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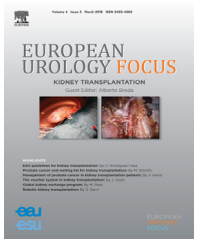

Stone Disease

Fluid Intake and Dietary Factors and the Risk of Incident Kidney Stones in UK Biobank: A Population-based Prospective Cohort Study

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Abstract

Background: Fluid intake and diet are thought to influence kidney stone risk. However, prospective studies have been limited to small samples sizes and/or restricted measures.
Objective: To investigate whether fluid intake and dietary factors are associated with the risk of developing a first kidney stone.
Design, setting, and participants: Participants were selected from UK Biobank, a population-based prospective cohort study.
Outcome measurements and statistical analysis: Cox proportional hazards models were used to investigate the association between fluid intake and dietary factors and the risk of a first incident kidney stone, ascertained from hospital inpatient records.
Results and limitations: After exclusion, 439 072 participants were available for the analysis, of whom 2057 had hospital admission with an incident kidney stone over a mean of 6.1 yr of follow-up. For every additional drink (200 ml) consumed per day of total fluid, the risk of kidney stones declined by 13% (hazard ratio [HR] = 0.87, 95% confidence interval [CI] 0.85–0.89). Similar patterns of associations were observed for tea, coffee, and alcohol, although no association was observed for water intake. Fruit and fibre intake was also associated with a lower risk (HR per 100 g increase of fruits per day = 0.88, 95% CI 0.83–0.93, and HR per 10 g fibre per day = 0.82, 95% CI 0.77–0.87), whereas meat and salt intake was associated with a higher risk (HR per 50 g increase in meat per week = 1.17, 95% CI 1.05–1.29, and HR for always vs never/rarely added salt to food = 1.33, 95% CI 1.12–1.58). Vegetable, fish, and cheese intake was not associated with kidney stone risk.
Conclusions: The finding that high intake of total fluid, fruit, and fibre was associated with a lower risk of hospitalisation for a first kidney stone suggests that modifiable dietary factors could be targeted to prevent kidney stone development.
Patient summary: We found that higher intake of total fluid, specifically tea, coffee, and alcohol (but not water), and consumption of fruit and foods high in fibre are linked with a reduced likelihood of developing kidney stones.

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1. Introduction

Kidney stones are a common cause of morbidity, with a lifetime prevalence of 13% in England, with incidence rates having increased substantially over the last few decades worldwide [1–4]. Taking into account diagnostic and treatment costs and the additional socioeconomic burden from sickness leave, the fiscal impact of kidney stones on the wider economy is considerable [5]. Kidney stones also have a high recurrence rate, with approximately half of patients having a recurrent episode over 10 yr and up to 90% over 30 yr [6,7]. It is therefore important to identify modifiable risk factors that can be targeted for the prevention of developing kidney stones.

Certain dietary factors are considered to be major contributors to the increasing incidence of kidney stones, specifically a diet low in fibre and high in animal protein, fat, and sodium [8,9]. Additionally, it has been suggested that increasing fluid intake is an effective method to reduce the risk of kidney stone formation [10,11]. However, whilst there have been several prospective studies on diet and fluid intake and the subsequent risk of developing kidney stones, they have typically been small or focused on a narrow range of dietary factors.

To address these limitations, we investigate the association between a wide range of dietary factors and fluid intake, including specific types of beverages, and the risk of developing incident kidney stones, as assessed through hospital inpatient records, in a large UK-based prospective cohort of half a million participants without prevalent kidney stones.

2. Patients and methods

2.1. Population

Participants were selected from UK Biobank, a population-based study designed to improve the prevention, treatment, and diagnosis of a range of diseases and conditions [12]. Between 2006 and 2010, approximately 500 000 women and men aged between 40 and 69 yr attended one of 22 baseline assessment centres located throughout England, Scotland, and Wales. All participants provided sociodemographic, lifestyle, and health-related information collected through touchscreen questionnaires and verbal interviews, as well as completed a range of physical measurements. Electronic signed consent was obtained, which included consent for on-going linkage to medical and health-related records.

UK Biobank received approval from the National Information Governance Board for Health and Social Care and the National Health Service North West Centre for Research Ethics Committee (Ref: 11/NW/0382).

2.2. Diagnosis of kidney stones

Kidney stones were ascertained using hospital inpatient records, which contain data on hospital admissions, operations, and procedures obtained for the entire cohort from Hospital Episode Statistics for England, Scottish Morbidity Record for Scotland, and Patient Episode Database for Wales. Diagnoses were recorded using the International Classification of Diseases (ICD) coding system; operations and procedures were recorded using the Office of Population Censuses and Surveys: Classification of Intervention and Procedures, version 4 (OPCS-4) coding system. Participants with a kidney stone or renal colic were identified using ICD-10 codes N20 and N23 (as either a primary or a secondary diagnosis), and OPCS-4 codes M09, M14, M26–28, and M31 (as either a primary or a secondary operative procedure). The codes are described in detail in Supplementary Table 1.

