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Heat exposure and chronic kidney disease: a temporal link in a Taiwanese agricultural county

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ABSTRACT
Heat stress-related kidney injury has drawn public health attention. This study explored the temporal relationships between impaired kidney function and preceding outdoor heat exposure Taiwan. Data of participants collected through a health screening program was used to assess the association between chronic kidney disease (CKD) and average ambient temperature with various time lag structures. A total of 1,243 CKD cases and 38,831 non-CKD participants were included in the study. After adjusting for demographic, socioeconomic, lifestyle factors, and comorbidities, CKD was positively associated with the ambient temperature within 1–9 months. The 9-month average ambient temperature yielded the highest odds ratio of CKD (OR = 1.22; 95% CI = 1.09–1.37). Furthermore, females and farmers were found to be more vulnerable to CKD risk after outdoor heat exposure. These findings suggest that the prevention of heat stress-related kidney injury should consider relevant time frames and focus on vulnerable populations.

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Hot temperature; farmers; aged; renal insufficiency; epidemiologic studies

Introduction

Hot weather has a significant impact on human health and sustainable development, with adverse effects on vulnerable populations drawing public health attention (Borg et al. 2021). Notably, chronic kidney disease of nontraditional aetiology (CKDnt) has been reported in recent decades, primarily in Central America and South Asia, and epidemiological evidence has linked these cases to environmental heat stress (Athuraliya et al. 2011; Peraza et al. 2012). These patients were mostly agricultural workers in coastal areas with hot climates and lacked common causes of kidney disease such as hypertension, diabetes, or glomerular disease (Johnson et al. 2019; Pearce and Caplin 2019). Animal models have also demonstrated heat stress-induced renal injury on mice through daily exposure to a heated and dehydrated environment for several weeks (Roncal-Jimenez et al. 2018). Pathophysiologic perspectives suggest plausible mechanisms such as increased renin – angiotensin–aldosterone system (RAAS), renal sympathetic nerve activity (RSNA), hyperuricemia induced by rhabdomyolysis and fructokinase-dependent pathway, and endotoxins through increased intestinal permeability

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(Basile et al. 2012; Roncal Jimenez et al. 2014; Sánchez-Lozada et al. 2018; Hansson et al. 2020). Other causes of CKDnt include infectious diseases (e.g. leptospirosis), toxins or toxicants (e.g. agrochemicals, heavy metals, and silica), and genetic factors (Nanayakkara et al. 2014). While development of chronic kidney disease can be multifactorial, heat stress may serve both as the primary cause of kidney injury or as a catalyst to accelerate other underlying pathologies (Chapman et al. 2021).

There is a knowledge gap on the time-lagged effect of environmental heat exposure and its contribution to chronic kidney disease. Rather, most studies explored short-term impact of extreme air temperature or heat waves on acute events of kidney diseases. A recent meta-analysis revealed that high temperatures are associated with a 30% increase in kidney disease morbidity, with time lags ranging from 0 to 21 days (Lee et al. 2019). Among these studies, the composition of "kidney disease" were heterogeneous, largely renal colic or kidney stones; the definitions of "high temperatures" were various, mostly using a high threshold (e.g. 35°C) or high percentile (90iequation1 > –99th) of air temperature to compare with a low normal (20–25°C). On the other hand, cohort studies on CKDnt had reported increased risk of kidney damage among agricultural workers following several months of harvesting crops (Hansson et al. 2019; Sorensen et al. 2019; Dally et al. 2020). However, current evidence does not support that the time-lagged effect of hot weather on chronic kidney disease can last for months. To address this research question, the objective of this study was to identify the proper time frame and effect size of the impact of elevated ambient temperature on chronic kidney disease. We hypothesized that the risk of chronic kidney disease would increase with each Celsius degree increase in monthly mean temperature.

Materials and methods

Settings

We conducted a retrospective observational study of the Changhua Community-based Integrated Screening program (CHCIS) from 1 September 2005 to 30 September 2014. Our previous research has described the design and implementation of CHCIS (Chang and Yang 2021). This county-wide health screening program is free-of-charge to all residents in Changhua, with an aim to screen for chronic diseases (e.g. hyperlipidemia, hypertension, hyperglycemia, chronic liver or kidney diseases) and malignancies (e.g. hepatocellular carcinoma, colorectal cancer, breast cancer, cervical cancer and oral cancer). It provides body height and weight measurement, blood pressure measurement, fasting blood test including complete blood count and biochemistry profiles, routine urinalysis, and a health questionnaire.

To achieve our research objective, it is crucial to understand the temperature patterns and trends in the study area. Changhua, located in central Taiwan, has a subtropical climate characterized by hot summers and mild winters. High temperatures may occur frequently and persistently during the summer months. The annual mean temperature was approximately 22°C, while the average daily maximum temperature in July ranged from 31°C to 33°C. Figure S1 shows the annual mean temperature and the daily maximum temperature in the hottest month (July) for the period from 2004 to 2014.

Participants

Our study population included CHCIS participants aged 15 or older. To reduce potential healthy-worker effects, we excluded participants who reported working part-time without a specified occupation. The sample size was determined by the number of participants who met our eligibility criteria during the study period. If a participant attended the health screening program multiple times, only their first visit was included.

Variables from health data

The outcome of interest is the development of CKD. Based on the criteria from Kidney Disease Improving Global Outcomes (KDIGO) collaboration, we defined CKD as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, which is consistent with CKD stages 3–5 (CKD Work Group 2013). Although medical diagnosis of CKD generally required two measurements of eGFR, considering the setting of the health screening program, we inevitably used a single measure of eGFR <60 mL/min/1.73 m^2 to define CKD in this epidemiological study.

Variables we collected from CHCIS included participants demographic factors (age, sex, education, urbanization level of township), occupation, lifestyle factors (cigarette use, Chinese herbal medicine, body mass index), and comorbidity status (hypertension, diabetes, hyperlipidemia, heart diseases, chronic liver diseases, stroke, asthma, anemia, gout, hyperuricemia, urolithiasis). To reduce recall bias, comorbidities were determined by both participants' past medical histories and laboratory test results. Diabetes was defined by a positive history or a fasting serum glucose over 126 mg/dL, hyperlipidemia by past history or a serum low-density lipoprotein over 130 mg/dL, or serum triglycerides over 150 mg/dL, hyperuricemia as a serum uric acid over 7 mg/dL, and anemia as a serum hemoglobin less than 11 g/dL in females or less than 13 g/dL in males. Other comorbidities were determined by past medical history collected in the survey.

