Ambient heat exposure and kidney function in patients with chronic kidney disease: a post-hoc analysis of the DAPA-CKD trial

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Summary

Background Higher temperatures are associated with higher rates of hospital admissions for nephrolithiasis and acute kidney injury. Occupational heat stress is also a risk factor for kidney dysfunction in resource-poor settings. It is unclear whether ambient heat exposure is associated with loss of kidney function in patients with established chronic kidney disease. We assessed the association between heat index and change in estimated glomerular filtration rate (eGFR) in participants from the DAPA-CKD trial in a post-hoc analysis.

Methods DAPA-CKD was a randomised controlled trial of oral dapagliflozin 10 mg once daily or placebo that enrolled participants aged 18 years or older, with or without type 2 diabetes, with a urinary albumin-to-creatinine ratio of 200–5000 mg/g, and an eGFR of 25–75 mL/min per 1·73 m². In this post-hoc analysis, we explored the association between time-varying daily centre-level heat index (ERA5 dataset) and individual-level change in eGFR in trial participants using linear mixed effect models and case-time series. The DAPA-CKD trial is registered with ClinicalTrials.gov, NCT03036150.

Findings Climate and eGFR data were available for 4017 (93·3%) of 4304 participants in 21 countries (mean age: 61·9 years; mean eGFR: 43·3 mL per 1·73 m²; median 28 months follow-up). Across centres, a heat index of more than 30°C occurred on a median of 0·6% of days. In adjusted linear mixed effect models, within each 120-day window, each 30 days' heat index of more than 30°C was associated with a –0·6% (95% CI –0·9% to –0·3%) change in eGFR. Similar estimates were obtained using case-time series. Additional analyses over longer time-windows showed associations consistent with haemodynamic or seasonal variability, or both, but overall estimates corresponded to an additional 3·7 mL per 1·73 m² (95% CI 0·1 to 7·0) loss of eGFR per year in a patient with an eGFR of 45 mL per 1·73 m² located in a very hot versus a temperate environment.

Interpretation Higher ambient heat exposure is associated with more rapid eGFR decline in those with established chronic kidney disease. Efforts to mitigate heat exposure should be tested as part of strategies to attenuate chronic kidney disease progression.

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Introduction

There is evidence that the kidney is adversely affected by high temperatures; for example, kidney stone events are more frequent in people living in regions with higher ambient temperatures.[1] Additionally, acute kidney injury is a well described complication of clinical heat illness,[2] and hospital admissions with acute kidney injury are more frequent during the warmer seasons in several hot countries studied.[3,4]

Chronic kidney disease is a common and progressive condition due to a range of causes, including diabetes, glomerulonephritis, and inherited disorders, with an estimated global prevalence of 9·1%.[5] Combined extreme environmental and physiological heat stress has been proposed as the primary cause of Mesoamerican nephropathy and other forms of chronic kidney disease of uncertain aetiology, with some investigators making the case for the entity to be referred to as climate-change nephropathy.[6] Others have hypothesised that increased environmental temperatures put all people with established chronic kidney disease, of whatever cause, at increased risk of adverse events.[7] For example, patients with chronic kidney disease have been reported to have impaired autoregulatory responses to dehydration.[8] Furthermore, and perhaps in part because of these impaired responses, there is the possibility that high ambient temperatures, in the absence of clinical heat illness, might exacerbate the loss of kidney function in people with reduced estimated glomerular filtration rate (eGFR) or albuminuria, or both. Globally, some, but not all, of the world's hottest regions are estimated to have a high prevalence of chronic kidney disease;[9] however, to

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Research in context

Evidence before this study

We searched PubMed for publications between Jan 1, 1990, and Dec 31, 2022, using the search terms "heat" AND "kidney" AND "epidemiology" along with "temperature" AND "estimated glomerular filtration rate", limiting the results to human studies. Global estimates suggest chronic kidney disease is more common in some, but not all, hotter regions. Studies using electronic health records exploring associations between climate variables and kidney outcomes report associations among periods of higher temperatures and kidney disease-related morbidity and mortality, primarily manifested as hospital admissions with diagnoses of nephrolithiasis or acute kidney injury. Reports from cross-sectional hospital-based analyses suggest measures of kidney function are lower in patients tested during summer months. In low-income and middle-income settings, there are also reports that surrogates of occupational heat exposure are associated with urinary markers of kidney injury and measures of impaired kidney function.

Added value of this study

By analysing data from the multinational DAPA-CKD trial along with publicly available climate data, we show an association between increased ambient heat index and loss of kidney function in patients with pre-existing chronic kidney disease of diverse causes. Point estimates suggest that exposure to a very hot versus a temperate environment is associated with up to 8% additional loss of estimated glomerular filtration rate each year after accounting for seasonal effects.

Implications of all the available evidence

Ambient heat exposure, at levels commonly experienced in the hotter parts of the world, is associated with adverse kidney outcomes including progression of chronic kidney disease of diverse primary causes. Whether heat exposure is associated with loss of kidney function in people with normal or near-normal kidney function is unknown. Mitigating heat exposure might help to attenuate the progression of chronic kidney disease.

date, there is no empirical evidence, outside of short-term occupational studies done in Central America,[10] that heat exposure is associated with an accelerated loss of kidney function in this group of patients.