2.3. Assessment of dietary factors and fluid intake

Dietary and fluid intake was self-reported at baseline for all 500 000 participants using a short touchscreen Food-Frequency Questionnaire (FFQ), designed to capture "usual" intake of common food and drink items, as well as to seek information about common sources of various nutrients [13]. Daily intake of tea, coffee, water, fresh fruit, dried fruit, cooked vegetables, and salad/raw vegetables, and weekly intake of oily fish, nonoily fish, processed meat, poultry, beef, lamb/mutton, pork, cheese, bread, and cereal were collected. Participants were also asked whether they added salt to their food.

Dietary data from the Oxford WebQ, a more detailed questionnaire than the FFQ [14], available for 188 784 participants at either baseline or 2–3 yr after recruitment, was used to account for regression dilution bias (ie, random error in estimated intake introduced by fluctuations in dietary intake over time and/or measurement error using the FFQ). For more detail on the derivation of dietary variables from the FFQ and the Oxford WebQ, see the Supplementary material.

2.4. Covariates

Townsend deprivation score was used as an indicator of socioeconomic status and was assigned to each participant corresponding to the output area of their residential postcode at recruitment. Educational qualifications, ethnic background, smoking status, alcohol intake frequency, and calcium supplementation use were collected via the touchscreen questionnaire at recruitment. Body mass index (BMI; kg/m^2) was derived from weight (kg) using scales and standing height (metres) measured during the physical examination at recruitment.

2.5. Statistical analysis

Of the 502 638 participants enrolled in UK Biobank, 7112 participants with a prevalent kidney stone identified via either self-report at recruitment and/or hospital inpatient records (ie, with a relevant diagnostic or operation code before the date of recruitment) were excluded. In an attempt to account for the possibility that pre-existing conditions would confound any observed associations, a

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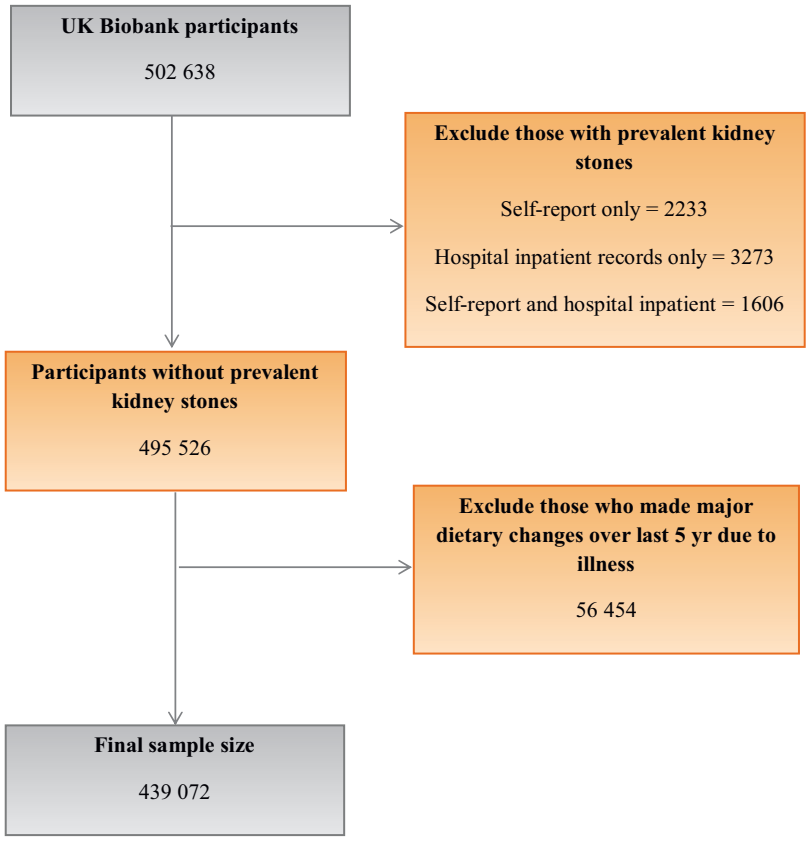

Fig. 1 – Flowchart for final analytic sample size.

further 56 454 participants who reported in the touchscreen questionnaire as making major changes to their diet over the last 5 yr due to illness were also excluded. This resulted in an analytical dataset of 439 072 participants (see Fig. 1 for a flowchart of the exclusion criteria).

Person years were calculated from the date of recruitment (2006–2010) until the first incident diagnosis of kidney stones, date of death, or last date of hospital admission (31 March 2015), whichever came first. Cox proportional hazards models were used to assess the association between dietary factors as measured using the FFQ at recruitment and subsequent risk of the first kidney stone. As the analyses presented here generally involve a comparison of risks across more than two categories, the floating absolute risk method was used to estimate the 95% confidence intervals (CIs) [15]. Tests for linear trends across the baseline FFQ categories of intake were based on the mean intake derived from the Oxford WebQ. All models were assessed for the proportionality of hazards assumption using Schoenfeld residuals. The main analyses were adjusted for age (in single years), sex, Townsend deprivation score (quintiles), education (no qualifications, CSE/O-Level/GCSE or equivalent, AS/A-Level or equivalent, higher education, or other professional qualification), ethnicity (white, mixed background, black, Asian, or other), smoking (never, former, and current), alcohol (never, special occasions only, one to three times a month, once or twice a week, three or four times a week, daily, or almost daily), BMI (<18.5, ≥ 18.5–<25, ≥ 25–<30, ≥ 30–<35, ≥ 35–40, and ≥ 40 kg/m^2), and use of calcium supplementation (no and yes). Participants with missing data or who responded "prefer not to answer/do not know" for any of the covariates were assigned to a separate category for that covariate. The proportion of data that was assigned as missing or prefer not to answer/do not know was $<0.5\%$ for each covariate, with the exception of education (1.7%).

