Non-formers	**57%**	**35%**	**7%**	
	Sex	Men	**56%**	**36%**	**8%**	0.78
		Women	**59%**	**35%**	**6%**	
	Linguistic region	French-speaking	49%	40%	11%	**0.01**
		German-speaking	**64%**	**32%**	**5%**	
	BMI	BMI <25	**63%**	**32%**	**6%**	0.27
		BMI >=25	**54%**	**38%**	**7%**	

* $\chi 2$ tests were used to compare the distribution in the different tertiles between the different subgroups

Table 4. Correlation coefficients between 24-h dietary recalls and 24-h urine collections estimates and comparison between subgroups

Variable	Subgroup		Correlation coefficient (Pearson)	Agreement	95% CI - lower value	95% CI - upper value	p-value*
Sodium (mg/24-h)		All	0.3	Acceptable	0.2	0.39	
	Kidney stone status	Formers	0.32	Acceptable	0.18	0.44	0.67
		Non-formers	0.28	Acceptable	0.14	0.4	
	Sex	Men	0.22	Acceptable	0.09	0.34	0.76
		Women	0.25	Acceptable	0.1	0.4	
	Linguistic region	French-speaking	0.37	Acceptable	0.22	0.5	0.25
		German-speaking	0.26	Acceptable	0.13	0.38	
	BMI	BMI <25	0.26	Acceptable	0.13	0.39	0.38
		BMI >=25	0.34	Acceptable	0.21	0.47	
Potassium (mg/24-h)		All	0.46	Acceptable	0.38	0.54	
	Kidney stone status	Formers	0.37	Acceptable	0.24	0.49	0.15
		Non-formers	0.49	Acceptable	0.38	0.6	
	Sex	Men	0.41	Acceptable	0.3	0.52	0.22
		Women	0.51	Good	0.39	0.62	
	Linguistic region	French-speaking	0.44	Acceptable	0.3	0.56	0.79
		German-speaking	0.46	Acceptable	0.35	0.56	
	BMI	BMI <25	0.47	Acceptable	0.35	0.57	0.84
		BMI >=25	0.45	Acceptable	0.33	0.56	
Protein GD (g/24-h)		All	0.6	Good	0.53	0.66	
	Kidney stone status	Formers	0.51	Good	0.39	0.61	**<0.01**
		Non-formers	0.69	Good	0.61	0.76	
	Sex	Men	0.58	Good	0.49	0.66	0.24
		Women	0.49	Good	0.36	0.6	
	Linguistic region	French-speaking	0.56	Good	0.44	0.66	0.3
		German-speaking	0.63	Good	0.54	0.7	
	BMI	BMI <25	0.63	Good	0.54	0.71	0.46
		BMI >=25	0.58	Good	0.48	0.67	
Protein FC (g/24-h)		All	0.58	Good	0.5	0.64	
	Kidney stone status	Formers	0.51	Good	0.39	0.6	0.05
		Non-formers	0.64	Good	0.55	0.72	
	Sex	Men	0.56	Good	0.47	0.65	0.12
		Women	0.44	Acceptable	0.31	0.56	
	Linguistic region	French-speaking	0.58	Good	0.46	0.67	0.93
		German-speaking	0.57	Good	0.48	0.65	
	BMI	BMI <25	0.61	Good	0.52	0.69	0.29
		BMI >=25	0.54	Good	0.43	0.64	

Volume GD (ml/24-h)		All	0.51	Good	0.44	0.59	
	Kidney stone status	Formers	0.54	Good	0.43	0.63	0.51
		Non-formers	0.49	Acceptable	0.37	0.59	
	Sex	Men	0.53	Good	0.43	0.62	0.94
		Women	0.52	Good	0.4	0.63	
	Linguistic region	French-speaking	0.45	Acceptable	0.32	0.57	0.21
		German-speaking	0.55	Good	0.45	0.64	
	BMI	BMI <25	0.54	Good	0.44	0.64	0.51
		BMI >=25	0.49	Acceptable	0.38	0.6	
Volume FC (ml/24-h)		All	0.58	Good	0.51	0.64	
	Kidney stone status	Formers	0.58	Good	0.48	0.67	0.82
		Non-formers	0.57	Good	0.46	0.66	
	Sex	Men	0.56	Good	0.47	0.65	0.25
		Women	0.64	Good	0.54	0.73	
	Linguistic region	French-speaking	0.48	Acceptable	0.35	0.59	**0.04**
		German-speaking	0.63	Good	0.54	0.7	
	BMI	BMI <25	0.63	Good	0.54	0.71	0.12
		BMI >=25	0.53	Good	0.41	0.63	

* we used the package cocor in R to perform a test of significance for the difference between two correlations based on dependent groups.

