Supplementary appendix

AMBIENT HEAT EXPOSURE AND KIDNEY FUNCTION IN PATIENTS WITH DIABETIC AND NON-DIABETIC CHRONIC KIDNEY DISEASE: A POST-HOC ANALYSIS OF THE DAPA-CKD TRIAL: SUPPLEMENTARY MATERIAL

Supplementary Methods

Derivation of exposure variable

Heat Index (HI; as defined by the U.S. National Oceanic and Atmospheric Administration (NOAA)—National Weather Service (NWS) in °C) was derived using a multiple regression equation of ambient dry-bulb air temperature (T_a) and relative humidity (RH) (computed using T_a and dewpoint temperature) from the European Centre for Medium Range Weather Forecasts (ECMWF)-ERA5 climate reanalysis[1]. The NOAA-NWS implemented HI as formulated by Rothfusz[2] utilizes least squares fit on data using a polynomial function in T_a (in °F) and RH [Equation 1] along with the conditional adjustments [Equations (2)–(4)], and is not defined for $T_a \leq 80$ °F (27 °C) and RH $\leq 40\%$:

$$\text{HI} = -42.38 + 2.05 \times T_a + 10.14 \times H - 0.22 \times T_a \times RH - 6.84 \times 10^{-3} \times T_a^2 - 5.48 \times 10^{-2} \times RH^2 + 1.23 \times 10^{-3} \times T_a^2 \times RH + 8.5 \times 10^{-4} \times T_a \times RH^2 - 1.99 \times 10^{-6} \times T_a^2 \times RH^2 \tag{1}$$

where T_a is in °F and RH in % (although the HI assembled in the current study is converted to °C). For RH < 13% and 80 °F $\leq T_a <$ 112 °F, Equation (1) becomes:

$$HI_{adjusted} = HI + \left[\frac{13 - RH}{4}\right] \times \sqrt{\left[17 - \frac{Abs(T_a - 95)}{17}\right]} \tag{2}$$

For RH > 85% and 80 °F < T_a < 87 °F, the following adjustment is added to HI and Equation (1) therefore becomes:

$$HI_{adjusted} = HI + \left[\frac{RH - 85}{10}\right] \times \left[\frac{87 - T_a}{5}\right] \tag{3}$$

If the resulting HI for any combination of T_a and RH is below 80 °F when using Equations (1)-(3) above, the Rothfusz regression is replaced by Steadman's formula[3] expressed as:

$$\text{HI} = 0.5 \times [T_a + 61 + [1.2 \times (T_a - 68)] + 0.094 \times RH] \tag{4}$$

The HI was computed using the python package xclim v.0.39.0[4].

Model of eGFR trajectory excluding climate associated variables

eGFR was log-transformed to reduce the heteroskedasticity observed when examining the distribution in the change in untransformed eGFR values. Initially a best fit linear mixed effect (LME) model of change in eGFR was developed including all potential non-climate-related explanatory variables using the R packages lme4[5] and nlme[6] (for which model outputs were identical). Models with both two (change in estimated glomerular filtration rate, eGFR, nested within individuals) or three levels (change in eGFR nested within individuals nested within study centre), a random intercept or a random intercept and slope for time, with and without a quadratic slope term were examined. An unstructured covariance matrix was specified. Fixed effects entered into the model included: participant demographics (age; sex; ethnicity), social and clinical history (smoking status; diagnosis of diabetes; history of cardiovascular disease; heart failure), clinical measurements (body mass index; systolic and diastolic blood pressure; urinary albumin creatinine ratio, UACR; baseline eGFR) and medications (angiotensin converting enzyme inhibitor /angiotensin-2 receptor blocker, ACE/ARB, use; statin use; diuretic use; DAPA-CKD study arm). Inclusion of interactions terms with time for all the above variables were also explored, along with an UACR-eGFR interaction. UACR values were centred and scaled by the mean and standard deviation of the population to facilitate interpretation of the coefficients after fitting the eGFR*UCR interaction but were not transformed as examination of model residuals did not demonstrate influential outliers.