In secondary analyses, dietary factors significantly associated with the risk of kidney stones in the main analyses were included as covariates in order to explore whether mutual adjustment for dietary factors affected previously observed associations. To account for reverse causation, participants who were censored within the first 2 yr of follow-up were excluded from the analyses.

All p values were two sided, with statistical significance set at <0.05. Analyses were performed using Stata SE version 13 (StatCorp, College Station, TX, USA) and figures were produced using RStudio version 1.0.136 using the in-house package "Jasper".

3. Results

Of the 439 072 participants included in the analysis, 2057 developed a first incident kidney stone during a total of 2 685 079 yr of follow-up (mean = 6.1 yr; standard deviation = 0.97). Participants who developed an incident kidney

Table 1 – Baseline characteristics of the study population according to the population at risk and with kidney stone incidence.

Characteristic, % (*n*)	Population at risk	Incident kidney stones
Number	495 526	2327
Age at recruitment, mean (SD)	56.5 (8.1)	57.1 (7.9)
Women	54.8 (271 292)	35.9 (836)
Upper quintile of Townsend deprivation score, most deprived	20.0 (98 963)	25.2 (586)
Professional qualification	60.3 (292 512)	55.4 (1248)
White ethnic background	94.6 (466 096)	93.5 (2153)
Current smoker	10.6 (52 131)	13.7 (316)
BMI 30+ kg/m^2	24.4 (119 944)	34.3 (788)
Use of calcium supplementation	6.8 (29 635)	5.5 (112)

BMI = body mass index; SD = standard deviation.

stone were slightly older, were more likely to be male, lived in more deprived areas, were less educated, had a nonwhite ethnic background, were current smokers, and were more likely to be obese compared with the total population (Table 1). Unadjusted correlations between all dietary factors are shown in Supplementary Table 4.

Total fluid intake is defined as the sum of tea, coffee, water, and alcohol intake. Intake of fluid from all beverages as assessed by the Oxford WebQ increased across all categories of baseline total fluid intake as assessed by the FFQ; for baseline categories of zero to six, seven to eight, nine to 10, 11–12, and ≥13 cups/glasses per day, the mean intake of