See Online for appendix

The DAPA-CKD trial was an international randomised placebo-controlled trial examining the effects of dapagliflozin on kidney and cardiovascular events in patients with established diabetic and non-diabetic chronic kidney disease[11] across 393 centres in 21 countries from around the world, encompassing a wide range of ambient temperatures and humidity. The results of this trial provide a unique opportunity to explore the longitudinal relationship between climate and change in kidney function. We did a post-hoc analysis examining the association between time-updated local ambient heat exposure and changes in eGFR over time among participants of the DAPA-CKD trial.

Methods

Study design

The DAPA-CKD trial randomly assigned 4304 patients with chronic kidney disease (eGFR 25-75 mL/min per 1·73 m²) and albuminuria (urine albumin-to-creatinine ratio [UACR] 200-5000 mg/g [23-566 mg/mmol]) to dapagliflozin 10 mg daily or placebo in addition to standard of care. The regulatory approval, methods, and results of the DAPA-CKD trial have been previously described.[11]

We considered temperature and humidity over both day and night combined, as the 24-h average heat index,[12] at each study centre location as a surrogate for participant heat exposure. We estimated the heat index (in °C) at each study centre from the 24-h mean ambient dry-bulb temperature and the relative humidity (in turn, indirectly estimated from the ambient dry-bulb temperature and dew point temperature), both from the ERA5 climate reanalysis dataset for the period of May 1, 2016, to June 30, 2020 (appendix p 2).[13] We then classified each day as heat-exposed if the heat index was above a threshold and set the initial threshold at 30°C as exposure around this temperature has been associated with health risks in other contexts.[14,15]

We then generated each trial participant's unique exposure history by summing the number of days with a heat index above the threshold in each 120-day follow-up window and dividing by 30 to generate the exposure variable, termed HEAT-30. Hence, for each 120-day study visit window, with the heat index threshold at 30°C, the HEAT-30 exposure variable could take a value from zero to four (in 0·03 increments) with a one-unit change reflecting 30 days of a heat index of more than 30°C. The HEAT-30 variable could vary among individuals from the same centre as participants recruited on different dates will have differing exposure histories. We did companion analyses at thresholds up to 32°C and down to 27°C (below which the calculation of heat index is no longer valid), in 1°C increments.

Outcomes

eGFR values were calculated from centrally measured, isotope-dilution mass spectrometry referenced, serum creatinine assays, using the 2009 CKD-EPI equation.[11] Baseline values were defined as the average of the eGFR at screening and randomisation (where both were available) and follow-up values obtained at each of the protocolised 4-monthly interval study visits until last follow-up visit. Values from the study visits at 2 weeks and 2 months following randomisation were excluded to