Variables from meteorological data

From ERA5-Land, a climate reanalysis dataset provided by the European Centre for Medium-Range Weather Forecasts (ECMWF), we extracted hourly ambient temperature (two meters above land surface) in Taiwan throughout 2004–2014 (Muñoz-Sabater 2019). We then converted this data into daily mean temperature using arithmetic mean and applied zonal estimation to aggregate the raster data and calculate the mean values within each geographic polygon. This approach allowed us to obtain historical representative temperature for each township and the entire Changhua County.

However, due to the small size of Changhua County (only 40 kilometers in diameter), most of the volatility of ambient temperature in the region arises from temporal change rather than geographical distribution (Chang and Yang 2021). Therefore, for any given time point we calculated a county-wide average of ambient temperature and linked it to the participants based on their time of health examination.

Statistical methods

We compared the characteristics of participants between those with and without CKD, including age (grouped by ten), gender, education level, urbanization level of township, occupation (by Taiwan Standard Classification of Occupation), use of cigarette, use of Chinese herbal medicine, body mass index, serum creatinine, blood urea nitrogen (BUN), eGFR, CKD staging, and all comorbidities. We presented serum creatinine, BUN, eGFR, and ambient temperature as means and standard deviations for descriptive analysis, while all other variables were categorized and presented as numbers and percentages.

To explore the temporal relationship between CKD risk and preceding outdoor heat exposure, we used box plots to visualize the participants' kidney function corresponding to various mean temperatures at different time-lagged structures, and multiple logistic regression models to estimate the crude and adjusted odds ratios of CKD. The explanatory variable was the average ambient temperature exposed over various lagged time frames, including the 1iequation1 $> -12^{st}$ month before health examination (single lag structures) and within 1–12 months before health examination (cumulative lag structures). The odds ratios of CKD for average ambient temperature were iterated over each time frame.

We adjusted the odds ratios for pre-selected risk factors for CKD, including age (in years), gender, education level, urbanization level of township, occupation (farmers vs. non-farmers), use of cigarette, use of Chinese herbal medicine, BMI (normal, overweight, underweight), binary disease status of hypertension, diabetes, hyperlipidemia, hyperuricemia, heart disease, and chronic liver disease, as well as a linear term of years passed from the beginning of the study period. All statistical analyses were conducted using SAS software (V.9.4; SAS Institute) and R (version 4.2.0), with a two-tailed p value of 0.05 considered to be statistically significant.

Additional analysis

To investigate the potential of heat stress-induced kidney injury, we conducted a multivariate analysis of subgroups categorized by age (over or under 65), gender, occupation (farmers and non-farmers), and disease status of hypertension and diabetes. We tested for interactions within subgroups by assessing the significance of the interaction term (e.g. gender * temperature) in the regression model. By default, outdoor heat exposure was estimated using daily mean temperature, with sensitivity analyses conducted using daily maximum and minimum temperatures. To consider other factors influencing heat stress, such as humidity, wind, and sun exposure, we further calculated wet bulb globe temperature (WBGT) from air temperature, dew point temperature, solar radiation, and wind speed using an R package implementation (https://github.com/anacv/HeatStress) of the Liljegren formula (Liljegren et al. 2008).

Results

Descriptive analysis

Of 92,602 participants in the CHCIS study from 2005–2014, 40206 were eligible for our analysis. (Figure S2) After the exclusion of 132 participants with incomplete data, the study comprised 1,243 cases of CKD and 38,831 non-CKD individuals. Table 1 summarizes the demographic characteristics of the population, which showed that the cases were on average older, more male-predominant, less educated, and living in less urbanized areas compared to the non-CKD individuals. Additionally, the cases were more likely to be working in primary industries, current smokers, and overweight, as well as having higher rates of hypertension, diabetes, hyperlipidemia, heart diseases, stroke, anemia, gout, hyperuricemia, and urolithiasis.

Figure 1 visualizes the relationship between kidney function (in eGFR) and outdoor heat exposure prior to the health examination. Generally speaking, the median kidney function was negatively associated with average ambient temperature. However, this trend disappeared for average ambient temperature within 12 months before the examination, due to the small range of temperatures within this time frame. As such, further analysis of time frames longer than 12 months was not possible.

Main results

Figure 2 summarizes the association of CKD risk and outdoor heat exposure for different lag structures. Specifically, single lags showed a positive association between CKD and increased ambient temperature in the 1iequation1 > −5st month before health examination, while a negative association was found between CKD and increased ambient temperature in the 8iequation3 > −11th month before health examination. Cumulative lags showed a positive association between CKD and the average ambient temperature within 1–9 months before health examination, with an increasing trend for longer time frames. Detailed values of odds ratio and 95% CI were shown in the supplement (Table S1).

Table 1. Characteristics of the study population.