Table 5. Mean absolute and relative differences between 24-h dietary recalls and 24-h urine collections estimates and comparison between subgroups

Variable	Subgroup		Mean absolute difference*	SD for the mean absolute difference	p-value	Mean relative difference (%)*	p-value mean absolute difference **	p-value mean relative difference **
Sodium (mg/24-h)		All	-1212	1702	**<0.01**	-21.5		
	Kidney stone status	Formers	-1206	1724	**<0.01**	-21.5	0.95	1
		Non-formers	-1218	1685	**<0.01**	-21.5		
	Sex	Men	-1313	1848	**<0.01**	-21.3	0.15	0.93
		Women	-1065	1457	**<0.01**	-21.7		
	Linguistic region	French-speaking	-1026	1552	**<0.01**	-18.3	0.07	0.22
		German-speaking	-1342	1792	**<0.01**	-23.7		
	BMI	BMI <25	-874	1591	**<0.01**	-14.9	**<0.01**	**<0.01**
		BMI >=25	-1574	1747	**<0.01**	-28.5		
Potassium (mg/24-h)		All	-1172	1145	**<0.01**	-30		
	Kidney stone status	Formers	-968	1052	**<0.01**	-26.3	**<0.01**	**0.02**
		Non-formers	-1378	1201	**<0.01**	-33.8		
	Sex	Men	-1188	1111	**<0.01**	-29.5	0.74	0.68
		Women	-1147	1198	**<0.01**	-30.8		
	Linguistic region	French-speaking	-1195	1033	**<0.01**	-28.6	0.73	0.47
		German-speaking	-1155	1220	**<0.01**	-30.9		
	BMI	BMI <25	-1139	1206	**<0.01**	-29.3	0.57	0.67
		BMI >=25	-1206	1079	**<0.01**	-30.7		
Protein GD (g/24-h)		All	1.1	25.2	0.4	4		
	Kidney stone status	Formers	1.2	26.1	0.52	5.7	0.93	0.34
		Non-formers	1	24.4	0.58	2.4		
	Sex	Men	0.2	27.1	0.9	2.5	0.4	0.28
		Women	2.4	22.3	0.19	6.3		
	Linguistic region	French-speaking	1.4	22.8	0.46	5.3	0.86	0.54
		German-speaking	0.9	26.9	0.61	3.2		
	BMI	BMI <25	4.2	22.8	**0.01**	8.5	**0.01**	**0.01**
		BMI >=25	-2.2	27.3	0.28	-0.7		

Protein FC (g/24-h)		All	1.7	24.8	0.18	5.4		
	Kidney stone status	Formers	1.9	26.3	0.31	6.8	0.86	0.45
		Non-formers	1.5	23.4	0.39	4		
	Sex	Men	0.3	25.6	0.87	3.1	0.18	0.15
		Women	3.8	23.7	0.05	8.7		
	Linguistic region	French-speaking	3.4	23.7	0.07	7.5	0.26	0.33
		German-speaking	0.5	25.6	0.77	3.9		
	BMI	BMI <25	4.9	23	**<0.01**	9.7	**0.01**	**0.01**
		BMI >=25	-1.7	26.3	0.39	0.7		
Volume GD (ml/24-h)		All	297	831	**<0.01**	25.7		
	Kidney stone status	Formers	375	816	**<0.01**	33.1	0.06	**0.01**
		Non-formers	217	840	**<0.01**	18.3		
	Sex	Men	434	856	**<0.01**	32.7	**<0.01**	**<0.01**
		Women	96	750	0.11	15.6		
	Linguistic region	French-speaking	203	844	**<0.01**	23.2	0.07	0.47
		German-speaking	362	817	**<0.01**	27.5		
	BMI	BMI <25	229	768	**<0.01**	21.6	0.1	0.14
		BMI >=25	369	890	**<0.01**	30.2		
Volume FC (ml/24-h)		All	1049	815	**<0.01**	67.5		
	Kidney stone status	Formers	1103	825	**<0.01**	76.3	0.2	**0.01**
		Non-formers	995	803	**<0.01**	58.5		
	Sex	Men	1198	860	**<0.01**	76.2	**<0.01**	**<0.01**
		Women	831	692	**<0.01**	54.7		
	Linguistic region	French-speaking	961	824	**<0.01**	67.9	0.08	0.92
		German-speaking	1110	805	**<0.01**	67.2		
	BMI	BMI <25	990	737	**<0.01**	62.5	0.15	0.14
		BMI >=25	1113	889	**<0.01**	72.8		