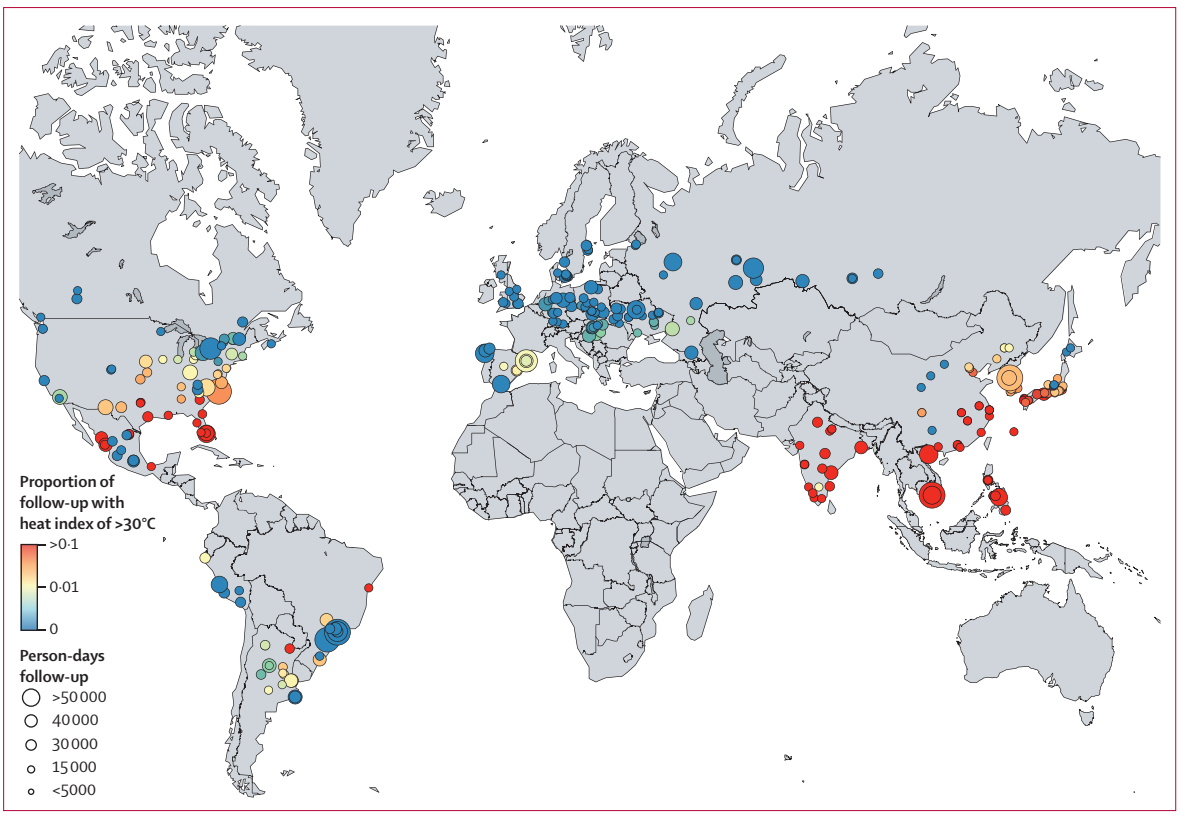

Figure 1: **Proportion of days with heat index of more than 30°C over the entire study period, by study centre**
Study centre locations by number of patients recruited (marker size) and proportion of days with heat index of more than 30°C (colour) at each centre over the entire DAPA-CKD study follow-up period (February, 2017 to June, 2020).

maintain a constant interval between eGFR measures. Participants were censored at the commencement of kidney replacement therapy (ie, dialysis or kidney transplantation). Change in eGFR from baseline at each 4-month study visit follow-up window was then calculated on the natural log scale and the outcome interpreted as a percentage change in eGFR (as log(e) change approximates to percentage change at values of less than 5% as observed with the exposures of interest).

Statistical analysis

Data were collected on all covariates as part of DAPA-CKD study visits. We defined obesity as a Quételet BMI of 30 kg/m² or more (except in Asian participants for whom BMI was defined as 25 kg/m² or more).[16] We defined high-income countries using World Bank criteria (ie, a gross national income per capita of more than US $12 696 in 2020).

To minimise potential confounding due to differing patient characteristics between hotter and cooler regions, we first developed a linear mixed effect model of change in eGFR, including non-climate-related explanatory variables. Individual eGFR measures were clustered within participants, which were in turn clustered within centres to account for the effects of centre-level factors on chronic kidney disease progression. Details of the model development are described in the appendix (p 3). Once the optimal model of eGFR change over time, excluding climate variables, had been developed, we included the time-updated HEAT-30 variable for each 120-day window before each eGFR measure.

We also employed a case-time series approach to further address residual confounding unaccounted for by the multilevel model. The case-time series is a conditional analysis that controls by design for all measurable and unmeasurable time-constant subject-specific differences, and therefore is less exposed to biases.[17] However, it is limited to including people who have both exposed and unexposed time-windows during follow-up, so it usually has less power than the linear mixed effect model. The case-time series was fitted with identical exposure and outcome definitions as were used for the linear mixed effect model with further details provided in the appendix (p 4).

To examine if there was a specific threshold for heat index associated with eGFR trajectory, we repeated the linear mixed effect and case-time series analyses using heat index thresholds from 27°C to 32°C. Then, to explore whether observed associations were explained by reversible effects—ie, due to haemoconcentration or intravascular depletion (either around the day of the test or over a season), or were a persistent effect, reflecting

	Centre-level heat index quartile 1 and 2 (n=186)	Centre-level heat index quartile 3 (n=90)	Centre-level heat index quartile 4 (n=97)
Percentage of study days heat index of >30°C, range	0·0–0·6%	0·6–10·5%	10·5–79·7%
Number of participants per centre	8 (4–15)	7·5 (4–14)	6 (4–13)
Country-level gross domestic product, US$ per capita	25 198 (19 863)	33 232 (18 111)	21 146 (21 610)
Country-level human development index	0·860 (0·0684)	0·881 (0·0647)	0·790 (0·114)
Country			
Argentina	7 (4%)	14 (16%)	1 (1%)
Brazil	8 (4%)	5 (6%)	1 (1%)
Canada	21 (11%)	0	0
China	4 (2%)	7 (8%)	12 (12%)
Denmark	6 (3%)	0	0
Germany	14 (8%)	0	0
Hungary	12 (6%)	0	0
India	0	1 (1%)	17 (18%)
Japan	5 (3%)	19 (21%)	24 (25%)
South Korea	0	15 (17%)	0
Mexico	8 (4%)	0	7 (7%)
Peru	15 (8%)	1 (1%)	0
Philippines	0	0	10 (10%)
Poland	16 (9%)	0	0
Russia	17 (9%)	0	0
Spain	4 (2%)	7 (8%)	0
Sweden	5 (3%)	0	0
Ukraine	22 (12%)	0	0
UK	8 (4%)	0	0
USA	14 (8%)	21 (23%)	14 (14%)
Viet Nam	0	0	11 (11%)

Data are median (IQR), mean (SD), or n (%), unless otherwise stated.