The random effect structures were fitted from simplicity to complexity (whilst retaining all fixed effects) and compared using Akaike information criterion (AIC), Bayesian information criterion (BIC), the chi-square statistics, representing the difference in deviance between successive models, and p-values based on likelihood ratio test comparisons (which were all consistent across comparisons). After the selection of the random effect structure, fixed effects were included on the basis of *a priori* evidence for associations with eGFR or volume status to minimise potential confounding, and retained except where there was collinearity between explanatory variables. Finally, interactions of all included baseline variables with time were added, and retained if there was evidence of improved model fit using the Wald test.

Case time series

The CTS was fitted using the R package gnm[3] with identical exposure and outcome definitions were used as for the LME model. A linear and quadratic slope term was also included. To test the hypothesis that ambient climate was associated with change in eGFR, the time-updated heat exposure variable for the 120 days prior to each eGFR measure was then included in the model. No other fixed effects were included in case time series.

Model diagnostics

Once the linear mixed model including the climate exposure variable had been fitted diagnostic plots examined for influential outliers or skewed distributions (Supplementary Figure 4).

[1] Hersbach, H., et al., ERA5 hourly data on single levels from 1959 to present. , Copernicus Climate Change Service (C3S) Climate Data Store (CDS), Editor. 2018.

[2] Rothfusz, L. The Heat Index "Equation" (or, More Than You Ever Wanted to Know About Heat Index). 1990 [accessed 12/04/2023]; Available from: https://www.weather.gov/media/ffc/ta_htindx.pdf

[3] Steadman, R.G., The Assessment of Sultriness. Part I: A Temperature-Humidity Index Based on Human Physiology and Clothing Science. Journal of Applied Meteorology and Climatology, 1979. 18(7): p. 861-873.

[4] Logan, T et al, (2022). Ouranosinc/xclim: v0.39.0 (v0.39.0). Zenodo. https://doi.org/10.5281/zenodo.7796479

[5] Bates, D., Mächler, M., Bolker, B., and Walker, S., Fitting Linear Mixed-Effects Models Using lme4. Journal of Statistical Software, 67(1): p. 1 - 48(2015).

[6] Pinheiro, J., Bates, D., and R Core Team, Nlme: Linear and Nonlinear Mixed Effects Models R Package Version 3.1-162. 2023.

[3] Turner, H. and D. Firth, Generalized nonlinear models in R: An overview of the gnm package. 2022.

Supplementary Table 1: Linear Mixed Model of eGFR Decline Without Climate-Related Exposure Variables.

		log(e) eGFR change	95% confidence interval		
Time,	per year	**-0.407**	**-0.497**	**to**	**-0.316**
Time^2,	per year	**-0.006**	**-0.011**	**to**	**-0.001**
Sex,	male, versus female	0.007	-0.004	to	0.019
Statin use,	yes, versus no	0.008	-0.003	to	0.020
Smoking,	former, versus current	-0.005	-0.022	to	0.012
	never, versus current	-0.004	-0.021	to	0.012
ACEi/ARB use,	yes, versus no	0.012	-0.019	to	0.044
Diuretic use,	yes, versus no	0.000	-0.011	to	0.012
Type 2 diabetes,	yes, versus no	0.012	-0.001	to	0.024
Cardiovascular disease,	yes, versus no	-0.005	-0.017	to	0.007
Ethnicity,	black, versus asian	-0.03	-0.057	to	0.002
	other, versus asian	-0.016	-0.040	to	0.009
	white, versus asian	0.003	-0.013	to	0.019
Body mass index,	per kg/m^2	0.001	0.000	to	0.002
log(e) baseline eGFR,	per log(e) ml/min/1.7m^2	**-0.032**	**-0.054**	**to**	**-0.011**
Age,	per year	**-0.001**	**-0.001**	**to**	**0.000**
DAPA-CKD study arm,	placebo versus active arm	**0.049**	**0.037**	**to**	**0.061**
Systolic blood pressure,	per mmHg	**-0.001**	**-0.001**	**to**	**0.000**
Urinary ACR,	per 1 SD change	**-0.120**	**-0.186**	**to**	**-0.055**
Body mass index * time interaction,	per kg/m^2 per year	**0.001**	**0.000**	**to**	**0.002**
log(e) baseline eGFR * time interaction,	per log(e) ml/min/1.7m^2 per year	**0.066**	**0.047**	**to**	**0.085**
Age * time interaction,	per year per year	**0.002**	**0.001**	**to**	**0.002**
DAPA-CKD study arm * time interaction,	placebo versus active arm per year	**-0.048**	**-0.058**	**to**	**-0.037**
Systolic blood pressure * time interaction,	per mmHg per year	**0.000**	**-0.001**	**to**	**0.000**
Urinary ACR* time interaction,	per 1 SD change per year	**-0.060**	**-0.066**	**to**	**-0.055**
Urinary ACR* log baseline eGFR interaction,	per 1 SD change per log ml/min/1.7m^2	**0.029**	**0.011**	**to**	**0.046**