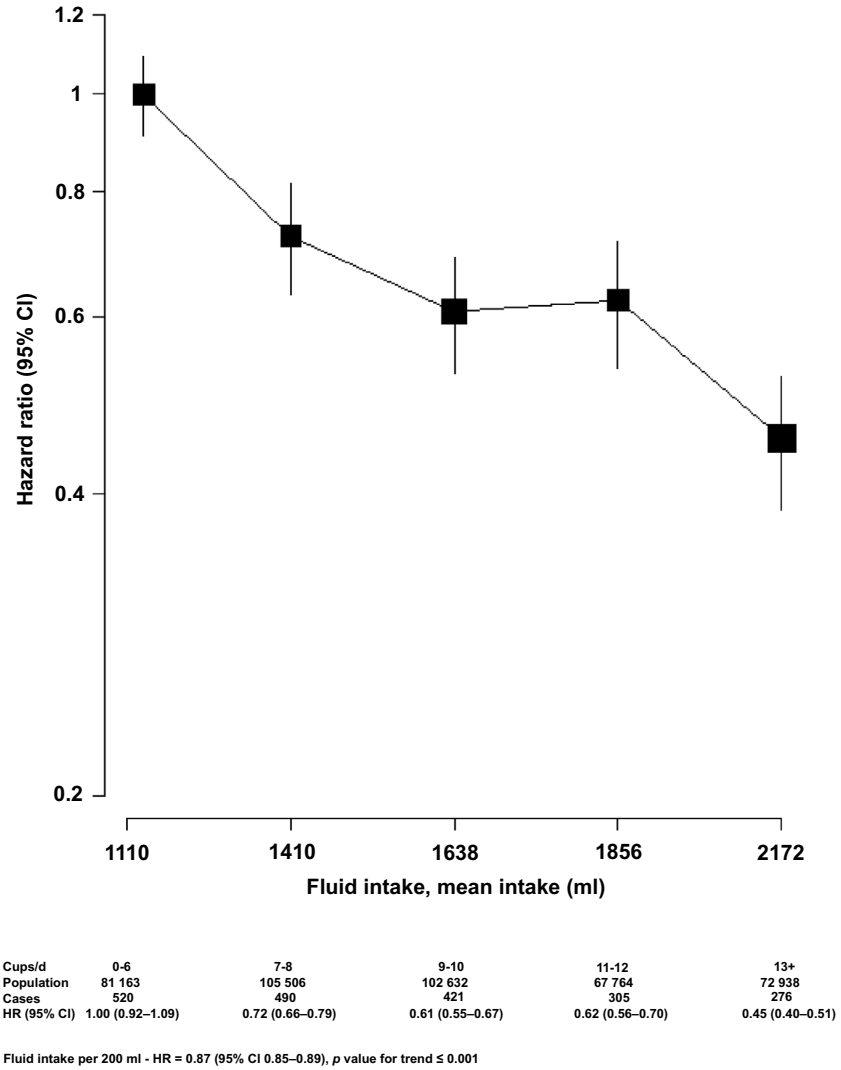

Fig. 2 – Cox proportional hazards models investigating the association between total fluid intake and the risk of developing incident kidney stones, adjusted for age, sex, Townsend deprivation score, education, ethnicity, smoking, body mass index, and calcium supplementation. CI = confidence interval; HR = hazard ratio.

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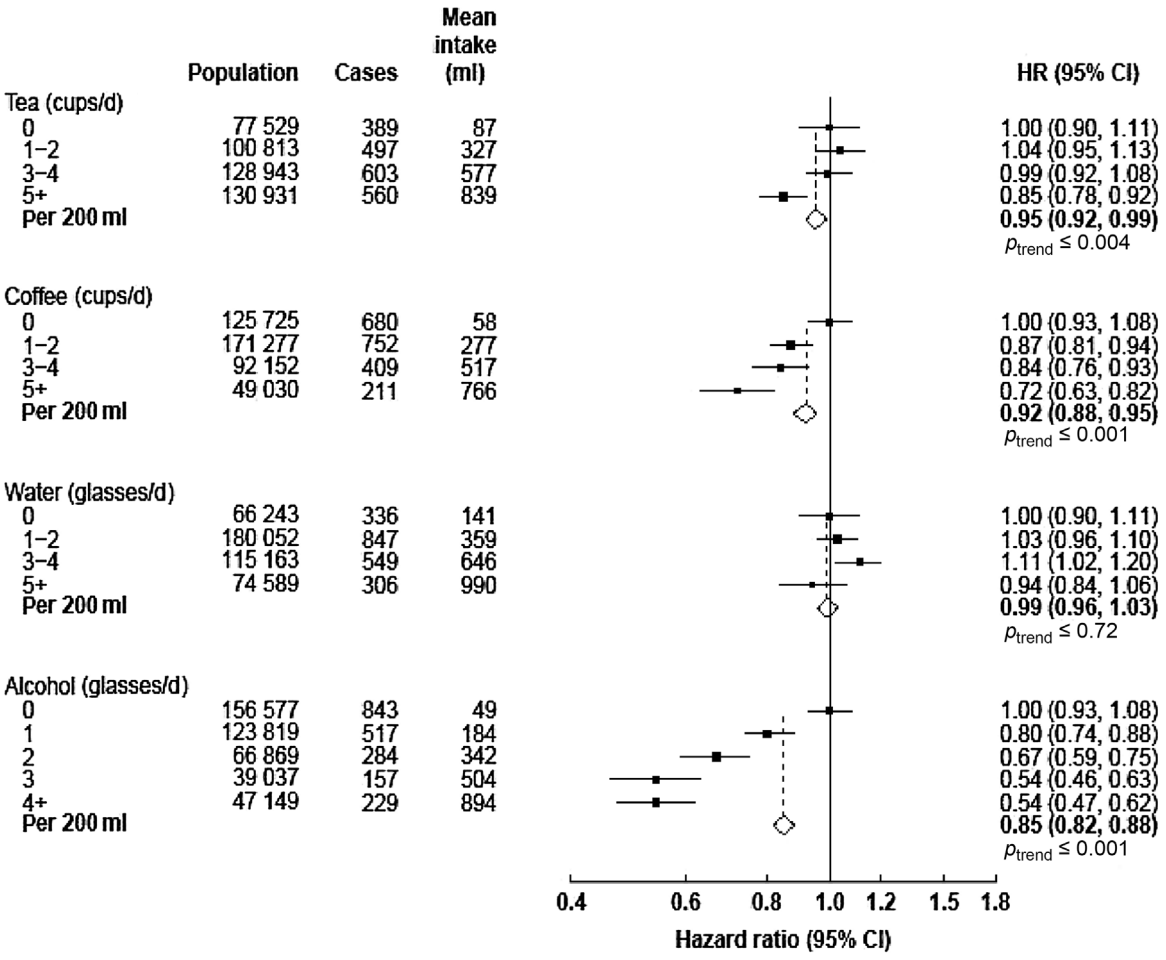

Fig. 3 – Cox proportional hazards models investigating the association between fluid intake and the risk of developing incident kidney stones. Alcohol was adjusted for age, sex, Townsend deprivation score, education, ethnicity, smoking, body mass index, and calcium supplementation. Tea, coffee, and water were adjusted for the same covariates as well as alcohol. For all figures, the position of the square indicates the value of the relative risk, and its area is inversely proportional to the variance of the logarithm of the relative risk, providing an indication of the amount of statistical information available for that particular estimate. CI = confidence interval; HR = hazard ratio.

all fluids from the 24 h dietary questionnaire was 1503, 1729, 1942, 2160, and 2484 ml/d (Supplementary Table 5). This suggests that despite total fluid, as assessed by the FFQ, being limited to tea, coffee, water, and alcohol intake, this is nonetheless a reliable indicator of overall fluid intake.