Table 1: **Centre-level characteristics by centre-level heat index quartile**

	Centre-level heat index quartile 1 and 2 (n=2064)	Centre-level heat index quartile 3 (n=1007)	Centre-level heat index quartile 4 (n=946)
Age, years	62·5 (11·7)	62·5 (11·5)	60·1 (13·0)
Sex			
Female	667 (32·3%)	294 (29·2%)	366 (38·7%)
Male	1397 (67·7%)	713 (70·8%)	580 (61·3%)
Race			
White	1595 (77·3%)	504 (50·0%)	101 (10·7%)
Black	80 (3·9%)	70 (7·0%)	33 (3·5%)
Asian	145 (7·0%)	413 (41·0%)	740 (78·2%)
Other	244 (11·8%)	20 (2·0%)	72 (7·6%)
Weight	86·9 (19·1)	83·7 (21·6)	69·9 (17·7)
BMI	30·9 (5·88)	30·1 (6·42)	26·5 (5·47)
Smoking status			
Current smoker	269 (13·0%)	156 (15·5%)	118 (12·5%)
Former smoker	664 (32·2%)	422 (41·9%)	263 (27·8%)
Never smoker	1131 (54·8%)	429 (42·6%)	565 (59·7%)
Type 2 diabetes	1395 (67·6%)	675 (67·0%)	668 (70·6%)
Cardiovascular disease	887 (43·0%)	363 (36·0%)	265 (28·0%)
Use of angiotensin-converting enzyme inhibitor or angiotensin-2 receptor blocker	2027 (98·2%)	979 (97·2%)	928 (98·1%)
Use of diuretics	1074 (52·0%)	444 (44·1%)	268 (28·3%)
Use of statin	1337 (64·8%)	749 (74·4%)	561 (59·3%)
Use of insulin in those with diabetes	798 (57·2%)	353 (52·3%)	359 (53·7%)
Blood pressure, mm Hg			
Systolic	138 (16·8)	138 (17·8)	135 (17·6)
Diastolic	78·0 (10·1)	76·7 (11·2)	77·4 (10·5)
Estimated glomerular filtration rate, mL/min per 1·73 m²	43·7 (12·7)	43·1 (12·4)	42·8 (11·7)
Urinary albumin-to-creatinine ratio, mg/mmol	108·3 (54·0–210·1)	106·8 (53·8–211·8)	102·9 (52·4–215·8)
Participant-level proportion of days with heat index of >30°C follow-up	0	0·04 (0·01–0·06)	0·43 (0·19–0·74)

Data are mean (SD), n (%), or median (IQR). Seven participants were excluded from the linear mixed model due to missing covariate data.

Table 2: **Selected individual baseline characteristics by centre-level heat index quartile**

progressive eGFR decline, we did further sensitivity analyses. First, we additionally adjusted the original linear mixed effect and case-time series models for a heat index of more than 30°C on the day of the test. Second, to examine whether any heat-associated drop in eGFR was seasonal, we did an extended exposure analysis by repeating the original HEAT-30 linear mixed effect model above but including additional exposure windows up to 360 days before testing (ie, we quantified the association between the change in eGFR and the HEAT-30 variable at 0–120, 120–240, and 240–360 days before each eGFR test in a single model).

To show the potential effect size of ambient heat exposure, we estimated the mean and 95% CIs of additional annual eGFR loss associated with heat exposure by combining each of the 120-day window percentage changes in eGFR over 360 days for a notional patient with a baseline eGFR of 45 mL/min per 1·73 m². For this calculation, we compared a notional patient located in one of the hottest centres, where the proportion of days with a heat index of more than 30°C was above the 95th percentile (ie, a proportion of days with a heat index of more than 30°C of 0·77), versus centres where the proportion of days with a heat index of more than

30°C was at the median (ie, a proportion of days with a heat index of more than 30°C was zero).

We further examined the association between HEAT-30 (0–120 days before eGFR test) and eGFR decline using the linear mixed effect model in subgroups defined by (1) baseline eGFR category, (2) baseline UACR category, (3) baseline type 2 diabetes, (4) baseline BMI category, (5) baseline systolic blood pressure category, (6) baseline diuretic use, and (7) DAPA-CKD study group, along with (8) the combination of baseline diuretic use and DAPA-CKD study group, by fitting interaction terms with each of the above exposure variables individually to the linear mixed effect model used to test the primary hypothesis. Marginal means were reported for all the subgroups with all covariates held at the mean. We also explored differences in the association between exposure and eGFR decline among participants based in developed regions versus less-developed regions by comparing the coefficients in analyses restricted to centres in high-income or middle-income country groupings.

Finally, we examined the association between HEAT-30 and a doubling of serum creatinine (57% decline in eGFR) in a time-to-event analysis. For this outcome, we estimated associations using a complementary log–log multilevel discrete-time survival model (again censoring for death or end-stage kidney disease), with study visits nested within individuals nested within centres, using the same exposure and adjustment for the same baseline covariates as the linear mixed effect model described above. The DAPA-CKD trial is registered with ClinicalTrials.gov, NCT03036150.

