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Global warming, renal function and heart failure over 20 years

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A R T I C L E I N F O

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A B S T R A C T

Background: The impact of increasing temperatures on renal function in heart failure (HF) outpatients has never been specifically analyzed.
Methods: We retrieved creatinine and estimated glomerular filtration rate (eGFR) values of all HF outpatients followed at a HF clinic and temperature data from 2002 to 2021. For each patient and each year we averaged values of creatinine, eGFR and monthly temperatures during summer and the rest of the year.
Results: The study cohort included 2167 HF patients undergoing 25,865 elective visits, with a median of 14 visits for each patient (interquartile range 7–23). At the first visit, patients (70% men) had an age of 67 ± 13 years, and a left ventricular ejection fraction of 35 ± 14%. Creatinine was 1.25 ± 0.51 mg/dL, and eGFR was 65 ± 25 mL/min/1.73 m^2. When pooling together all average values of creatinine and eGFR measured during summer or in the rest of the year, creatinine was significantly higher in summer (difference 0.04, 95% confidence interval [CI] 0.04 to 0.05, $p < 0.001$), and eGFR was slightly lower (difference − 2.0, 95% CI -2.3 to −1.8, p < 0.001). Temperature rise during summer increased from 2002 to 2021. The absolute (Δ) and percent (Δ%) elevation in temperature during summer displayed independent associations with Δ and Δ% creatinine and eGFR after adjusting for age, sex, plasma creatinine, and HF therapies.
Conclusions: The magnitude of temperature elevation during summer has increased over 20 years. This elevation correlates with the decline in renal function during summer. This might be an example of how global warming is affecting human health.

1. Background

Climate change is altering the Earth's global land and ocean temperatures. A 1 °C increase in global mean surface temperature was observed during the last years of the 2010s, relative to the pre-industrial period (1). As a consequence, temperature variability and extreme heat events have become more frequent in many parts of the world. For example, unusually hot weather was observed during the 2003 heatwave in Central Europe. Over 70,000 deaths were estimated to be attributable to these extreme conditions, with more than one-third of the deaths occurring in France, Italy and Spain (2). Since then, population exposure to extreme heat has increased worldwide, resulting in an additional 220 million heatwave exposure events in 2018 compared with the average in the years 1986–2005 (3). Climate change confers an increased risk of cardiovascular disease events in the general population as well as in individuals with type 2 diabetes mellitus or hypertension (4). Therefore, the health effects of altered temperature exposure are already detectable now and confer an additional burden on vulnerable subgroups, such as subjects with cardiovascular risk factors.

Patients with heart failure (HF) may be particularly vulnerable to the detrimental effects of climate changes, although we are not aware of specific studies so far. HF is characterized by alterations in kidney

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function that are associated with poor prognosis and can be related to the evolution of the disease or induced by medical treatment. High temperatures during summer may result in some degree of dehydration, especially in patients on diuretics, and may contribute to transient glomerular filtration rate (eGFR) reduction. In this study we try to elucidate the relationship between worsening renal function during summer and the temperature excursion, and how this relationship changed over a 20-year timespan.

2. Methods

2.1. Study population

Data from all consecutive ambulatory patients admitted to a structured multidisciplinary HF clinic at the Hospital Universitari Germans Trial i Pujol (Badalona, Spain) between January 2002 and December 2021 were retrieved. During this period, the clinical pathways and referral geographic area remained stable. Patients were referred to the HF clinic mostly by the Cardiology or Internal Medicine Departments, and to a lesser extent by the Emergency Department or other hospital departments. Patients were managed according to contemporary HF guideline recommendations (5–10). The structured follow-up protocol included one visit with a nurse every 3 months and one visit with a HF specialist every 6 months, plus additional visits if needed (11,12). Renal function was to be assessed during all elective visits and how many times as clinically necessary.

Anonymized patient data were prospectively collected in a dedicated data repository, including 42,185 visits as of December 31, 2021. For the purposes of this analysis, we considered only elective visits ($n = 29{,}059$), and we defined summer as the timespan from June 1st to September 30. We sequentially excluded values from patients who were on dialysis at baseline ($n = 427$), those starting dialysis ($n = 124$), those visited just once ($n = 397$) or visited only during summer or in the rest of the year ($n = 1902$). We then excluded outlier values (defined as creatinine <0.2 or ≥ 4 mg/dL; $n = 344$). We thus ultimately evaluated 25,865 visits of 2167 patients.