Higher total fluid intake was associated with a lower risk of kidney stones following adjustment for multiple lifestyle and socioeconomic factors (Fig. 2). Compared with those who drank zero to six cups/glasses per day of total fluid, the hazard ratios (HRs) were 0.72 (95% CI 0.66–0.79), 0.61 (95% CI 0.55–0.67), 0.62 (95% CI 0.56–0.70), and 0.45 (95% CI 0.40–0.51) for those who drank seven to eight, nine to 10, 11–12, and ≥13 cups/glasses per day, respectively. This corresponded to a 13% reduction in risk for each additional drink per day (equivalent to 200 ml; HR = 0.87, 95% CI 0.85–0.89).

For specific beverages, we found that higher consumption of tea (HR per 200 ml/d = 0.95, 95% CI 0.92–0.99), coffee (HR per 200 ml/d = 0.92, 95% CI 0.88–0.95), and alcohol (HR per 200 ml/d = 0.85, 95% CI 0.82–0.88) was individually significantly associated with a reduced risk of incident kidney stones, although no association was observed with water intake (HR per 200 ml/d = 0.99, 95% CI 0.96–1.03; Fig. 3).

Vegetable intake was not associated with incident kidney stones (HR per 100 g/d = 0.94, 95% CI 0.87–1.03), whilst fruit intake (HR per 100 g/d = 0.88, 95% CI 0.83–0.93) and fibre intake (HR per 10 g/d = 0.82, 95% CI 0.77–0.87) were significantly associated with a reduced risk (Fig. 4).

Consumption of total fish (HR per 25 g/wk = 1.00, 95% CI 0.90–1.12), oily fish (HR per 10 g/wk = 0.97, 95% CI 0.91–1.04), and nonoily fish (HR per 10 g/wk = 1.04, 95% CI 0.95–1.13) was not associated with incident kidney stones (Fig. 5). However, total meat intake was associated with an increased risk (HR per 50 g/wk = 1.17, 95% CI 1.05–1.29), with qualitatively similar estimates of risk observed for processed meat (HR per 25 g/wk = 1.12, 95% CI 0.97–1.29), poultry (HR per 50 g/wk = 1.22, 95% CI 1.00–1.49), and red meat (HR per 50 g/wk = 1.19, 95% CI 1.00–1.41), although these did not reach statistical significance (Fig. 5). Adding salt to food (not cooking) was also associated with an increased risk; compared with those never/rarely added salt to food, those

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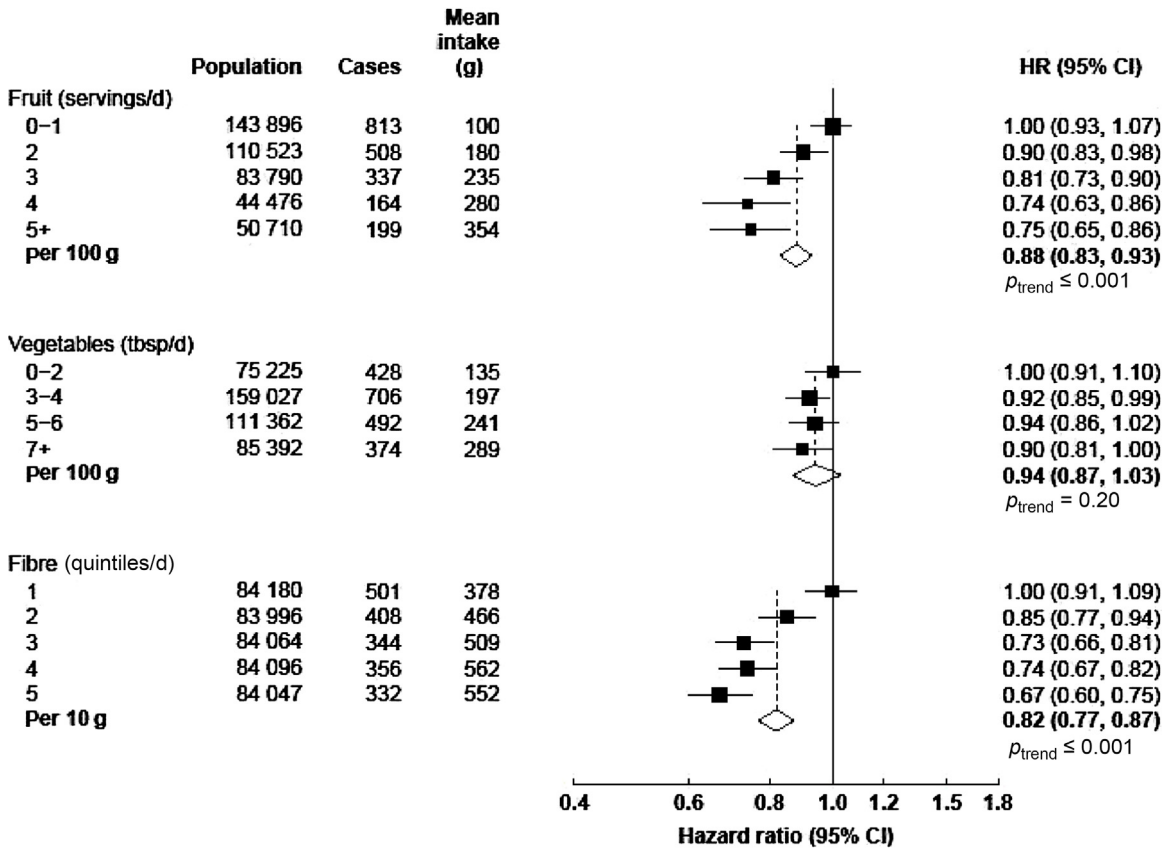