* the method of reference was the 24-h urine collection estimate

** t-tests were used to compare respectively the mean absolute and relative differences between the different subgroups

6. Discussion

Research work conducted as part of this thesis allows gaining insight into kidney stone formers' diet in Switzerland. It contributed to describe for the first time the diet of kidney stone formers and also evaluate the dietary assessment methods used in the SKSC.

6.1. Summary of results

In **Chapter 1**, the scoping review showed that research in this field relies mostly on observational and cross-sectional studies. It also highlighted that studies were mainly conducted in the USA and Europe and reflected predominantly Western diets. Regarding the methods used to assess the dietary intake, short and self-report methods such as FFQs were preferred over more demanding methods such as 24-h dietary recalls or objective nutritional biomarkers measured in 24-h urine collections. Also, we found that the description of the dietary assessment methods used in the studies was very heterogeneous across the articles and was sometimes lacking important elements, for instance the validation process for FFQs. Finally, we identified that food diaries were often collected in parallel to 24-h urine collections but that objective dietary biomarkers were not always measured and analyzed in comparison to self-reported dietary data in those studies.

This thus reveals the need for more interventional and longitudinal studies, better descriptions of the methods used to collect dietary data and use of combined dietary assessment methods whenever possible, for instance 24-h dietary recalls with objective nutritional biomarkers or new methods such as metabolomics, phone apps… Nevertheless, contrary to general nutritional epidemiology, as 24-h urine collections are often part of the metabolic evaluation of kidney stone formers, objective nutritional biomarkers were often available and could be more exploited.

In the description of kidney stone formers' diet and comparison to the control group (**Chapter2**), we identified differences in the consumption of vegetables and beverages between the two groups. Those results are consistent with previous findings described in the literature. Furthermore, the dietary consumption was similar to menuCH for the food groups that were comparable between the two studies, which is a good indicator regarding the data collection quality in the SKSC and control group.

This is the first description of kidney stone formers 'diet in Switzerland. As kidney stone prevalence continues to rise, it is important to have data to build evidence-based dietary recommendations that can take into account local settings and cultural habits. This study is thus a first step towards understanding kidney stone formers diet' specificities and can inform future studies.

Chapter 3 identified that protein estimated intake showed better agreement and correlation between 24-h dietary recalls and 24-h urine collections than sodium, potassium and volume estimated intakes. This comparison revealed the complexity of the notion of validity and its various facets. Also, the potential impact of personal characteristics (e.g. sex, BMI, linguistic region) on the performance of those methods should be kept in mind when conducting analysis. Overall, these observations highlight the need for further research and development in dietary assessment methods.

6.2. Strengths and limitations of the thesis

The SKSC is the first multi-center cohort to study kidney stone formers in Switzerland. Data collected will help better characterize the pathophysiology and progression of kidney stone disease in the Swiss population. Thanks to the diversity of data collected, from dietary to socio-

economic data or bio samples, many approaches such as epidemiology, metabolomics or even genetics can be used and combined to investigate kidney stone formation.

The SKSC is quite unique in that regard, and for nutritional epidemiology in particular, the combination of 24-h dietary recalls and objective nutritional biomarkers is one major strengths of this study (FFQs were also conducted but the data is not processed yet). Regarding the quality of the dietary data available, the 24-h dietary recalls were performed by trained dietitians and the data was collected with GloboDiet, which has been validated in several previous studies [1, 2]. Moreover, a dietitian involved in the menuCH study was also implicated in the SKSC, bringing knowledge and expertise to the project. Quality controls were regularly performed to identify potential issues with the data collection.

Recommendations in nutritional epidemiology regarding the dietary assessment methodology are to combine several methods, and if possible methods with independent errors [3-5]. As 24-h urine collections were collected and objective nutritional biomarkers such as sodium, potassium or urea excretions were measured, this thus represented the opportunity to compare the dietary intakes estimated with the two methods.