Coefficients from the best fit linear mixed effects model fitted using restricted maximum likelihood with the outcome of log(e) eGFR change. 3-level model specified with a random intercept and random linear slope for time at centre level (n=373), and a random intercept along with both random linear and random quadratic slopes for time at the individual level (n=4010). Standard deviation of random effects parameters for log(e) eGFR change: intercept: 0.0306 log(e) ml/min/1.7m^2 and linear slope: 0.0274 log(e) ml/min/1.7m^2 per year at level-3 (centre); intercept 0.1555 log(e) ml/min/1.7m^2, linear slope 0.1322 log(e) ml/min/1.7m^2 per year and quadratic slope 0.0641 log(e) ml/min/1.7m^2 per year^2 at level-2 (participant). Residual variance 0.1302 log(e) ml/min/1.7m^2. Correlations between random effects: intercept and linear slope: -0.14 at level-3; intercept and linear slope: -0.23, intercept and quadratic slope: -0.48, linear slope and quadratic slope: -0.16 at level-2. ACEi/ARB: angiotensin converting enzyme inhibitor/ angiotensin-2 receptor blocker; eGFR: estimated glomerular filtration rate; ACR: urinary albumin-to-creatinine ratio; SD: standard deviation. Coefficients in bold where 95% confidence intervals (CI) exclude zero.

Supplementary Table 2: Association Between Heat Exposure and Change in eGFR – Comparison of Linear Mixed Model and Case Time Series.

		LME	CTS
Change in eGFR (%)[a] for each unit change in HEAT-30	change	**-0.60**	**-0.68**
	95% CI	**-0.95 to -0.26**	**-1.14 to -0.22**

a. log(e) eGFR change interpreted as percentage change. LME model adjusted for baseline age; sex; ethnicity; smoking status; diagnosis of diabetes; history of cardiovascular disease; BMI; systolic blood pressure; urinary ACR; eGFR; ACE/ARB use; statin use; diuretic use; DAPA-CKD study arm and including interactions with time of the following baseline variables: age; BMI; systolic BP; eGFR; urinary ACR and DAPA-CKD study arm (see Supplementary Table 1). Crude model for heat index>30ºC standard deviation of random effects parameters: intercept: 0.0294 log(e) ml/min/1.7m^2 and linear slope: 0.0271 log(e) ml/min/1.7m^2/year at level-3 (centre); intercept 0.1555 log(e) ml/min/1.7m^2, linear slope 0.1321 log(e) ml/min/1.7m^2 per year and quadratic slope 0.0640 log(e) ml/min/1.7m^2 per year^2 at level-3. Residual variance 0.1302 log(e) ml/min/1.7m^2. Correlations between random effects: intercept and linear slope: -0.10 at level-3; intercept and linear slope: -0.23, intercept and quadratic slope: -0.48, linear slope and quadratic slope: -0.16 at level-2. Centre n=373; participant n=4010 (7 individuals excluded due to missing covariate data). CTS includes linear and quadratic coefficient for time; participant n=4017. Coefficients in bold where 95% confidence intervals (CI) exclude zero. LME: linear mixed effects model; CTS: case time series model; HEAT-30: 30 days heat index>30ºC within each 120-day window.

Supplementary Table 3: Association Between Heat Exposure and Change in eGFR with Adjustment for Heat Index>30°C on Day of Test.