Variable		CKD cases (*n* = 1,243)	Non-CKD (*n* = 38,831)
Age (year)		64.71 (9.09)	50.73 (10.23)
	15–20	3 (<0.1%)	0 (0%)
	20–30	190 (0.5%)	0 (0%)
	30–40	5,263 (14%)	8 (0.6%)
	40–50	13,230 (34%)	56 (4.5%)
	50–60	12,847 (33%)	300 (24%)
	Over 60	7,298 (19%)	879 (71%)
Sex			
	Female	360 (29%)	24,428 (63%)
	Male	883 (71%)	14,403 (37%)
Education			
	College and postgraduate	66 (5.3%)	7,634 (20%)
	Middle school	279 (22%)	17,546 (45%)
	Elementary school or below	896 (72%)	13,595 (35%)
Urbanization			
	Suburban	232 (19%)	11,508 (30%)
	Rural	1,011 (81%)	27,323 (70%)
Occupation (TSCO classification)			
	1: Manager	5 (0.4%)	170 (0.4%)
	2: Professional	38 (3.1%)	5,032 (13%)
	3: Technician or associate professional	53 (4.3%)	4,460 (11%)
	4: Clerical support worker	9 (0.7%)	669 (1.7%)
	5: Service or sales worker	98 (7.9%)	6,230 (16%)
	6: Skilled agricultural, forestry or fisheries worker	760 (61%)	9,154 (24%)
	7: Craft and related trades worker	106 (8.5%)	4,326 (11%)
	8: Plant or machine operator or assembler	86 (6.9%)	5,579 (14%)
	9: Elementary occupation	53 (4.3%)	2,478 (6.4%)
	0: Armed forces occupation	0 (0%)	8 (<0.1%)
	Not classifiable	35 (2.8%)	725 (1.9%)
Cigarette use			
	Non-smoker	966 (78%)	33,268 (86%)
	Current smoker	277 (22%)	5,563 (14%)
Herbal medicine use			
	Nonuser	1,218 (98%)	38,431 (99%)
	Current user	25 (2.0%)	400 (1.0%)
BMI			
	Normal (18.5–24)	431 (35%)	18,099 (47%)
	Under (<18.5)	25 (2.0%)	1,216 (3.1%)
	Over (≥24)	787 (63%)	19,513 (50%)
Renal function			
	CRE (mg/dL)	1.54 (0.87)	0.78 (0.18)
	BUN (mg/dL)	20.05 (7.78)	12.43 (3.79)
	eGFR (mL/min/1.73 m^2)	49.02 (11.18)	96.70 (14.53)
CKD stage			
	III (60 > eGFR ≥ 30)	1,149 (92%)	-
	IV (30 > eGFR ≥ 15)	65 (5.2%)	-
	V (eGFR <15)	29 (2.3%)	-
Disease status			
	Hypertension	479 (39%)	4,463 (11%)
	Diabetes	269 (22%)	2,892 (7.4%)
	Hyperlipidaemia	706 (57%)	18,046 (46%)
	Heart disease	120 (9.7%)	1,083 (2.8%)
	Chronic liver disease	48 (3.9%)	1,454 (3.7%)
	Stroke	11 (0.9%)	127 (0.3%)
	Asthma	13 (1.0%)	414 (1.1%)
	Anaemia	211 (17%)	2,284 (5.9%)
	Gout	160 (13%)	936 (2.4%)
	Hyperuricaemia	439 (35%)	2,882 (7.4%)
	Urolithiasis	42 (3.4%)	828 (2.1%)

(*Continued*)

Table 1. (Continued).

Variable		CKD cases (*n* = 1,243)	Non-CKD (*n* = 38,831)
Average ambient temperature before the month of examination (°C)			
	within 3 months	24.51 (2.66)	23.72 (2.96)
	within 6 months	22.22 (2.41)	21.52 (2.21)
	within 9 months	21.78 (0.70)	21.62 (0.57)
	within 12 months	22.70 (0.24)	22.69 (0.23)

The study included participants over 15 years old who attended the CHCIS between September 2005 and September 2014. Scalar variables are presented as the mean (standard deviation); categorical variables are presented as the count (percentage).

CKD was determined as reduced kidney function (eGFR <60 ml/min/1.73 m2) at the health examination. The eGFR calculation was based on the CKD-EPI formula. The serum creatinine measurement was traceable to an isotope dilution mass spectrometry (IDMS) reference.

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CHCIS, Changhua Community-based Integrated Screening Program; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRE, serum creatinine; eGFR, estimated glomerular filtration rate; TSCO, Taiwan Standard Classification of Occupations.

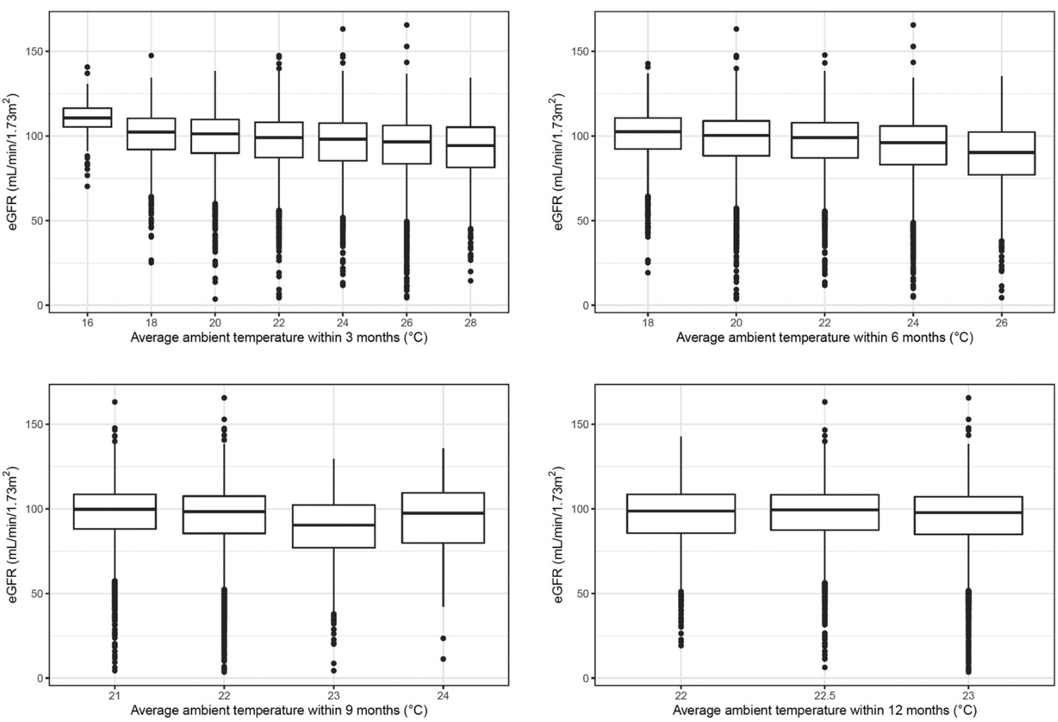

Figure 1. Relationships between kidney function and ambient temperature. **Legend**: The box plots show the kidney function (in eGFR) of participants and the average ambient temperature within 3 (left upper), 6 (right upper), 9 (left lower), and 12 (right lower) months before the health examination. The midline in the box represents the median, the two hinges represent the 25% and 75% quantiles, and the two whiskers represent the 1.5 times interquartile range outside of the hinges. Each outlying point represents a patient whose kidney function was beyond the whiskers. The primary objective of this figure is to illustrate the trend of the association between kidney function and ambient temperature. Additional examination of the time-lagged effect of ambient temperature on chronic kidney disease (CKD) can be found in Figure 2 and Table S1. **Abbreviations**: eGFR, estimated glomerular filtration rate