The study was performed in compliance with the law protecting personal data in accordance with the international guidelines on clinical investigations from the World Medical Association's Declaration of Helsinki. The local ethics committee approved the study (ethic code REGI-UNIC PI-18-037).

2.2. Temperature data

Temperature data from the Badalona municipality (Barcelonès-Badalona station) were requested to the Meteocat service (https://es.meteocat.gencat.cat/). Temperature data for every month from 2002 to 2003 and from 2006 to 2021 were available. We considered average monthly temperatures and average maximal monthly temperatures.

2.3. Renal function assessment

Serum creatinine levels were analyzed using the CREA method with a Dimension Clinical Chemistry System (Siemens, Newark, New Jersey), using a modification of the kinetic Jaffe reaction with picrate as the reactant (12). Creatinine values before 2011 were standardized according to IDMS reference method as the manufacturer recommended (13). To obtain standardized creatinine values the following equation was applied: standardized creatinine values (mg/dL) = 1.00 x Dimension® RxL creatinine values (mg/dL) - [0.168]. eGFR was calculated through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (14). eGFR categories were assigned according to the National Kidney Foundation (15).

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 23 (SPSS, Chicago, Illinois), R (http://www.r-project.org/, version 3.4.4) and the statsmodels.OLS module in Python 3.6.8 (StatsModels version 0.11.1). Variables from the first elective visit from January 2002 onwards were considered. Normal distribution was assessing through the *quantile-quantile* (Q-Q) plots. Variables with normal distribution were presented as mean ± standard deviation, and those with non-normal distribution as median and interquartile interval. Categorical variables were presented as absolute numbers and percentages. Values of creatinine, eGFR and patient weight during summer and the rest of the year were compared through a paired Student's *t*-test.

For each year, we calculated the average values of average monthly temperatures and maximal monthly temperatures during summer (June to September) and the rest of the year. We also calculated absolute (Δ) and percent differences (Δ%) between average monthly temperatures and maximal monthly temperatures during summer and the rest of the same year. LOcally weighted Error Sum of Squares (LOESS) curves were plotted to represent temperatures and their elevation in summer as a function of years. LOESS is a non-parametric regression method used to estimate a regression surface by a multivariate smoothing procedure (16). Briefly, a linear or quadratic function of the independent variables is fit in a moving fashion that is analogous to how a moving average is computed for a time series. LOESS is very flexible, making it ideal for modelling complex processes for which no theoretical models exist. The confidence interval was fixed to the 95th percentile. We also used a polynomial regression model to investigate the association between temperatures and years through an ordinary least square fitting routine; the R-squared value of 0.8 was considered as cut-off (17).

For each patient and each year, we averaged creatinine and eGFR values measured during summer and the rest of the same year; for example, if a patient had 2 creatinine values measured in June and August 2012, and 3 creatinine values measured in March, November and December 2012, we obtained 1 average value for summer 2012 and 1 average value for the rest of 2012. We first compared average creatinine and eGFR values through a paired Student *t*-test: through this approach we derived couples of average creatinine and eGFR values measured during the same year in the same patients ($n = 6612$ couples of values from 2033 patients), and we compared average creatinine and eGFR values in summer and in the rest of the year. For each patient, we then calculated Δ and Δ% between average values of creatinine and eGFR during summer and the rest of the same year. We investigated the association between renal function and years through a polynomial regression model. We then calculated the correlations of Δ or Δ% temperatures with Δ or Δ% creatinine and eGFR through multivariable linear regression analysis. The model for adjustment included age, sex, plasma creatinine, ischemic etiology, New York Heart Association class, therapy with beta-blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers/sacubitril-valsartan, mineralocorticoid receptor antagonists, loop diuretics; for each couple of creatinine/eGFR values, these variables were considered at the time of the first sampling outside of summer. Multicollinearity was excluded by calculating the variance inflation factor, with a conservative threshold of 3. Missing data were discarded. p values <0.05 were considered significant.