However, there are also several limitations to the study. First, the inclusion criteria for the SKSC were broad, including various comorbidities such as metabolic syndrome, osteoporosis, chronic urinary tract infection or chronic renal failure, and all types of kidney stones. The population of kidney stone formers is thus quite heterogeneous. As we mentioned in the introduction, the physiopathological mechanisms underlying the formation of different stone types probably reveal different pathologies. Second, another important limitation is the fact that both recurrent and incident stone formers were included. Indeed, recurrent stone formers might have already been exposed to dietary recommendations or given advice during

their follow-up and could have already changed elements of their diets. Their diet at baseline might thus not be representative of their diet preceding kidney stone formation.

Finally, another limitation is inherent to the method chosen for the dietary assessment, the 24-h recalls. As mentioned, all self-report methods have measurement errors and biases [5-8]. Moreover, 24-h dietary recalls are less accurate than other methods such as FFQs to measure episodically consumed foods [9]. To mitigate these errors, data from FFQs could be integrated in future analyses. Also, the gold-standard regarding 24-h recalls is to conduct non-consecutive and repeated recalls [10] but in the SKSC, it was chosen to do consecutive recalls to reduce the burden for the participants and maximize their adhesion.

Furthermore, longitudinal follow-up is available in kidney stone formers but the participants to the control group were seen only once. As a result, changes in kidney stone formers' can be evaluated across time but can't be compared to non-kidney stone formers.

6.3. Implications for further research

These analyses only exploited part of the data available in the SKSC and there is an important potential for future studies. Current studies conducted include metabolomics and further explorations about the dietary intake, especially the consumption of fermented foods. Moreover, whole exome DNA sequencing is also ongoing. Based on the present work, I would have several proposition for research both specific to the SKSC and also nutritional epidemiology in kidney stone formers.

First, the description and comparison of the diet identified some differences between stone and non-stone formers (see **Chapter 2**). It would thus be interesting to investigate in more details the potential specificities of kidney stone formers' diet, and in particular to study associations between dietary patterns and kidney stone formation. The addition of data

extracted from the FFQs could help mitigate errors and biases, inherent to those self-report methods, and help model more accurately usual intakes [9, 11].

Second, it would also be of interest to analyze longitudinal data and evaluate the evolution of dietary patterns across time. Indeed, all stone formers in the cohort had an extensive metabolic evaluation, including blood analysis and 24-h urine collections, allowing to identify specific metabolic imbalances. Following this evaluation, kidney stone formers are given dietary counseling adapted to their situation. It would thus be interesting to evaluate dietary changes following the dietary counseling and look at the recurrence of stones.

As for nutritional epidemiology in kidney stone formers, we identified similar issues to address than for general nutritional epidemiology [3, 7, 12-14]. For instance, the review we conducted [15] revealed the need for more interventional studies or the development of new and more accurate methods for the dietary assessment. Also, we noted that 24-h urine collections were often available in kidney stone studies as they are part of the evaluation of kidney stone formers. Yet, we identified that the potential for the dietary assessment of those 24- h urine collections was not always fully exploited and in particular that objective nutritional biomarkers were not systematically measured and analyzed. We would thus advise to take advantage of the availability of those objective biomarkers and more systematically combine them with self-report methods to increase the accuracy of dietary assessment estimates.

Finally, regarding the micronutrients, their estimated intakes rely on national food composition databases. In that context, we would recommend maintaining those databases as up-to-date and as accurate as possible as it would contribute to improve the dietary analyses.

6.4. Public health perspective

As mentioned in the introduction of this thesis, the prevalence of kidney stone is on the rise [16, 17] and as kidney stone formation has been linked to metabolic disease such as obesity and diabetes [18, 19], this prevalence is likely to keep increasing over the next years. It is thus of key importance to identify and implement effective preventive measures.

According to numbers published by the Swiss Health Observatory, in 2019, Switzerland spent 1.8 billion francs in the sectors of health promotion and prevention. Between 2010 and 2019, those expenses represented only between 2.2 and 2.7% of the total health care system costs, placing Switzerland in the lower half of the OECD countries regarding expenses invested in health promotion and prevention [20]. This reveals that the Swiss health system is mainly focused on a curative approach and that prevention is not at the forefront of the health strategy.

As previously stated, kidney stones are a major concern in terms of health-care system costs [21], are associated with high morbidity and can generate great pain for the patients [16]. Furthermore, projections in the US estimate that by 2030, the rise of obesity and diabetes [22, 23] could contribute to an additional increase of $1.24 billion/year related to kidney stone disease [24]. In this context, more money and effort should be invested in prevention and health promotion, as benefits from reducing the burden of kidney stones and other preventable diseases could manifest at both the individual and societal levels.