Role of the funding source

There was no funding source for this study. AstraZeneca funded the DAPA-CKD trial, which generated the data used for this subsequent analysis, and agreed to the study design and analysis plan, and approved the manuscript and decision to submit, but did not conduct the analysis.

Results

The DAPA-CKD trial was done between Feb 2, 2017, and June 12, 2020. Data flows are shown in the appendix (p 10). Climate and clinical follow-up data were available on 4017 (93·3%) of 4304 participants across 373 centres in 21 countries (figure 1) with a median follow-up of 28 months. 1327 (33%) of the 4017 study population were female, the mean age was 61·9 years (SD 12·0), the mean baseline eGFR was 43·3 mL/min per 1·73 m² (SD 12·4), and the median UACR was 944 mg/g (25–75th centile: 476–1871 mg/g). Across centres, a heat index of more than 30°C occurred on a median of 0·6% of days over the entire follow-up period (25–75th centile: 0·0–10·5%; table 1) and similarly across study participants, the median of individual participant's proportion of days with a heat index of more than 30°C over follow-up was 0·002 (25–75th centile: 0·0–0·082; table 2). However,

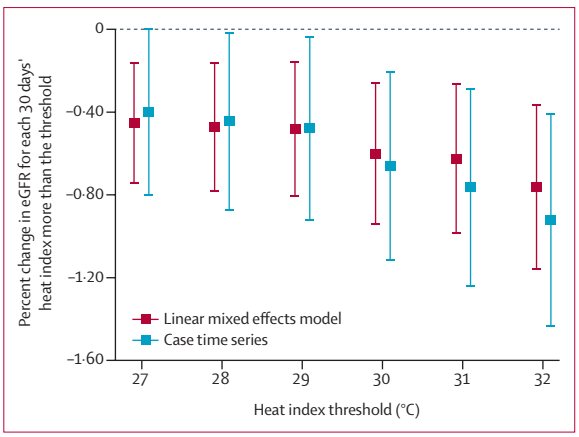

Figure 2: **Association between heat index and change in eGFR at different heat index thresholds**

Effect estimates and 95% CIs in which log(e) eGFR change is interpreted as percentage change. Results from the linear mixed effects model (n=4010 due to absent covariate data in seven participants) and case-time series (n=4017). Linear mixed effects model adjusted for baseline age, sex, ethnicity, smoking status, diagnosis of diabetes, history of cardiovascular disease, BMI, systolic blood pressure, UACR, eGFR, ACE or ARB use, statin use, diuretic use, and DAPA-CKD study group, including interactions with time of the following baseline variables: age, BMI, systolic blood pressure, eGFR, UACR, and DAPA-CKD study group, along with a baseline UACR×eGFR interaction (appendix p 5). ACE=angiotensin-converting enzyme inhibitor. ARB=angiotensin-2 receptor blocker. eGFR=estimated glomerular filtration rate. UACR=urine albumin-to-creatinine ratio.

participants based at the hottest 5% of centres had more than 60% of days with a heat index of more than 30°C (figure 1; appendix p 11). Centres in parts of the USA, Japan, Viet Nam, India, Mexico, the Philippines, and China were exposed to the highest numbers of days with a heat index of more than 30°C during the study (table 1; figure 1). Patients were more likely to be female, of designated Asian ethnicity, with a higher prevalence of diabetes, and a lower prevalence of baseline cardiovascular disease in centres with a higher level of heat exposure (table 2).

Age, BMI, systolic blood pressure, baseline eGFR, UACR, and treatment assignment were all associated with eGFR decline in the linear mixed effect without the inclusion of climate variables (appendix p 5).

eGFR trajectories by quartile of centre-level heat exposure showed a clear separation in eGFR decline over time with the most rapid decline in participants from centres with the highest heat exposure (appendix p 12). In the linear mixed effect model, heat exposure was associated with accelerated eGFR decline, with each one-unit increase in HEAT-30 in each 120-day window associated with a change in eGFR of –0·60% relative to baseline (95% CI –0·95 to –0·26). The analyses using case-time series led to very similar estimates of the effect size (appendix p 6).

Similar models using different heat index thresholds suggested the magnitude of this association was larger when the threshold for designating meaningful exposure was higher (figure 2). When exploring the contribution