Fig. 4 – Cox proportional hazards models investigating the association between fruit, vegetable, and fibre intake, and the risk of developing incident kidney stones. Models were adjusted for age, sex, Townsend deprivation score, education, ethnicity, smoking, alcohol, body mass index, and calcium supplementation. CI = confidence interval; HR = hazard ratio; tbsp = tablespoon.

who always added salt to food had a 33% higher risk (HR = 1.33, 95% CI 1.12–1.58). No significant association was observed with cheese intake (HR per 25 g/wk = 0.95, 95% CI 0.82–1.10; Fig. 6).

Mutual adjustment for dietary factors that were significant in the abovementioned analyses did not make a material difference to the associations found (Supplementary Table 6). The associations also remained similar when excluding participants censored within the first 2 yr of follow-up, with the exception of vegetable intake, which was associated with a lower risk of kidney stones after excluding those diagnosed within the first 2 yr (HR per 100 g/d = 0.89, 95% CI 0.80–0.99, based on 1359 cases; Supplementary Table 7).

4. Discussion

In this UK population-based prospective cohort of over 439 000 middle-aged participants, total fluid intake and a range of dietary factors were associated with the risk of developing a first incident kidney stone. These results provide further evidence that diet is a potentially important modifiable factor for the prevention of kidney stone formation.

Similar to meta-analyses of previous observational studies, we found a linear dose-response reduction in the risk of kidney stones with increasing amount of fluid intake [10,11]. When compared with fluid intake of zero to six glasses per day (approximately 1.2 l), individuals who drank 13 glasses or more (equivalent to ≥2.3 l) had a 50% reduced risk of developing kidney stones. This level of fluid intake is similar to that administered in trials, which have found that increased fluid intake decreases the recurrence of kidney stones [6]. International guidelines recommend that patients with kidney stones should increase their fluid intake to achieve a urine volume of ≥2.5 l/d in order to reduce stone recurrence [16,17]. In our study, the reduction in risk with total fluid intake was primarily due to tea, coffee, and alcohol, which is consistent with the findings of a recent meta-analysis [10]. However, in contrast with the findings from the meta-analysis, we found no association between water intake and kidney stone risk, which suggests that specific beverages may have differential effects on kidney stone formation, and that beverages that exert a diuretic effect (thereby causing urine dilution) or that contain caffeine may be of particular relevance.

With regard to other dietary factors, we found that higher meat intake was associated with an increased risk of kidney stones; however, previous prospective studies that have focused mainly on animal protein intake have produced inconsistent findings [9,18–20]. Two randomised controlled trials have shown no reduction in kidney stone