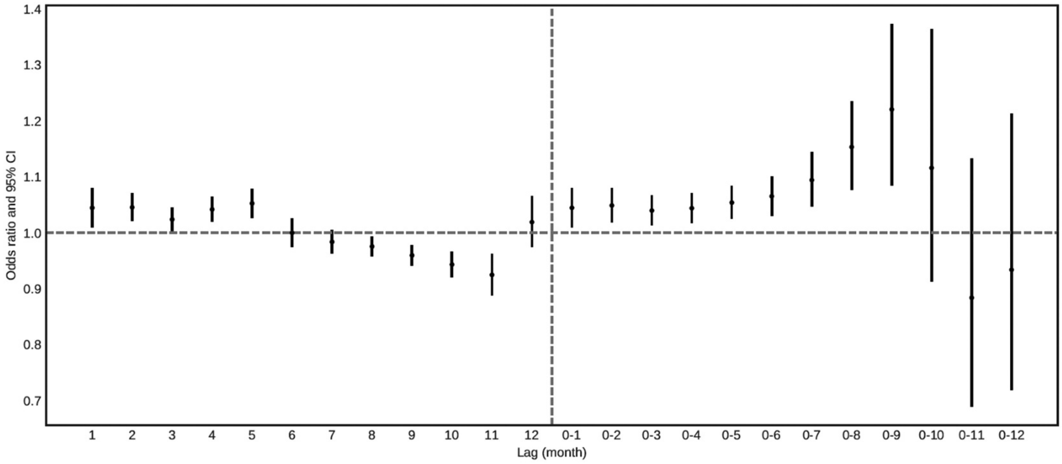

Figure 2. Association between CKD and the average ambient temperature: multivariate analyses for various time lags. **Legend**: The error bar plot shows the odds ratios and 95% confidence intervals of CKD per unit increase in average ambient temperature (°C) for the different lag structures. The model adjusted the odds ratios for age, sex, education, urbanization, occupation, smoking, body mass index, and comorbidities. The dots represent the odds ratios, and the vertical solid lines represent the 95% confidence intervals. The vertical dashed line separates the single month lags (left side) and the cumulative month lags (right side). For example, lag 3 represents the average ambient temperature of the third month before the health examination, and lag 0-9 represents the average ambient temperature within 9 months before the examination. The horizontal dashed line represents an odds ratio of 1; therefore, any dot with its vertical line entirely above this dashed line indicates an increased risk of CKD, and vice versa. **Abbreviations**: CKD, chronic kidney disease

Since the average ambient temperature within 9 months before health examination yielded the highest odds ratio of CKD (OR = 1.22; 95%CI = 1.09–1.37) among various lag structures (Figure 2), we summarized the multivariate analysis of that association in Table 2. In addition to outdoor heat exposure, other risk factors of CKD included age, male gender, and comorbidities such as hypertension, diabetes, hyperuricemia, hyperlipidemia, or heart diseases. A high level of education (college or postgraduate degree) was found to be a protective factor of CKD with a borderline significance.

Sensitivity analysis showed that changing the measure of outdoor heat exposure from daily mean temperature to alternatives, including daily maximum temperature, daily minimum temperature, daily mean WBGT, daily maximum WBGT, and daily minimum WBGT, did not alter the direction of results (Table S2). Similar findings were yielded when ambient temperature was estimated township-wide instead of county-wide.

Subgroup analysis

To identity populations potentially more vulnerable to heat stress, we explored the association of CKD risk and outdoor heat exposure (9-month average of ambient temperature) among different subgroups. As shown in Figure 3, we found that female participants and farmers were more vulnerable to heat stress, as evidenced by significantly higher odds ratios of CKD (OR = 1.39; 95%CI = 1.13–1.71; p for interaction = 0.004 and OR = 1.28; 95%CI = 1.11–1.49; p for interaction = 0.022 respectively). However, no significant changes in the association were observed when disease status of hypertension and diabetes were taken into account, and results from subgrouping with age were equivocal.

Table 2. Associations between CKD and the average ambient temperature within 9 months before the examination: a multivariate analysis.

Covariate		Odds ratio Crude	Odds ratio Adjusted
Age (year)		1.14 (1.13–1.15)	1.12 (1.11–1.13)
Sex			
	male	4.16 (3.67–4.71)	2.03 (1.74–2.35)
	female	1.00	1.00
Education			
	high (college and above)	0.13 (0.10–0.17)	0.75 (0.56–0.996)
	medium (middle school)	0.24 (0.21–0.28)	0.90 (0.76–1.07)
	low (elementary school and below)	1.00	1.00
Urbanization			
	suburban	0.54 (0.47–0.63)	0.93 (0.79–1.09)
	rural	1.00	1.00
Occupation			
	Farmers	5.13 (4.56–5.76)	1.01 (0.86–1.18)
	Nonfarmers	1.00	1.00
Cigarette use			
	Current smoker	1.71 (1.50–1.97)	1.03 (0.88–1.21)
	Non-smoker	1.00	1.00
Herbal medicine use			
	Current user	1.97 (1.31–2.97)	1.35 (0.87–2.11)
	Nonuser	1.00	1.00
BMI			
	Under (<18.5)	0.86 (0.57–1.30)	0.93 (0.60–1.45)
	Over (≥24)	1.69 (1.50–1.91)	1.11 (0.97–1.27)
	Normal (18.5–24)	1.00	1.00
Comorbidities			
	Hypertension	4.83 (4.29–5.43)	2.23 (1.95–2.56)
	Diabetes	3.43 (2.98–3.95)	1.78 (1.52–2.08)
	Hyperuricaemia	6.81 (6.03–7.70)	3.78 (3.28–4.35)
	Hyperlipidaemia	1.51 (1.35–1.70)	1.20 (1.05–1.36)
	Heart disease	3.72 (3.06–4.54)	1.47 (1.18–1.83)
	Chronic liver disease	1.03 (0.77–1.38)	1.32 (0.96–1.82)
Average ambient temperature within 9 months before the examination (°C)		1.56 (1.43–1.71)	1.22 (1.09–1.37)

The crude and adjusted odds ratios of CKD were estimated by multiple logistic regressions. The model adjusted the odds ratios for age, sex, education, urbanization, occupation, smoking, body mass index, and comorbidities. The reference group for each comorbidity was the participants without the disease. The 95% confidence intervals are presented in parentheses following the risk estimates.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Discussions

Our previous research revealed that 48.9% of chronic kidney disease (CKD) cases in Changhua did not have hypertension or diabetes, and the prevalence of CKD was 2.3% among farmers and 0.9% among non-farmers. Dehydration was also a common occurrence, with 22% of farmers affected (Chang and Yang 2021). In this study, we sought to further explore the temporal associations between impaired kidney function and preceding outdoor heat exposure by linking meteorological data to the study participants. Our findings showed that impaired kidney function was related to preceding outdoor heat exposure within 1–9 months, with an effect size ranging from 4–22% increased risk of CKD for every 1°C rise in average ambient temperature. The temporal association was more prominent in female participants and farmers, but did not change with the presence of hypertension or diabetes.