Change in eGFR[a]			HI Threshold (°C)																
			27			28			29			30			31			32		
LME	for each 30 days HI>threshold	change		0.1%			0.0%			-0.1%			-0.3%			-0.3%			**-0.4%**	
		95% CI	-0.2%	to	0.4%	-0.3%	to	0.3%	-0.5%	to	0.2%	-0.7%	to	0.1%	-0.7%	to	0.1%	**-0.8%**	**to**	**0.0%**
	HI>30 on day of test	change		**-4.0%**			**-3.3%**			**-2.7%**			**-2.3%**			**-2.6%**			**-2.8%**	
		95% CI	**-4.8%**	**to**	**-3.2%**	**-4.1%**	**to**	**-2.4%**	**-3.6%**	**to**	**-1.8%**	**-3.2%**	**to**	**-1.5%**	**-3.4%**	**to**	**-1.7%**	**-3.7%**	**to**	**-1.9%**
CTS	for each 30 days HI>threshold	change		-0.2%			-0.2%			-0.2%			-0.4%			**-0.5%**			**-0.7%**	
		95% CI	-0.6%	to	0.2%	-0.6%	to	0.2%	-0.7%	to	0.2%	-0.9%	to	0.0%	**-1.0%**	**to**	**0.0%**	**-1.2%**	**to**	**-0.1%**
	HI>30 on day of test	change		**-2.6%**			**-2.6%**			**-2.6%**			**-2.6%**			**-2.5%**			**-2.4%**	
		95% CI	**-3.7%**	**to**	**-1.5%**	**-3.7%**	**to**	**-1.5%**	**-3.7%**	**to**	**-1.5%**	**-3.7%**	**to**	**-1.4%**	**-3.6%**	**to**	**-1.4%**	**-3.5%**	**to**	**-1.3%**

a. log(e) eGFR change interpreted as percentage change. LME model adjusted for baseline age; sex; ethnicity; smoking status; diagnosis of diabetes; history of cardiovascular disease; BMI; systolic blood pressure; urinary ACR; eGFR; ACE/ARB use; statin use; diuretic use; DAPA-CKD study arm and including interactions with time of the following baseline variables: age; BMI; systolic BP; eGFR; urinary ACR and DAPA-CKD study arm (see Supplementary Table 1). CTS includes linear and quadratic coefficient for time; participant n=4017. Coefficients in bold where 95% confidence intervals (CI) exclude zero. LME: linear mixed effects model; CTS: case time series model; HI: heat index.

Supplementary Table 4: Association Between Heat Exposure and Change in eGFR in extended exposure model.

Change in eGFR (%) for each 30 days HI>30		
between 0-120 days prior to test	change	**-0.66**
	95% CI	**-1.04 to -0.27**
between 120-240 days prior to test	change	**0.47**
	95% CI	**0.09 to 0.85**
between 240-360 days prior to test	change	**-0.72**
	95% CI	**-1.10 to -0.33**

a. log(e) eGFR change interpreted as percentage change. LME model mutually adjusted for heat-exposure windows. Also adjusted for baseline age; sex; ethnicity; smoking status; diagnosis of diabetes; history of cardiovascular disease; BMI; systolic blood pressure; urinary ACR; eGFR; ACE/ARB use; statin use; diuretic use; DAPA-CKD study arm and including interactions with time of the following baseline variables: age; BMI; systolic BP; eGFR; urinary ACR and DAPA-CKD study arm (see Supplementary Table 1).. Coefficients in bold where 95% confidence intervals (CI) exclude zero. LME: linear mixed effects model; HI: heat index.

Supplementary Table 5: Association Between Heat Exposure and Change in eGFR Stratified by Centre Location in High- Versus Middle-Income Country.