3. Results

3.1. Study population

The study cohort included 2167 HF patients undergoing a median of 14 visits (interquartile range 7–23). At the first visit, patients (70% men) had an age of 67 ± 13 years. Among patients with available data ($n = 2152$, 99%), left ventricular ejection fraction (LVEF) value was 35 ± 14%; 1454 patients (67%) had a LVEF <40%, 340 (16%) had a LVEF 40–49%, and 358 (17%) had a LVEF ≥50%. Creatinine was 1.25 ± 0.51

mg/dL, and eGFR was 65 ± 25 mL/min/1.73 m^2; 45% of patients had stage G3a to G5 disease (i.e., eGFR <60 mL/min/1.73 m^2) (Table 1).

3.2. Summer temperatures across years

Maximal temperatures in summer and the rest of the year increased gradually, albeit not linearly, from 2002 to 2021. Even the rise in temperatures during summer increased across the years (Fig. 1). Accordingly, Δ and Δ% average temperatures and average maximal temperatures displayed positive associations with years (Table 2), as confirmed through a non-linear model.

3.3. Worsening renal function during summer

When considering all average creatinine and eGFR values (see Methods), creatinine was significantly higher in summer (1.26 ± 0.52 vs. 1.21 ± 0.49 mg/dL; difference 0.04, 95% confidence interval [CI] 0.04 to 0.05, $p < 0.001$), and eGFR was slightly lower (65 ± 26 vs. 67 ± 26 mL/min/1.73 m^2; difference − 2.0, 95% CI -2.3 to −1.8, p < 0.001). The magnitude of creatinine rise and eGFR decrease during summer did not increase linearly from 2002 to 2021 (Δ creatinine and years: p = 0.331; Δ% creatinine and years: p = 0.063; Δ eGFR and years: p = 0.492; Δ% eGFR and years: p = 0.558). Worsening renal function during summer was not accompanied by a significant decrease in patient weight: when comparing the last value before summer with the first value during summer, the mean change was −1.8 kg (95% CI -4.5 kg to +1.0; p = 0.209).

3.4. Rise in temperatures and worsening renal function

We then investigated if temperature elevation during summer was related to the degree of worsening renal function (Fig. 2). The magnitude of temperature elevation displayed significant, albeit weak,

Table 1
Patient characteristics at first visit.

	Patients (n = 2167)	Missing data, n (%)
Age (years)	67 ± 13	0 (0)
Male patients, n (%)	1513 (70)	0 (0)
LVEF (%)	35 ± 14	274 (13)
HFrEF/HFmrEF/HFpEF, n (%)	1377/208/308 (73/11/16)	274 (13)
Ischaemic aetiology, n (%)	931 (43)	0 (0)
NYHA class I/II/III, n (%)	162/1480/521 (7/68/24)	2 (0)
AF or flutter, n (%)	496 (23)	0 (0)
Creatinine (mg/dL)	1.25 ± 0.51	109 (5)
eGFR (mL/min/1.73 m^2)	65 ± 25	0 (0)
GFR category		
G1 (≥90)	275 (17)	0 (0)
G2 (60–89)	818 (38)	
G3a (45–59)	434 (20)	
G3b (30–44)	351 (16)	
G4 (15–29)	164 (8)	
G5 (<15)	25 (1)	
ACEi/ARB/ARNI, n (%)	1642 (76)	0 (0)
Beta-blocker, n (%)	1667 (67)	0 (0)
MRA, n (%)	318 (15)	0 (0)
SGLT2i, n (%)	7 (0)	0 (0)
Loop diuretic, n (%)	1680 (68)	0 (0)

These variables refer to the first visit at the outpatient clinic; not all patients had creatinine dosed during that visit. ACEi/ARB/ARNI; angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor; AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PM, pacemaker; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

relationships with changes in creatinine and eGFR, which were confirmed after adjusting for potential confounders including age, sex, plasma creatinine, and HF therapies (Fig. 3). The relationships between changes in temperatures and renal function became not significant when assessed in the subgroup of patients with LVEF <40% (Supplemental Table 1).