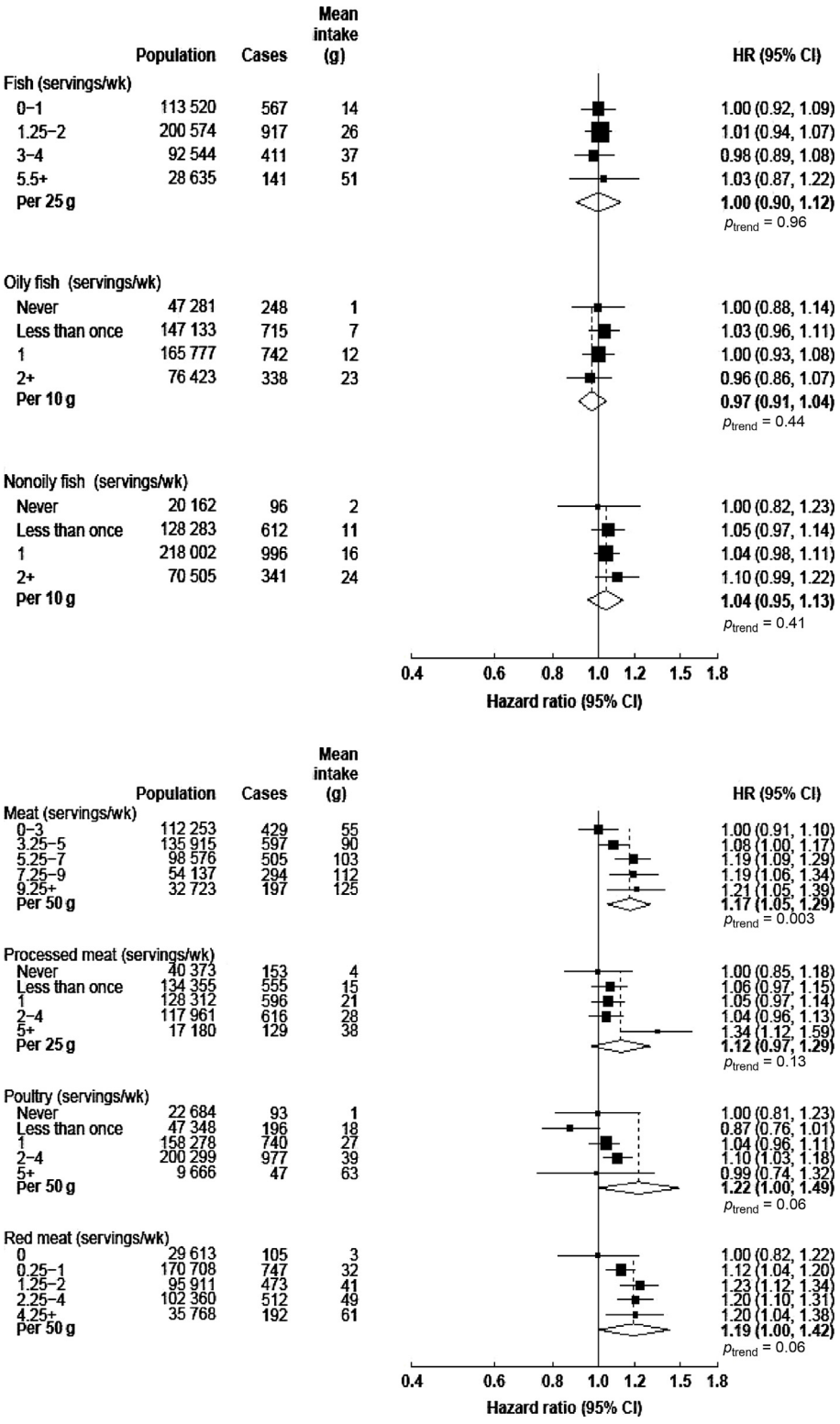

Fig. 5 – Cox proportional hazards models investigating the association between fish and meat intake, and the risk of developing incident kidney stone. Models were adjusted for age, sex, Townsend deprivation score, education, ethnicity, smoking, alcohol, body mass index, and calcium supplementation. CI = confidence interval; HR = hazard ratio.

recurrence with a diet low in animal protein, although they were small, consisting of 99 [21] and 175 [22] participants, respectively. In contrast, another trial in 120 men found that a diet low in both animal protein and salt reduced the risk of recurrent kidney stones by 50% compared with a low-calcium diet [23]. We also found that higher salt intake was associated with an increased risk of kidney stones, although findings from other observational studies have been