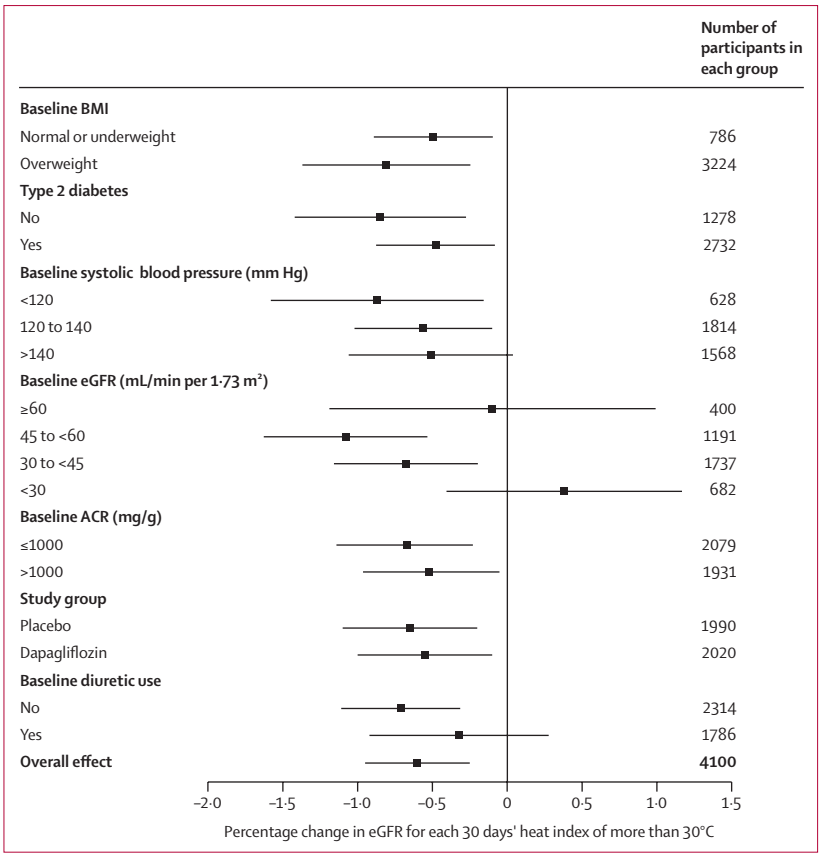

Figure 3: **Associations between heat index and change in eGFR in subgroups**
Marginal means (covariates held at the mean) and 95% CIs in which log(e) eGFR change is interpreted as percentage change. Results from the linear mixed effects model (n=4010 due to absent covariate data in seven participants). Model adjusted for baseline age, sex, ethnicity, smoking status, diagnosis of diabetes, history of cardiovascular disease, BMI, systolic blood pressure, UACR, eGFR, ACE or ARB use, statin use, diuretic use, and DAPA-CKD study group, including interactions with time of the following baseline variables: age, BMI, systolic blood pressure, eGFR, UACR, and DAPA-CKD study group, along with a baseline UACR×eGFR interaction (appendix p 5). Wald test p values for between group differences all more than 0·05 except baseline eGFR strata p=0·018. ACE=angiotensin-converting enzyme inhibitor. ARB=angiotensin-2 receptor blocker. eGFR=estimated glomerular filtration rate. UACR=urine albumin-to-creatinine ratio.

of reversible versus persistent effects, adjustment for a heat index of more than 30°C on the day of test partially attenuated the effect, although the 95% CIs for the estimate continued to exclude zero at the hottest heat index thresholds (appendix p 7). The extended exposure analysis showed that the early association between heat exposure and a drop in eGFR was followed by some recovery and then further deterioration over the course of a year. In this analysis, each unit HEAT-30 was associated with a change in eGFR of –0·65% (95% CI –1·04 to –0·27), 0·47% (95% CI 0·09 to 0·85), and –0·72% (95% CI 1·10 to 0·33) relative to baseline in each of the 0–120-day, 120–240-day, and 240–360-day windows, respectively (appendix p 8). Taken together, this suggests the net averaged effect of each unit HEAT-30 across a 360-day window was a –0·90% (95% CI –0·03 to –1·78) change in eGFR relative to baseline. This estimate is equivalent to an additional loss of 3·7 mL per 1·73 m² (95% CI 0·1 to 7·0) of eGFR per year for a theoretical patient with a baseline eGFR of 45 mL per 1·73 m² located in a very hot versus a temperate environment.

The association between HEAT-30 and eGFR decline was consistent across groups defined by baseline age, sex, type 2 diabetes, BMI, albuminuria, dapagliflozin treatment assignment, or diuretics (figure 3), and similarly there was no evidence for a difference in the association when considering the groups defined by a combination of dapagliflozin treatment assignment and diuretic use at baseline (data not shown). Analysis by baseline eGFR showed that the observed associations were mainly driven by those with stage 3 chronic kidney disease although there was less power to detect potential associations at higher or lower stages of chronic kidney disease (figure 3). Estimates for the association between HEAT-30 and eGFR decline did not qualitatively differ when restricted to centres located in either high-income or middle-income countries only (appendix p 9).

Declines in eGFR of 57% or greater occurred in 139 (3·5%) of 4010 participants. HEAT-30 was not associated with these declines in the time-to-event analyses (appendix p 9).