4. Discussion

This study reports the findings from a large cohort of HF outpatients from the Mediterranean area of Spain, followed over 20 years. After excluding patients with HF decompensations, on dialysis at baseline or requiring dialysis during follow-up, we found a slight deterioration in renal function during summer, which would have been likely missed in smaller cohorts. It is common knowledge that temperatures are rising, and this was confirmed also by local temperature data. The magnitude of renal function decline during summer displayed a significant, though very weak, correlation with the degree of temperature elevation during summer. This suggests that progressive temperature elevation may have a detrimental impact on body homeostasis in HF patients even when followed closely and managed according to current recommendations.

To our knowledge, this is the first report in the literature of worsening renal function during summer in patients with HF, and the main HF Guidelines do not include any specific advice on the modulation of HF therapy or water intake during summer (18,19). The combined effects of loop diuretics, therapies acting on the renin-angiotensin-aldosterone axis and restricted water intake can lead to a small but appreciable decline in creatinine and eGFR when temperatures increase and fluid loss through perspiration becomes more relevant. To capture this phenomenon, we compared average values of renal function during summer vs. the rest of the same year (defined as the months before summer and those after summer). It is then not possible to define how often renal function decreases during summer were transient or persistent. Nonetheless, it is reasonable to conclude that temperature rise during summer represents a further stress to the kidney and accelerates, at least temporarily, the physiological decline in renal function (with a decrease in eGFR of around 1 mL/min/1.73 m^2 per year beginning in the third decade of life) (20).

Worsening renal function (WRF) is common during the treatment of HF and has been associated with decreased survival, hospitalization, and disease progression (21). Several mechanisms by which a reduction in renal function could directly lead to mortality have been proposed, including inflammation, oxidant stress, or induction of apoptosis by uremic toxins (22,23). However, patients who experience WRF also often exhibit multiple markers of increased HF disease severity and are less likely to respond to diuretics (24). As a result, it is difficult to determine whether the association between WRF and adverse outcomes results directly from the reduction in eGFR or WRF merely denotes a greater HF disease severity (25). We may add that the magnitude of eGFR changes defined as WRF was much greater than the observed changes during summer. Further studies are needed to elucidate the prognostic implication of WRF during summer. Nonetheless, preservation of renal function is an important goal of HF therapy, and the renal protective effects of sacubitril/valsartan (26) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) (27–29) were greeted with much enthusiasm as possible contributors to long-term benefit from these drugs.

Seasonal variations of renal function will likely become increasingly important as the effects of climate change are progressively more evident. Temperature elevation was appreciable even in the relatively short period from 2002 to 2021. Such elevation was not linear, with great year-to-year variability. Even worsening renal function during summer displayed a quite large variability. Nonetheless, a relationship was found between the magnitude of temperature elevation and the decrease in renal function during summer. This relationship was found when considering either average temperatures or average maximal