The first step consists in conducting research to identify efficient preventive measures. Longitudinal epidemiological studies to look at diet-disease associations (based on cohorts such as the SKSC) and clinical or feeding studies could help better define the pathophysiology

and protective and risk factors of kidney stones. Once such factors have been identified, those findings can be translated into public health interventions.

Public health interventions are based on two main strategies: 1) actions at the individual level which targets more specific individuals, usually at high risk for the disease and 2) actions at the structural/environmental level which aims at modifying the general environment and impact a larger population [22, 25]. Swinburn and al. designed an interesting framework related to obesity that gives examples and illustrates the effects of those different levels of intervention [22]. For instance, public health interventions for kidney stones could be to give dietary advice adapted to a specific patient (individual level) and increase taxes on sugar-sweetened beverages or limit the amount of salt authorized in industrial food (structural level).

In the context of kidney stone disease, a preventive approach based on dietary recommendations would thus focus on the individual level and emphasize personal behavioral changes. Yet, it is difficult to sustainably change individuals' diets. For instance, results from menuCH showed that adherence of the Swiss population to the national dietary recommendations was low [26], despite efforts conducted to inform the public about healthy eating. In this context, accompanying structural and environmental measures such as taxes on unhealthy foods and beverages or regulation of nutritional composition (especially regarding the sodium content in the case of kidney stone formers) could help transform the food environment and tackle the major non-communicable diseases of our times.

6.5. Conclusion

This thesis was a first exploration into the nutritional epidemiology of kidney stone formers in Switzerland. It showed that there were some differences in the dietary intakes of

vegetables and beverages between stone formers and non-formers. Furthermore, we identified that on the methodological level, some of the methods widely used in nutrition research didn't estimate precisely the intake of certain nutrients. And finally, through our review, we observed the same challenges regarding kidney stone nutritional epidemiology than general nutritional epidemiology but identified some resources specific to kidney stone research, the more systematic 24-h urine collection that could be more exploited in future studies.

These first results regarding specificities in the kidney stone formers' diet are promising and should be explored further, in combination with fundamental and clinical research to better understand the pathophysiological mechanisms underlying kidney stone formation. The SKSC is a very rich database with an important research potential. Metabolomics and genetics data are also being analyzed in current studies. Exploring different and complementary aspects of kidney stone formation will help design efficient public health policies to improve the population' health and help the patients.

Finally, projects such as menuCH and the SKSC reveal an interest and a political will to improve nutrition research in Switzerland. Other studies are ongoing such as the Swiss Health Survey, which is currently in a pilot phase but aims at recruiting a national cohort of >100'000 participants and follow them up during several years to measure the exposition and nutritional status of the population, or menuCH Kids, that will collect nutritional data and biosamples in children. Hopefully, all of these projects exploring the links between diet and health status will create an environment more favorable to prevention and health promotion in Switzerland, for the benefit of the whole population.

6.6. References

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7. Appendices

7.1. List of publications

List of peer-reviewed publications included in this thesis:

Publications	Status
Methods for the dietary assessment of adult kidney stone formers: a scoping review **C. Legay**, T. Krasniqi, A. Bourdet, O. Bonny and M. Bochud J Nephrol 2022 Accession Number: 35167058 DOI: 10.1007/s40620-022-01259-3	Published
Differences in the food consumption between kidney stone formers and non-formers in the Swiss Kidney Stone Cohort	Revised version sent to the Journal of Renal Nutrition
Comparison between 24-h dietary recalls and 24-h urine collections to estimate sodium, potassium, protein, and volume intakes in the Swiss Kidney Stone Cohort	In preparation

7.2. List of courses and attended seminars/conferences

For the MD-PhD program, it is necessary to obtain 10 ECTS for the preparatory training. Furthermore, 12 ECTS are also required to complete the PhD thesis in Life Science program. Requirements for the PhD program in Public Health from the Swiss School of Public Health (SSPH+) were also completed (description of the requirements available on SSPH+ website).