Discussion

Projected increases in temperature in a warming climate are expected to have wide-ranging effects on human health,[18] and those with underlying kidney disease might be expected to be particularly affected. We observed an association between ambient heat exposure and accelerated eGFR decline in participants of the DAPA-CKD study. For a typical patient with chronic kidney disease, our central estimates translate into an additional loss of eGFR of about 3·7 mL per 1·73 m² per year, potentially attributable to ambient heat exposure in a very hot versus a temperate environment after accounting for reversible seasonal effects. This is clinically relevant with the estimated detrimental effect associated with heat exposure quantitatively similar to the beneficial effects on eGFR decline observed with active treatment in the original DAPA-CKD trial.[11] The association with heat appears dose-dependent, with more severe heat exposure associated with more rapid eGFR decline, without a clear threshold effect.

Heat exposure-associated reductions in eGFR potentially reflect a combination of: (1) a short-term reversible increase in serum creatinine due to haemoconcentration independent of changes in renal clearance; (2) a short-term reversible haemodynamic alteration in renal clearance resulting from reduced renal blood flow (ie, pre-renal kidney injury); and (3) an irreversible loss of functional nephrons, which might be at least partially mediated by (2). While acknowledging analyses cannot disaggregate the contribution of haemoconcentration from pre-renal injury on individual eGFR measures, we sought to explore the contribution of reversible versus persistent effects of heat exposure in sensitivity analyses. Taken together, these

additional analyses suggest that although day of test and seasonal variation does occur (with evidence for a degree of recovery followed by a further deterioration over the months following heat exposure), the association observed between heat exposure and eGFR decline is persistent, in turn providing evidence for a clinically important effect of ambient heat on long-term kidney function. This evidence for the effect of heat on kidney function supports testing the effects of interventions, which might mitigate the effect of heat exposure; for example, advice on maintaining hydration, avoiding direct sun exposure, and resting regularly when in hot environments, as part of trials of lifestyle interventions in patients with chronic kidney disease.

The effect of heat exposure on kidney outcomes has been explored using other methodologies. Higher ambient temperatures are associated with higher rates of hospital admission with renal diagnostic codes, although these findings are primarily driven by increased rates of nephrolithiasis and acute kidney injury.[1,3,4,19,20] However, analyses of hospitalisation or mortality have not uncovered, and would not necessarily be expected to uncover, associations between heat exposure and progression of chronic kidney disease, because chronic kidney disease is primarily managed as an outpatient (and availability of kidney replacement therapy might mean death is not directly attributed to chronic kidney disease). Notwithstanding the challenges of capturing chronic kidney disease using routine data sources, international comparisons based on the global burden of disease data report higher chronic kidney disease prevalence in some, but not all, hotter regions,[9] and have actually estimated a higher burden of chronic kidney disease mortality associated with lower rather than higher temperature.[21] Other groups have reported lower eGFR measures in summer versus winter (or warmer versus cooler) months using cross-sectional approaches,[22–26] but none have examined the longitudinal association between time-updated heat exposure and eGFR trajectory over the medium term. Finally, our findings also provide additional context to studies showing associations between temperature and kidney dysfunction in heat-intense agricultural settings,[10,27] suggesting the link between environmental temperature and the progression of kidney disease is not restricted to the forms of chronic kidney disease seen in Central America and South Asia.

Our approach has several strengths that address the challenges facing studies aimed at exploring the differences in kidney function across regions. First, as neither the distribution of measured glomerular filtration rate nor equations used to estimate the eGFR are generalisable across populations internationally,[28,29] we used a study design examining within-person change in kidney function. Second, we used two orthogonal methods to account for non-climate-related centre-level differences in eGFR decline. This approach is key as the average temperature and humidity are typically higher in less developed regions (generally located in the tropics), where patients often face barriers in accessing care and medications, resulting in fewer opportunities to attenuate disease progression. Third, our analyses were based on eGFR measures from protocolised testing as part of a clinical trial rather than tests from routine care, which are often done when individuals are clinically unwell. Finally, kidney function measures were ascertained from a central laboratory, which will reduce error, because despite international efforts aimed at improving laboratory quality assurance, serum creatinine assay results have been shown to vary across centres and with time.[30]

These analyses do have important limitations. The exposure variable, by necessity, combines both observed and modelled estimates (but is the gold standard for this type of analysis) and the windows for outcome assessment were wide, meaning we had limited granularity to explore detailed time-dependent relationships between heat and eGFR. Although the orthogonal methods we used produced similar effect estimates and are designed to control for factors such as access to or quality of care, or population characteristics that might confound the association between climate and eGFR loss, we cannot exclude the possibility of unmeasured confounding by factors that vary over time. In the primary analysis, we did not attempt any kind of competing risk approach and censored for death or renal replacement therapy. However, as faster eGFR decline is a risk for both of these outcomes, it is likely that this limitation would have attenuated the reported effect sizes and indeed might explain why the effect estimates for the subgroup with eGFR less than 30 mL/min per 1·73 m² appeared diminished. Similarly, we did not account for exposures before the baseline eGFR measurement that might have also diluted the observed associations.