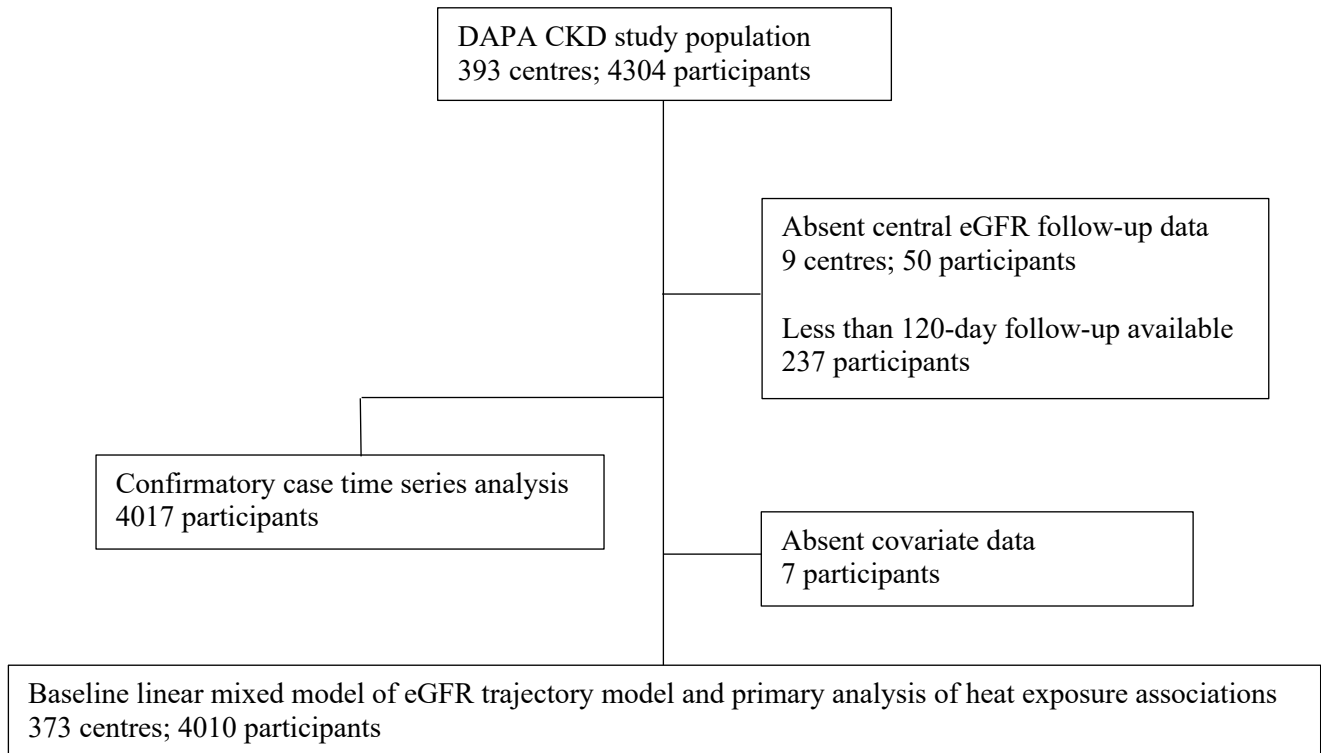| Change in eGFR (%)		Centres located in high-income countries only n=2036	Centres located in middle-income countries only n=1974
for each 30 days HI>30	change	-0.51	**-0.54**
	95% CI	-1.25 to 0.01	**-1.03 to -0.05**

a. log(e) eGFR change interpreted as percentage change. Linear mixed effects model restricted to country groupings. Model adjusted for baseline age; sex; ethnicity; smoking status; diagnosis of diabetes; history of cardiovascular disease; BMI; systolic blood pressure; urinary ACR; eGFR; ACE/ARB use; statin use; diuretic use; DAPA-CKD study arm and including interactions with time of the following baseline variables: age; BMI; systolic BP; eGFR; urinary ACR and DAPA-CKD study arm (see Supplementary Table 1). Coefficients in bold where 95% confidence intervals (CI) exclude zero. HI: heat index.

Supplementary Table 6: Association Between Time Updated Heat Exposure and Time to Doubling of Serum Creatinine

for each 30 days HI>30	Hazard ratio	0.90
	95% CI	0.70 to 1.15

Complementary log-log multilevel discrete time survival model. Individuals nested within centres. Adjusted for the same baseline covariates as the LME model in Supplementary Table 1. HI: heat index.