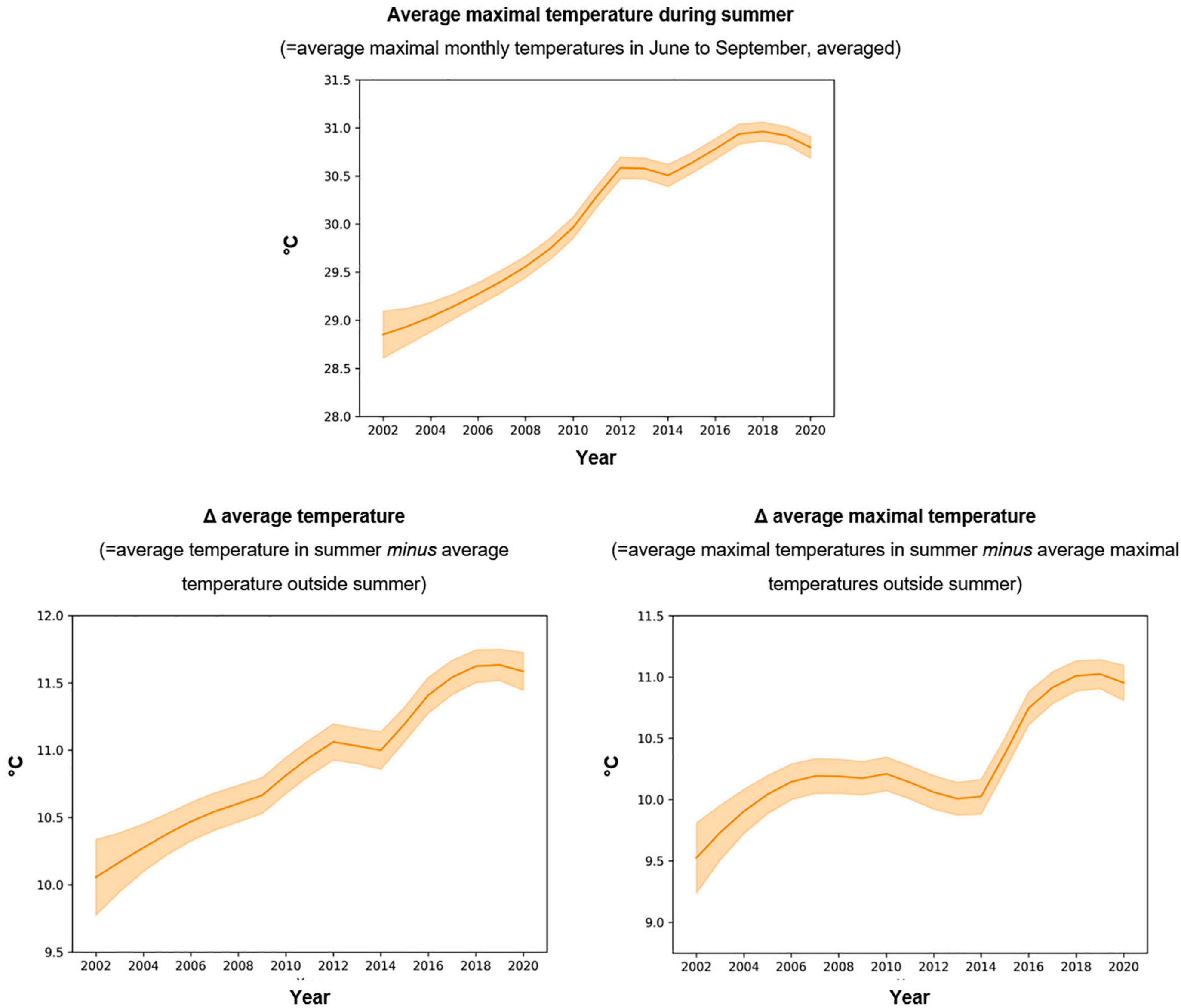

Fig. 1. Increase in temperatures and temperature elevation during summer. Loess curves. See Methods for details.

Table 2
Correlations between rise in temperature during summer and years.

	Years	
	rho	p
Δ average temperature	0.149	<0.001
Δ% average temperature	0.144	<0.001
Δ average maximal temperature	0.119	<0.001
Δ% average maximal temperature	0.052	<0.001

For the calculation of absolute (Δ) and percent (Δ%) differences, see Fig. 1.

temperatures, and was independent from many possible confounders including age and HF therapies.

Climate change has caused an increase in the difference between summer and winter temperatures across North America and Eurasia over the past four decades (30). We are now providing the evidence that a widening gap between temperatures during summer and the rest of the year may translate into a more profound decline in renal function during summer. This calls for actions at least to blunt WRF during summer through simple measures such as decreasing loop diuretic doses and allowing more water intake, switching from angiotensin converting enzyme inhibitors/angiotensin receptor blockers to sacubitril/valsartan, or even starting a SGLT2i when not already done.

Several limitations must be acknowledged. Although the cohort was quite large, well-characterized and managed according to contemporary recommendations, this remains a retrospective, single-center study. Urea values might have reflected more closely the hydration state, but were not considered because of the quite high proportion of missing data. All patients had at least a couple of creatinine/eGFR values during summer and the rest of the same year, but this number of measurements of renal function was variable. Single couples of average renal function and temperature values during summer and the rest of the same year were considered independently; therefore, patients with the greatest number of creatinine/eGFR measurements had the greatest influence on final results. Nonetheless, this factor is not expected to affect significantly the strong and independent relationship between changes in temperatures and renal function. Another limitation is the lack of local temperature data from 2 years out of 20 (2004 and 2005). An assessment of temperatures and renal function on a large cohort cannot take into account many factors such as drug doses and their changes during summer, or the recommendations to individual patients about water restriction. On the other hand, patients were followed rather closely