Time-lagged effects

Heat stress has been associated with various health effects, though the temporal relationship between the two is not always clear. Many studies were focused on acute events such as

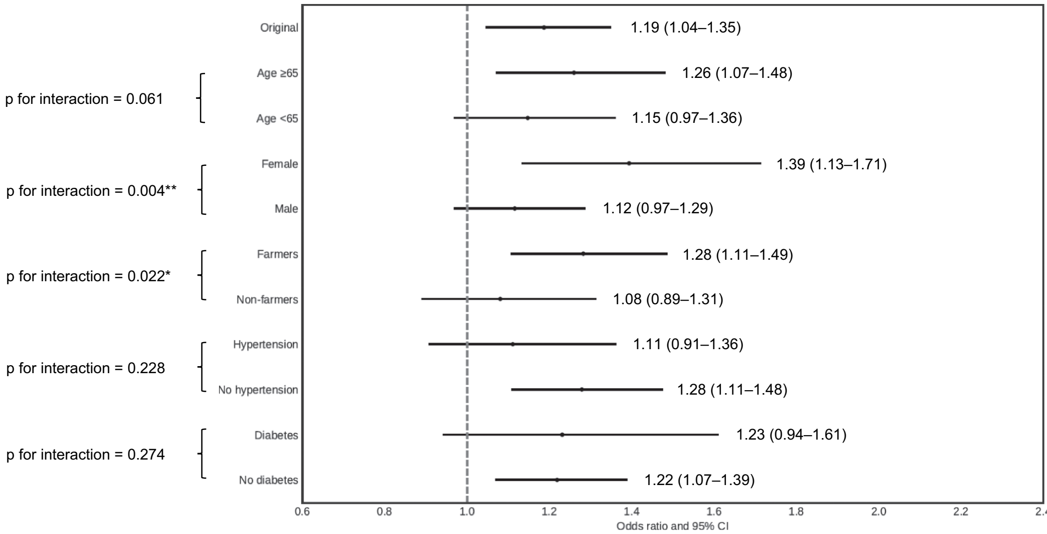

Figure 3. Subgroup analysis for the association between CKD and the average ambient temperature within 9 months before the examination. **Legend**: For the original study population and different subgroups, the error bar plot shows the odds ratios and 95% confidence intervals of CKD per unit increase in average ambient temperature (°C) within 9 months before the examination. The odds ratios were adjusted for age, sex, education, urbanization, occupation, smoking, body mass index, and comorbidities. The dots represent the odds ratios, and the horizontal solid lines represent the 95% confidence intervals. The vertical dashed line represents an odds ratio of 1; therefore, any dot with its horizontal line entirely to the right of this dashed line indicates an increased risk of CKD. Significance codes: 0 "***" 0.001 "**" 0.01 "*" 0.05 "." 0.1 " 1 **Abbreviations**: CKD, chronic kidney disease

deaths or hospitalizations from cerebrovascular and cardiovascular diseases, having a lag time generally between lag 0–1 to 0–3 days prior to the event (Bunker et al. 2016). A case-crossover study in New York State revealed a higher risk of acute kidney failure associated with a 1°C change in temperatures, lagged 0 to 7 days (Adeyeye et al. 2019). In Taiwan, a population-based ecological study found no significant increase in cardiovascular mortalities within 14 days after a heat event (Wu et al. 2011). In Nicaragua, a cohort study on sugarcane workers suggested that higher levels of workload during the sugarcane harvest (November – April) could lead to kidney damage (Hansson et al. 2019). This time frame is consistent with what has been discovered in the present study. It is possible that repeated acute kidney injuries over time can lead to irreversible kidney damage, resulting in a longer time-lagged effect for CKD.

In analyzing the temporal relationship between heat stress and health effects, it is important to consider the impact of extreme weather events. Previous literature has shown a significant positive correlation between heat stress and emergency department visits for CKD in metropolitan areas in Taiwan, with a cumulative lag of 0–7 days (Zafirah et al. 2022). Using the average temperature over a long period of time might mask the short-term effects of heatwaves. Nevertheless, it is worth noting that while the impact of extreme temperatures on human health is apparent, the effect of milder but sub-optimal weather is much greater (Gasparrini et al. 2015). To investigate the medium-term effects of heat stress, we used various single and cumulative lags from within 1 month to 12 months in our study.

Seasonality and year trends are important issues in analyzing time-lagged effects. For example, daily mean temperature in Changhua rose by 0.25°C every decade from 1981 to 2018 (Chang and Yang 2021). To address this, we adjusted the odds ratios by a linear year trend. On the other hand, there is a collinearity issue between seasonal change and ambient temperature, where one predictor can be highly predicted from the other. Previous studies on temporal association have adjusted for year trend rather than seasonality (Gasparrini 2014). We also tried a multivariate analysis by subgrouping participants' time of health examination into warm (May – October) and cold seasons (November – April), which did not affect the results of our analysis.

For exploring time-lagged effects, we iterated the regression model over various choices of single and cumulative lags for exposure. This method has been recognized as appropriate for evaluating different exposures and outcome associations (Samoli et al. 2013; Lee et al. 2017). Researchers have also proposed more sophisticated methodologies, such as distributed lag non-linear models and treed distributed lag models (Gasparrini 2014; Mork and Wilson 2020). However, applying these methods did not yield a better fit of the model in our data than the original logistic regression.

A harvesting effect?

In Figure 2, we observed negative correlations at certain single lags, including the prior 8^{th} –11^{th} month. This could be indicative of a "harvesting effect" of hot weather on impaired kidney function. The harvesting effect is a morbidity or mortality displacement caused by the dropout or death of susceptible individuals (Saha et al. 2014). It has been commonly observed in the impact of climate factors on acute events such as cardiovascular death (Braga et al. 2002). We argued that similar phenomena may exist in chronic conditions for the same reason. For example, a period of increased mortality or morbidity due to a prolonged drought could be followed by months of decreased mortality or morbidity due to the lack of resources available during the drought, leading to the death of those most vulnerable. From this perspective, our finding of negative correlations at the prior 8^{th} –11^{th} month was consistent with a harvesting effect of hot weather on CKD.