Supplementary Figure 1 Data Flows

DAPA CKD study population
393 centres; 4304 participants

Absent central eGFR follow-up data
9 centres; 50 participants

Less than 120-day follow-up available
237 participants

Confirmatory case time series analysis
4017 participants

Absent covariate data
7 participants

Baseline linear mixed model of eGFR trajectory model and primary analysis of heat exposure associations
373 centres; 4010 participants

Supplementary Figure 2 Distribution of Follow-up Days with Heat Index>30ºC.
Proportion of total follow-up days with heat index>30ºC by individual. Participant n=4017.
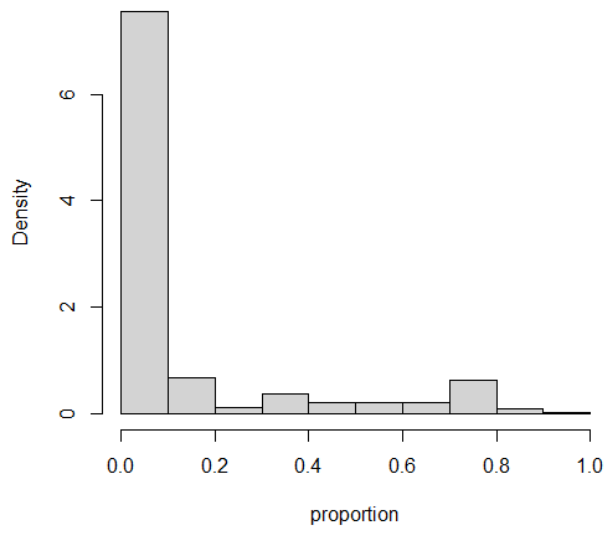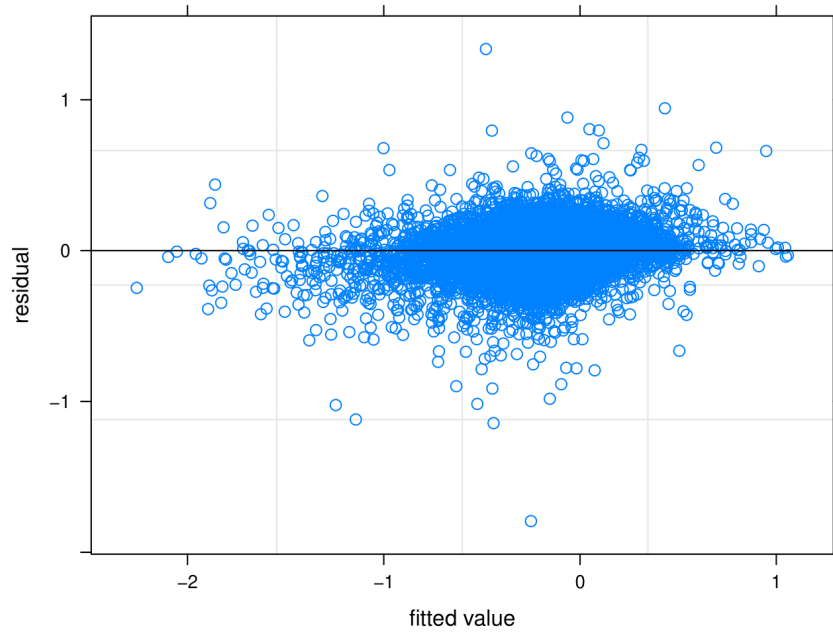