Here is the list of the different courses and formations I completed and conferences I attended:

	Course Name	Description	Institution	Dates
Courses and seminars	**CAS en Santé Publique (15 ECTS)**	Module 1 : Principes et méthodes de la santé publique (4 ECTS) Module 2 : Epidémiologie et état de santé de la population (4 ECTS) Module 3 : Niveaux d'intervention en santé publique et déterminants de l'état de santé (4 ECTS) Module 4 : Santé au travail, environnement et société (3 ECTS)	Unisanté	February-June 2020
	Tutorials (2 ECTS)	Cooperation and conflict: from the origins to the job world (1 ECTS) Genetic predispositions to obesity: is it all coded in our DNA? (1 ECTS)	Doctoral School, UNIL	4x2h courses, Oct 2020-Jan 2021 (1 practical session cancelled due to COVID-19) 5x2h courses, 17 Feb-17 March 2021
	Scientific writing and publishing (1.5 ECTS)		Doctoral School, UNIL	March 29th and 30th, May 10th 2021
	Writing a Journal Article and Getting It Published (2 ECTS)		SSPH+	September 7th-9th 2021
	Causal Inference in Observational Epidemiology (1 ECTS)		SSPH+	March 31st- April 2nd 2021
	Migration Health Course (1 ECTS)		SSPH+	December 6th-8th 2021
	Atelier Préparer sa soutenance de thèse		Graduate Campus, UNIL	June 16th 2022
	Colloques du DESS (1 ECTS)		Unisanté	1h conferences, on various topics related to Public Health

	Réunion scientifique mensuelle, secteur Maladies Chroniques	Unisanté	Usually once a month but partially interrupted during COVID-19
	Journal club	Unisanté	Usually once a month but partially interrupted during COVID-19
Conferences and Symposiums	**Swiss Public Health Conference**	SSPH+	September 2nd and 3rd 2020
	Geneva Health Forum	Geneva University Hospitals and the University of Geneva	November 16th-18th 2020
	NCCR Annual Retreat (0.25 ECTS)	NCCR Kidney	January 15th 2021
	Séminaire de veille sanitaire	Université de Franche-Comté-Unisanté	February 10th and 11th 2021
	Swiss Public Health Conference (1 ECTS)	SSPH+	August 25th-26th 2021
	MD-PhD Retreat (0.5 ECTS)	MD-PhD program	November 11th 2021
	Renal metabolism in health and disease (1 ECTS)	Doctoral school, UNIL	November 26th 2021
	53rd Annual Meeting of the Swiss Society of Nephrology (1 ECTS)	Swiss Society of Nephrology	December 9th-10th 2021
	NCCR Annual Retreat (0.75 ECTS)	NCCR Kidney	April 7th-8th 2022
	Symposium Kidney Stone Disease, Bruxelles	Centre Hospitalier Universitaire de Bruxelles	May 5th-6th 20222
	Dessiner la santé publique de demain	Unisanté	June 27th 2022

7.3. Research work conducted during PhD not part of this thesis

I conducted further analysis on dietary consumption, using data from the SKSC and control group, in the context of the "Mémoire DIUE Nutrition Clinique et Métabolisme" presented by Nadia Ammor, dietician working at the Lausanne SKSC center.

In this analysis, we wanted to compare the volume, calcium and protein intakes of a subgroup of participants, who had a baseline visit date between December 2017 and December 2019, between kidney stone formers and controls. I used a linear mixed effects regression model using the two-consecutive 24-h dietary recalls for each to compare the total energy intake, total protein intake, total liquid intake and calcium intake from dairy products and water between the SKSC and the control group. Fixed effects were age, BMI, sex and the linguistic region and the random effect was participants. We did not observe statistically significant differences in the total energy, total protein, total liquid intake or calcium intake from dairy products and water between the SKSC and the control group.

7.4. List of oral and poster presentations

Colloque DESS (Unisanté), September 2020: talk with Prof. Olivier Bonny, presentation of the SKSC and preliminary results

NCCR.Kidney Annual Retreat (online), January 2021: virtual poster with preliminary results of the 24-h urine collections analysis

Lunch meeting secteur Maladies Chroniques (Unisanté), March 2021: presentation about the different methods in nutritional epidemiology research

Conférence de Santé Publique (Bern), August 2021: virtual poster presenting preliminary results of the dietary consumption in the SKSC

MD-PhD Retreat (Lausanne), November 2021: physical poster presenting results of the dietary consumption in the SKSC

53rd Annual Meeting of the Swiss Society of Nephrology (Interlaken), December 2021: physical poster presenting results of the dietary consumption in the SKSC

NCCR.Kidney Annual Retreat (Zurich), April 2022: oral presentation about updates in the SKSC and physical poster presenting results of the dietary consumption in the SKSC

Symposium Kidney Stone Disease (Bruxelles), May 2022: physical poster presenting results of the dietary consumption in the SKSC