Vulnerable populations

As heat stress is being identified as a contributor to kidney injury, its influence on populations is not equal. Occupations that require working outdoors, such as farming, are often associated with a higher risk of heat-related injuries. One study in Sri Lanka conducted proteinuria screening in community samples from the northern, central, and southern provinces, and found that farmers had a higher risk of proteinuria (Athuraliya et al. 2011). Another study in nine rural communities in Nicaragua screened for kidney function and found that farmers, outdoor workers, and those without shade during rest were all significant risk factors for declining kidney function after a 2-year follow-up (González-Quiroz et al. 2017). A recent study in three rural communities in Mexico found that farmers had an odds ratio of CKD as high as 4.38 (95% CI 1.05 to 18.20) (Aguilar-Ramirez et al. 2021). From an environmental and occupational perspective, farmers are more likely to be exposed to high temperatures, prolonged physical labor, and agrochemical exposure, which may contribute to their vulnerability to heat stress and CKD.

The role of gender in CKD risk is not yet clear. Research conducted in Mesoamerica suggests that CKD primarily affects young male agricultural laborers residing in coastal regions, particularly those employed in low-altitude agricultural occupations. These individuals share a common trait of working in physically demanding jobs under hot weather conditions, with men in these localities being more prone to such work. However, with respect to the time-lagged effect of heat stress on CKD, our study suggests that it is particularly apparent among females. Several factors, including biological differences, personal behaviors, and work-related characteristics, might potentially account for this phenomenon (Lin et al. 2012; Schmeltz et al. 2016; Wondmagegn et al. 2019). Females might be more susceptible to heat stress than males due to biological factors such as pregnancy and a higher percentage of body fat, which can potentially cause a decrease in tolerance to various environmental and occupational hazards. Higher body fat leads to less thermal energy being required to raise its temperature, and results in less heat propagating from the tissue into the bloodstream, which independently decreases an individual's vulnerability to heat stress (Foster et al. 2020).

Gender differences in work patterns also affect the risk of CKD. Studies in Central America and Sri Lanka did not consistently find that female farmers had a higher risk of

CKD, which may be due to the fact that local male farmers engage in most of the heavy physical labor. However, in Taiwan, female farmers may not necessarily engage in less physical labor; in fact, a Taiwanese agricultural census revealed that women accounted for 59.3% of the non-managing workforce in farming, which may increase their exposure to high temperatures and physical workloads (Zhou 2018). It is worth noting that the role of gender in heat stress-related CKD, like the causes of CKD, is multifactorial and may vary by region. Therefore, more research is needed to clarify the role of gender in susceptibility to heat stress.

Elderly people are more vulnerable to heat stress due to their reduced physiological capability to dissipate heat, multiple comorbidities, and slow behavioral response to stress (Van Someren 2007). Previous research in physiology has investigated the impact of heat exposure on health and found that older adults are particularly susceptible, displaying greater increases in core temperature and reduced survival durations (Ou et al. 2023). These effects may be due to impaired sweating responses, reduced cardiovascular function, and increased susceptibility to dehydration among older adults. Consequently, when exposed to heat stress, older adults experience more rapid increases in core temperature and higher overall temperatures. Nevertheless, in our studied cohort, the association between heat and CKD was only marginally higher among the elderly than those under 65 (OR = 1.26 vs. 1.15; p-value for interaction = 0.061). This could be attributed to the healthy worker effect, where those elderly who still qualified for work were considered less vulnerable.

It is also essential to look at common etiologies of CKD to explore the association between heat stress and CKD. Chronic diseases such as hypertension and diabetes have been suggested to be positive effect modifiers of heat exposure, but evidence specifically for renal outcomes is limited (Kenny et al. 2010). In this study, no significant interactions between heat stress and these comorbidities were found. However, since the disease status was mainly determined through past medical history, recall bias should be taken into consideration when interpreting the results.

Generalisability

Our study population was composed of a higher percentage of women (62%) and older participants (mean age 51) than the census data in Changhua (51% male, 49% female, mean age 38). (National Development Council of Taiwan 2021) The prevalence of CKD (3.1%) in our study was much lower than the 6.9% reported in a nationally representative survey (Hsu et al. 2006). This discrepancy could be due to the voluntary nature of our health screening program, where asymptomatic people with higher health awareness are more likely to participate. As a result, the differences between our study and the national survey may lead to an underestimation of the risk of CKD.

Limitations

Our study has several limitations that must be taken into account. Firstly, the health screening program used for data collection and study design did not link to exposure assessment of nephrotoxic agents, such as agrochemicals, heavy metals, silica, or the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Secondly, there may have been selection bias in the recruitment of participants due to those who lacked health awareness or were too busy or sick not showing up to the program. This could also lead to an underestimate of the risk of CKD. Thirdly, the outcome measurement only calculated the eGFR once for each participant without active follow-up. This could lead to overestimation of the risk of CKD, as impaired kidney function might be temporary. Finally, the assessment of comorbidities and lifestyle factors was subjective to recall bias, as the data quality depended on whether participants accurately reported their past medical history. This could lead to both an overestimation and underestimation of the risk of CKD.

Conclusions

Our ten-year pooled cross-sectional data from a health screening program has revealed an association between impaired kidney function and preceding 1–9 months of outdoor heat exposure. We observed that the risk of CKD increased 4–22% for every 1°C rise in average ambient temperature, depending on the exposure duration. Positive effect modifiers included female gender and farming occupation. Based on these findings, we suggest that prevention of heat stress-related kidney injury should consider relevant time frames and focus more on vulnerable populations. To further validate the exposure-lag-response associations, studies of larger scale are warranted.

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Author contributions

Jerry Che-Jui Chang and Hsiao-Yu Yang: Study concept and design. Jerry Che-Jui Chang: Collecting the data. Jerry Che-Jui Chang: Statistical Formal analysis. Jerry Che-Jui Chang: Drafting of the manuscript. Chun-Yi Chi and Hsiao-Yu Yang: review and editing. Hsiao-Yu Yang: supervision. All authors participated in approving of the manuscript.

Consent to participate

All authors of this paper consent to participate.

Consent to publish

All authors of this manuscript have consented to its publication.

Ethics approval

This research was approved by the Research Ethics Committee of National Taiwan University (No. 202004HM030).

Data availability statement

Deidentified participant data from the Community-based Integrated Screening program may be obtained from Changhua County Public Health Bureau (CCPHB) in Taiwan but are not publicly available. The contact details of CCPHB are available on their official website (https://www.chshb.gov.tw/en).