The sensitivity analysis adjusting for a heat index of more than 30°C on the day of the test will likely account for any short-term reversible effects of heat exposure but will also dilute the association of interest across the entire exposure window as temperatures are strongly correlated across time windows. Furthermore, we did not explore any associations with cold exposure. We also relied on a centre-level exposure variable rather than basing the heat index on a participant's home or work address, although, as participants are unlikely to have travelled large distances to study centres, the effect of doing so is likely to be small. Last, and perhaps most importantly, although we identified no difference in the associations of interest between high-income and middle-income countries, the DAPA-CKD dataset contains no individual-level information on occupation or the availability of mitigating measures (eg, fluid intake or air conditioning), which might affect the relationship between temperature and eGFR loss. Further exploration of these latter two issues should be prioritised.

Despite the limitations mentioned, the dataset used in this analysis provides a unique opportunity to answer a key question surrounding the effect of climate on the kidney. Although these data provide no insight into any association between heat and loss of kidney function in the general population, the findings support a clinically meaningful role of ambient environmental heat exposure in exacerbating disease progression in patients with chronic kidney disease. Given the projected increase in global temperatures, interventions to mitigate heat exposure in the chronic kidney disease population should be evaluated as part of a comprehensive strategy aimed at ameliorating disease progression.

Contributors

BC and DN conceived the study. BC, DN, AG, and ZZ drafted the initial analysis plan, which was then further developed by all the authors. ZZ did the analysis. ZZ, PV, and NJ, had direct access to the complete dataset. BC, DN, and ZZ drafted the manuscript. All authors take responsibility for the accuracy and integrity of the data, edited and approved the manuscript, and accept responsibility to submit it for publication.

Declaration of interests

HJLH has received honoraria, paid to his institution (University Medical Center Groningen), for participation in steering committees from AstraZeneca, Janssen, Gilead, Bayer, Chinook, and CSL Pharma; honoraria for participation in advisory boards from Merck, Mitsubishi Tanabe, Janssen, and Mundipharma; fees for consultancy from AstraZeneca, AbbVie, Retrophin, Boehringer Ingelheim, and Novo Nordisk; and research grant support from AstraZeneca, AbbVie, Janssen, and Boehringer Ingelheim. GMC has received fees from AstraZeneca for the DAPA-CKD trial steering committee; serves on the Board of Directors for Satellite Healthcare, a non-profit dialysis provider; has received research grants from the US National Institute of Diabetes and Digestive and Kidney Diseases, US National Institute of Allergy and Infectious Diseases, US National Heart, Lung, and Blood Institute, and CSL Behring; has served on trial steering committees with Akebia, AstraZeneca, Gilead, Sanifit, and Vertex; has served as an adviser to Ardelyx, CloudCath, Durect, Miromatrix, Outset, Renibus, Reata, Sanifit, Unicycive, and Vertex; and has served on data and safety monitoring boards for the National Institute of Diabetes and Digestive and Kidney Diseases, Bayer, Mineralys, and ReCor. RC-R has received honoraria as a consultant from AstraZeneca (DAPA-CKD Steering Committee), Boehringer Ingelheim, Bayer, Chinook, and Novo Nordisk; and research support and speaker fees from AstraZeneca, GSK, and Novo Nordisk. AML is an employee and stockholder of AstraZeneca. NJ has received support from AstaZeneca to attend conferences. JJVM has received payments for his work on clinical trials paid to his employer, Glasgow University; has received payments for consulting; is on the advisory board of Alnylam, Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cardurion, Cytokinetics, DAICor, GSK, Ionis Pharmaceuticals, KBP Biosciences, Novartis, and Theracos; and has received personal lecture fees from Abbott, Alkem Metabolics, Eris Lifesciences, Hikma, Lupin, Sun Pharmaceuticals, Medscape/Heart.org, ProAdWise Communications, Radcliffe Cardiology, Servier, and the Corpus. PR has received honoraria to Steno Diabetes Center Copenhagen for lecture fees, steering group participation, and advisory board participation from AstraZeneca, Bayer, Boehringer Ingelheim, Gilead, Novo Nordisk, Sanofi, and Eli Lilly, and research support from AstraZeneca. RDT has received consulting fees from Boehringer Ingelheim, Reata Pharma, and Chinook Pharma; received speakers fees from Medscape; participated in advisory boards for Bayer and Viofor; and participated in data monitoring committees for Akebia and Otsuka. DN reports unrelated work funded by GSK involving studies of kidney function in sub-Saharan Africa. DCW provides ongoing consultancy services to AstraZeneca and has received honoraria for participation in advisory boards and other activities, consultancy fees, or both from Amgen, AstraZeneca, Boehringer Ingelheim, Bayer, KSk, Janssen, Napp, Mundipharma, Medscape, Merck Sharp & Dohme, Pharmacosmos, Reata, Takeda, and Vifor Fresenius. BC has received research grant funding, paid to his employers (University College London and Royal Free London NHS Foundation Trust), from the UK Medical Research Council, the Colt Foundation, and AstraZeneca along with consultancy fees (also paid to his employer) from LifeArc. All other authors declare no competing interests.

Data sharing

Data underlying the findings described in this Article can be obtained in accordance with AstraZeneca's data sharing policy described online at https://www.astrazenecaclinicaltrials.com/our-transparency-commitments.

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