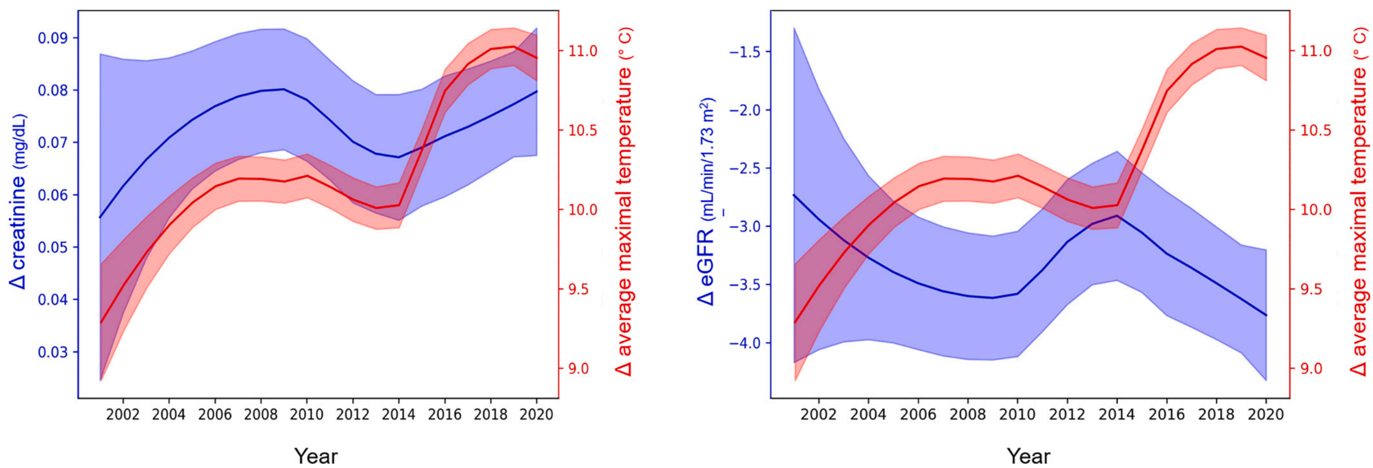

Fig. 2. Temperature elevation during summer and worsening renal function. Absolute changes in average maximal temperatures and in creatinine (*left*) or estimated glomerular filtration rate (eGFR; *right*) are represented. The 95% confidence intervals of both measures are provided.

Decline in renal function during summer

Temperature rise during summer

	Δ creatinine	**Δ% creatinine**	**Δ eGFR**	**Δ% eGFR**
Δ average temperature	**p<0.001** r=0.053	**p<0.001** r=0.053	**p<0.001** r=-0.062	**p<0.001** r=-0.057
Δ% average temperature	**p=0.001** r=0.044	**p=0.001** r=0.049	**p<0.001** r=-0.056	**p<0.001** r=-0.048
Δ average maximal temperature	**p<0.001** r=0.052	**p<0.001** r=0.052	**p<0.001** r=-0.059	**p<0.001** r=-0.056
Δ% average maximal temperature	p=0.125	**p=0.019** r=0.031	**p=0.016** r=-0.032	**p=0.049** r=-0.026

Relationship independent from: age, sex, plasma creatinine, ischemic etiology, New York Heart Association class, therapy with beta-blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers/sacubitril-valsartan, mineralocorticoid receptor antagonists, loop diuretics

Fig. 3. Relationship between temperature increase during summer and worsening renal function. Temperature elevation during summer displayed significant relationships with the degree of worsening renal function, measured as creatinine elevation or decrease in estimated glomerular filtration rate (eGFR), even after extensive adjustment for potentially relevant variables. See the Methods section for further details.

with repeated measurements of renal function, and fluctuations in renal function in less controlled settings could be even more prominent. Finally, this study predated the introduction of the renal protective drugs SGLT2i and, up to 2016, sacubitril/valsartan.

5. Conclusions

There has been an increase in temperatures in summer and in the rest of the year, and the temperature excursion between summer and the rest of the year over a 20-year timespan. In a cohort of HF outpatients, this elevation correlates with the decline in renal function during summer. This might be an example of how global warming is affecting human health.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.07.043.

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