References

Adeyeye TE, Insaf TZ, Al-Hamdan MZ, Nayak SG, Stuart N, DiRienzo S, Crosson WL. 2019 Apr 18. Estimating policy-relevant health effects of ambient heat exposures using spatially contiguous reanalysis data. Environ Health. 18(1):35. Epub 2019 04 20. 10.1186/s12940-019-0467-5.

Aguilar-Ramirez D, Raña-Custodio A, Villa A, Rubilar X, Olvera N, Escobar A, Johnson RJ, Sanchez-Lozada L, Obrador GT, Madero M. 2021 May 27. Decreased kidney function and agricultural work: a cross-sectional study in middle-aged adults from Tierra Blanca, Mexico. Nephrol Dial Transplant. 36(6):1030–1038. Epub 2020 05 23. 10.1093/ndt/gfaa041.

Athuraliya NT, Abeysekera TD, Amerasinghe PH, Kumarasiri R, Bandara P, Karunaratne U, Milton AH, Jones AL. 2011 Dec. Uncertain etiologies of proteinuric-chronic kidney disease in rural Sri Lanka. Kidney Int. 80(11):1212–1221. Epub 2011 08 13. 10.1038/ki.2011.258.

Basile DP, Anderson MD, Sutton TA. 2012 Apr. Pathophysiology of acute kidney injury. Compr Physiol. 2:1303–1353. Epub 2012 04 1.

Borg MA, Xiang J, Anikeeva O, Pisaniello D, Hansen A, Zander K, Dear K, Sim MR, Bi P. 2021 Apr. Occupational heat stress and economic burden: a review of global evidence. Environ Res. 195:110781. Epub 2021 02 1. doi:10.1016/j.envres.2021.110781

Braga ALF, Zanobetti A, Schwartz J. 2002. The effect of weather on respiratory and cardiovascular deaths in 12 U.S. cities. Environ Health Perspect. 110(9):859–863. doi:10.1289/ehp.02110859.

Bunker A, Wildenhain J, Vandenbergh A, Henschke N, Rocklöv J, Hajat S, Sauerborn R. 2016. Effects of air temperature on climate-sensitive mortality and morbidity outcomes in the elderly; a systematic review and meta-analysis of epidemiological evidence. EBioMedicine. 6:258–268. doi:10.1016/j.ebiom.2016.02.034.

Chang JCJ, Yang H-Y. 2021. Epidemiology of chronic kidney disease of undetermined aetiology in Taiwanese farmers: a cross-sectional study from Changhua Community-based Integrated Screening programme. Occup Environ Med. 78(12):849–858. doi:10.1136/oemed-2021-107369.

Chapman CL, Johnson BD, Parker MD, Hostler D, Pryor RR, Schlader Z. 2021. Kidney physiology and pathophysiology during heat stress and the modification by exercise, dehydration, heat acclimation and aging. Temperature. 8:108–159. 2021 04 3. doi:10.1080/23328940.2020.1826841

CKD Work Group. 2013. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 3:1–150.

Dally M, Butler-Dawson J, Johnson RJ, Krisher L, Jaramillo D, Newman KL, Newman LS. 2020. Creatinine fluctuations forecast cross-harvest kidney function decline among sugarcane workers in guatemala. Kidney Int Reports. 5:1558–1566. doi:10.1016/j.ekir.2020.06.032.

Foster J, Hodder SG, Lloyd AB, Havenith G. 2020. Individual responses to heat stress: implications for hyperthermia and physical work capacity. Front Physiol. 11(11):541483. Epub 2020 10 6. 10.3389/fphys.2020.541483.

Gasparrini A. 2014 Feb 28. Modeling exposure–lag–response associations with distributed lag non-linear models. Statist Med. 33(5):881–899. Epub2013 09 13. 10.1002/sim.5963.

Gasparrini A, Guo Y, Hashizume M, Lavigne E, Zanobetti A, Schwartz J, Tobias A, Tong S, Rocklöv J, Forsberg B, et al. 2015. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. Lancet. 386(9991):369–375. doi:10.1016/S0140-6736(14)62114-0.

González-Quiroz M, Camacho A, Faber D, Aragón A, Wesseling C, Glaser J, Le Blond J, Smeeth L, Nitsch D, Pearce N, et al. 2017. Rationale, description and baseline findings of a community-based prospective cohort study of kidney function amongst the young rural population of Northwest Nicaragua. BMC Nephrol. 18(1):16. 2017 01 13. doi:10.1186/s12882-016-0422-4.

Hansson E, Glaser J, Jakobsson K, Weiss I, Wesseling C, Lucas RAI, Wei JLK, Ekström U, Wijkström J, Bodin T, et al. 2020. Pathophysiological mechanisms by which heat stress potentially induces kidney inflammation and chronic kidney disease in sugarcane workers. Nutrients. 12(6):1639. Nutrients.12:1639. doi:10.3390/nu12061639.

Hansson E, Glaser J, Weiss I, Ekström U, Apelqvist J, Hogstedt C, Peraza S, Lucas R, Jakobsson K, Wesseling C, et al. 2019. Workload and cross-harvest kidney injury in a Nicaraguan sugarcane worker cohort. Occup Environ Med. 76(11):818. doi:10.1136/oemed-2019-105986.

Hsu CC, Hwang SJ, Wen CP, Chang HY, Chen T, Shiu RS, Horng SS, Chang YK, Yang WC. 2006 Nov. High prevalence and low awareness of CKD in Taiwan: a study on the relationship between serum creatinine and awareness from a nationally representative survey. Am J Kidney Dis. 48(5):727–738. Epub 2006 10 25. 10.1053/j.ajkd.2006.07.018.

Johnson RJ, Wesseling C, Newman LS, Ingelfinger JR. 2019. Chronic kidney disease of unknown cause in agricultural communities. N Engl J Med. 380(19):1843–1852. doi:10.1056/NEJMra1813869.

Kenny GP, Yardley J, Brown C, Sigal RJ, Jay O. 2010. Heat stress in older individuals and patients with common chronic diseases. Can Med Assoc J. 182:1053. doi:10.1503/cmaj.081050.

Lee WS, Kim WS, Lim YH, Hong YC. 2019 Jan. High temperatures and kidney disease morbidity: a systematic review and meta-analysis. J Prev Med Public Health. 52(1):1–13. Epub 2019 02 12. 10.3961/jpmph.18.149.