Supplementary Figure 3 eGFR Trajectories by Centre Heat Index Quartile Over First 20-Months
eGFR in each group estimated from least-square mean. Quartiles defined by proportion of follow-up days with heat index>30ºC at centre-level. Participant n=4017; Centre n=373.
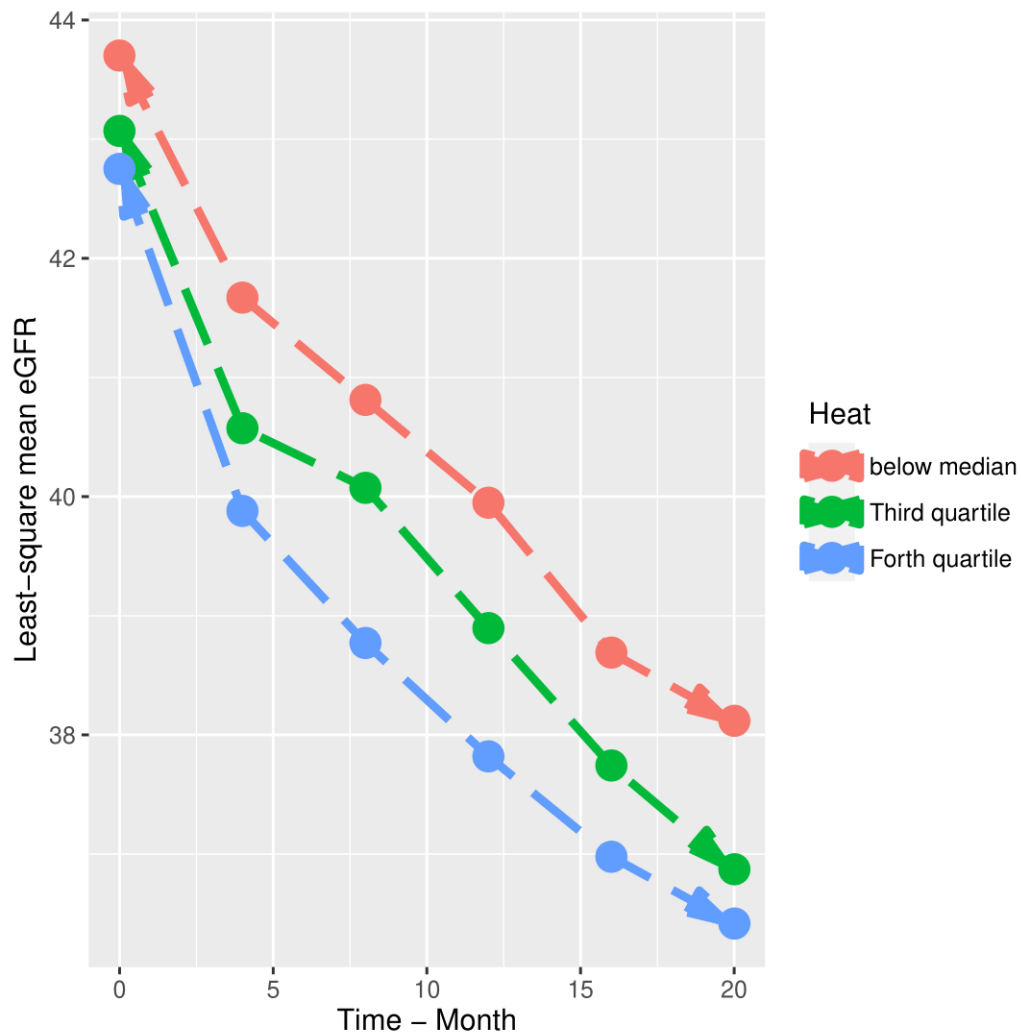
Supplementary Figure 4 Model Diagnostic Plots For Linear Mixed Model Including Exposure Variable as Heat Index>30ºC
(A) Fitted versus residual values; (B) QQ plot of residual values; (C) QQ plot of individual-level random effects (D) QQ plot of centre-level random effects. Participant n=4010; Centre n=373.