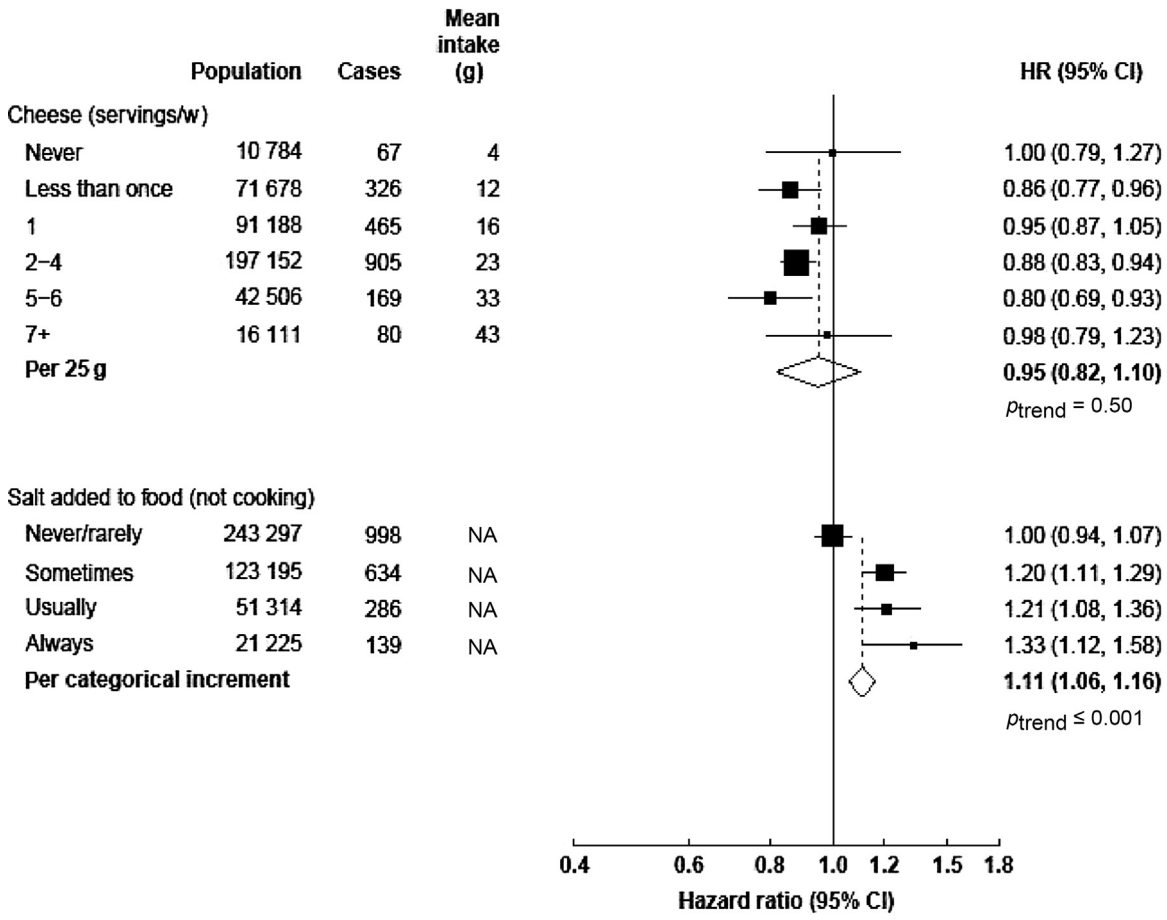

Fig. 6 – Cox proportional hazards models investigating the association between intake of other dietary factors and the risk of developing incident kidney stones. Models were adjusted for age, sex, Townsend deprivation score, education, ethnicity, smoking, alcohol, body mass index, and calcium supplementation. CI = confidence interval; HR = hazard ratio; NA = not available.

inconsistent [20,21,27,28]. We also found that higher consumption of fruit and fibre was associated with a significant risk reduction, as has been reported elsewhere in prospective studies [9,24] but not in the one small trial that assessed this in relation to recurrent kidney stones [22]. It is possible that fruit might reduce the risk through increased urinary citrate (even from noncitrus fruit) and/or its relatively high fibre content [25].

Strengths of the current study are the large sample size, wide range of measures available on dietary factors and possible confounders, and cohort-wide linkage to longitudinal data on hospital inpatient admissions. However, this does mean that patients who seek treatment solely through primary care or who do not seek any medical attention are not captured. Whilst this will lead to an underascertainment of cases, it is unlikely that the association with dietary factors differ markedly between those cases seeking hospital treatment and those who do not.

The availability of detailed data on dietary intake from multiple 24-h recall questionnaires (Oxford WebQ) suggests that total fluid intake corresponded well with categories as defined by the baseline FFQ, providing assurances that the latter is a robust indicator of overall fluid intake. The use of updated data from the Oxford WebQ meant that we could take into account random error caused by changes in diet over time and/or measurement error of the FFQ.

Whilst the FFQ used in UK Biobank has been shown to be a well-established and reliable tool [26], it does not enable an accurate estimation of nutrient intake, and hence we were unable to test the association specifically with intake of dietary calcium or animal protein, nor could we take into account other dietary factors that may be relevant for stone disease (eg, types of soft drinks or juice) [27,28]. We also had insufficient information to explore dietary patterns, and hence were not able to investigate the hypothesis that a DASH- or Mediterranean-style diet is associated with a lower kidney stone risk [8,29,30].

As many patients diagnosed with a first kidney stone may modify their diet (eg, by increasing fluid intake) based on medical advice after their initial diagnosis, our intention was not to assess the dietary determinants of kidney stone recurrence, but rather the extent to which dietary factors influence the risk of developing a first incident kidney stone. However, in order to examine whether our findings might have been caused by reverse causation, whereby participants experiencing symptoms may have changed their diet (eg, by drinking more fluids) prior to being admitted to hospital with a kidney stone, we excluded a

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priori participants who reported having changed their diet in the last 5 yr due to illness. We also excluded participants who were diagnosed within 2 yr of baseline and the results were not materially altered.

There are some other limitations to this study. No information was available on stone composition (such as uric acid, calcium oxalate), and hence it was not possible to investigate whether dietary factors differentially affect the development of stone subtypes. Whilst we were able to take into account a wide range of potential confounders that did not make an appreciable difference to the risk estimates, confounding by other factors remains a possibility and causality cannot be inferred based on these findings.

5. Conclusions

Increased fluid intake, as well as consumption of fruit and foods high in fibre, was associated with a lower risk of developing a first kidney stone, whilst higher meat consumption and salt intake were associated with a higher risk. The lower risk of kidney stones observed for tea, coffee, and alcohol, but not water, might reflect a potential diuretic effect and warrants further investigation. Overall, this study suggests that the risk of kidney stones could be decreased through relatively simple dietary modifications.

Author contributions: Thomas J. Littlejohns had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Littlejohns, Bradbury, Allen, Turney.
Acquisition of data: Littlejohns.
Analysis and interpretation of data: Littlejohns, Bradbury, Allen.
Drafting of the manuscript: Littlejohns, Neal.
Critical revision of the manuscript for important intellectual content: Littlejohns, Neal, Bradbury, Heers, Allen, Turney.
Statistical analysis: Littlejohns, Bradbury.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: None.
Other: None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euf.2019.05.002.

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