Lee H, Myung W, Kim DK, Kim SE, Kim CT, Kim H. 2017 Mar 16. Short-term air pollution exposure aggravates Parkinson's disease in a population-based cohort. Sci Rep. 7(1):44741. Epub 2017 03 17. 10.1038/srep44741.

Liljegren JC, Carhart RA, Lawday P, Tschopp S, Sharp R. 2008 Oct. Modeling the wet bulb globe temperature using standard meteorological measurements. J Occup Environ Hyg. 5(10):645–655. Epub 2008 08 01. 10.1080/15459620802310770.

Lin S, Hsu W-H, Van Zutphen Alissa R, Saha S, Luber G, Hwang S-A. 2012. Excessive heat and respiratory hospitalizations in New York State: estimating current and future public health burden related to climate change. Environ Health Perspect. 120:1571–1577. 2012 11 1. doi:10.1289/ehp.1104728

Mork D, Wilson A. 2020. Treed distributed lag nonlinear models. arXiv preprint arXiv:201006147. 23(3):754–771. doi:10.1093/biostatistics/kxaa051.

Muñoz-Sabater J. 2019. ERA5-land hourly data from 1981 to present. Copernicus Climate Change Service (C3S) Climate Data Store(CDS). 10.

Nanayakkara S, Senevirathna S, Abeysekera T, Chandrajith R, Ratnatunga N, Gunarathne E, Yan J, Hitomi T, Muso E, Komiya T, et al. 2014. An integrative study of the genetic, social and environmental determinants of chronic kidney disease characterized by tubulointerstitial damages in the North Central Region of Sri Lanka. Jrnl Of Occup Health. 56(1):28–38. doi:10.1539/joh.13-0172-OA.

National Development Council (Taiwan). 2021. Urban and regional development statistics (in Chinese). Available from https://stat.ncl.edu.tw/browse.jsp?p=98092975

Ou Y, Wang F, Zhao J, Deng Q. 2023. Risk of heatstroke in healthy elderly during heatwaves: a thermoregulatory modeling study. Build Environ. 237:110324. 2023 06 1. doi:10.1016/j.buildenv.2023.110324

Pearce N, Caplin B. 2019. Let's take the heat out of the CKDu debate: more evidence is needed. Occup Environ Med. 76(6):357. doi:10.1136/oemed-2018-105427.

Peraza S, Wesseling C, Aragon A, Leiva R, García-Trabanino RA, Torres C, Jakobsson K, Elinder CG, Hogstedt C. 2012. Decreased kidney function among agricultural workers in El salvador. Am J Kidney Dis. 59(4):531–540. doi:10.1053/j.ajkd.2011.11.039.

Roncal Jimenez CA, Ishimoto T, Lanaspa MA, Rivard CJ, Nakagawa T, Ejaz AA, Cicerchi C, Inaba S, Le M, Miyazaki M, et al. 2014 Aug. Fructokinase activity mediates dehydration-induced renal injury. Kidney Int. 86(2):294–302. Epub 2013 12 18. 10.1038/ki.2013.492.

Roncal-Jimenez CA, Sato Y, Milagres T, Andres Hernando A, García G, Bjornstad P, Dawson JB, Sorensen C, Newman L, Krisher L, et al. 2018 Sep 1. Experimental heat stress nephropathy and liver injury are improved by allopurinol. Am J Physiol Renal Physiol. 315(3):F726–f733. Epub 2018 04 19. 10.1152/ajprenal.00543.2017.

Saha MV, Davis RE, Hondula DM. 2014. Mortality displacement as a function of heat event strength in 7 US cities. Am J Epidemiol. 179:467–474. doi:10.1093/aje/kwt264.

Samoli E, Stafoggia M, Rodopoulou S, Ostro B, Declercq C, Alessandrini E, Díaz J, Karanasiou A, Kelessis AG, Le Tertre A, et al. 2013 Aug. Associations between fine and coarse particles and mortality in Mediterranean cities: results from the MED-PARTICLES project. Environ Health Perspect. 121(8):932–938. Epub 2013 05 21. 10.1289/ehp.1206124.

Sánchez-Lozada LG, García-Arroyo FE, Gonzaga G, Silverio O, Blas-Marron MG, Muñoz-Jimenez I, Tapia E, Osorio-Alonso H, Madero M, Roncal-Jiménez CA, et al. 2018. Kidney injury from recurrent heat stress and rhabdomyolysis: protective role of allopurinol and sodium bicarbonate. Am J Nephrol. 48(5):339–348. doi:10.1159/000494663.

Schmeltz MT, Petkova EP, Gamble JL. 2016. Economic burden of hospitalizations for heat-related Illnesses in the United States, 2001–2010. Int J Environ Res Public Health. 13(9):13. doi:10.3390/ijerph13090894.

Sorensen CJ, Butler-Dawson J, Dally M, Krisher L, Griffin BR, Johnson RJ, Lemery J, Asensio C, Tenney L, Newman LS. 2019 Mar. Risk factors and mechanisms underlying cross-shift decline in kidney function in Guatemalan sugarcane Workers. J Occup Environ Med. 61(3):239–250. Epub 2018 12 24. 10.1097/JOM.0000000000001529.

Van Someren EJW. 2007. Thermoregulation and aging. American J Physiol Regul Integr Comp Physiol. 292:R99–R102. 2007 01 1. doi:10.1152/ajpregu.00557.2006

Wondmagegn BY, Xiang J, Williams S, Pisaniello D, Bi P. 2019. What do we know about the healthcare costs of extreme heat exposure? A comprehensive literature review. Sci Total Environ. 657:608–618. 2019 03 20. doi:10.1016/j.scitotenv.2018.11.479

Wu P-C, Lin C-Y, Lung S-C, Guo H-R, Chou C-H, Su H-J. 2011. Cardiovascular mortality during heat and cold events: determinants of regional vulnerability in Taiwan. Occup Environ Med. 68(7):525. doi:10.1136/oem.2010.056168.

Zafirah Y, Lin Y-K, Andhikaputra G, Sung F-C, Deng L-W, Wang Y-C. 2022. Mortality and morbidity of chronic kidney disease associated with ambient environment in metropolitans in Taiwan. Atmos Environ. 289:119317. 2022 11 15. doi:10.1016/j.atmosenv.2022.119317

Zhou Y-L 2018. The changing roles of women in agriculture from the perspective of census data (In Chinese). Journal. Available from: https://www.gender.ey.gov.tw/gecdb/Stat_AnalysisReport_Content.aspx?s=yFNcGlMCFdG0nfsWPM7gSA%40%40