A

B

C

Quadratic centred years−since−randomisation

Intercept

years since randomisation

Standard normal quantiles

D

Centre level random effects

Intercept

years since randomisation

Standard normal quantiles
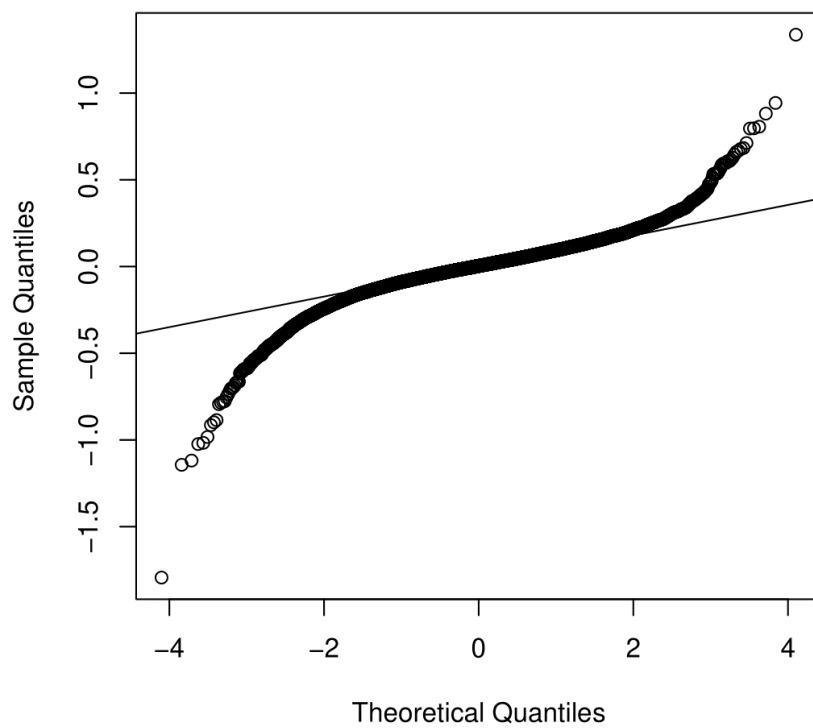
Supplementary Figure 5 STROBE checklist

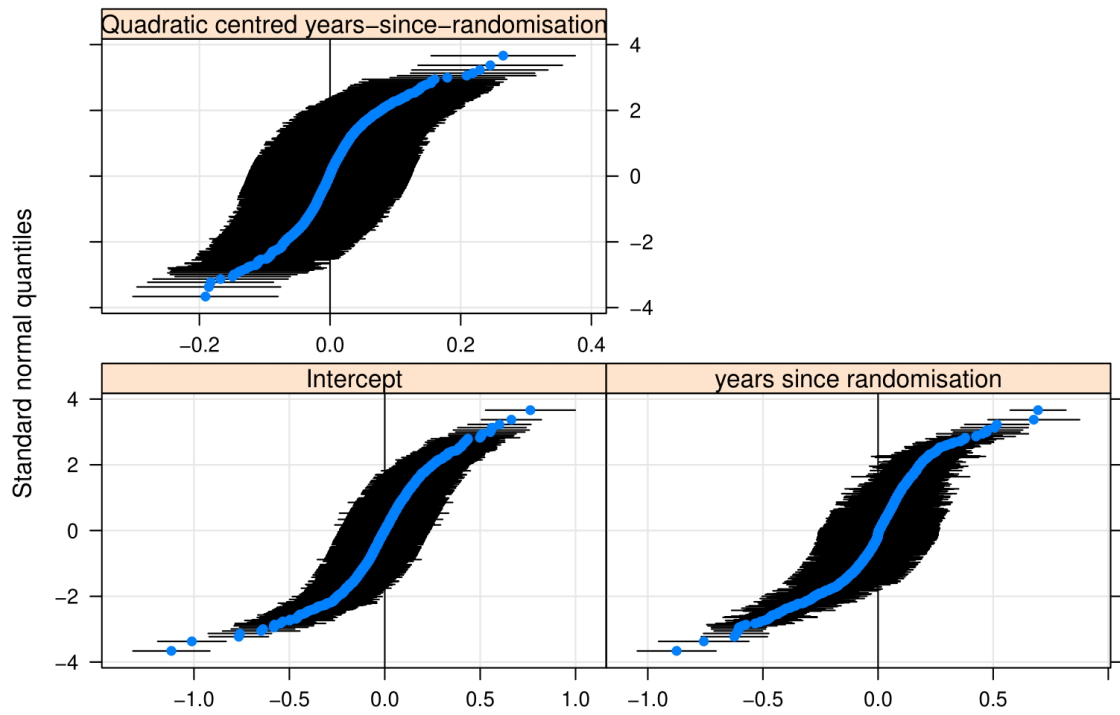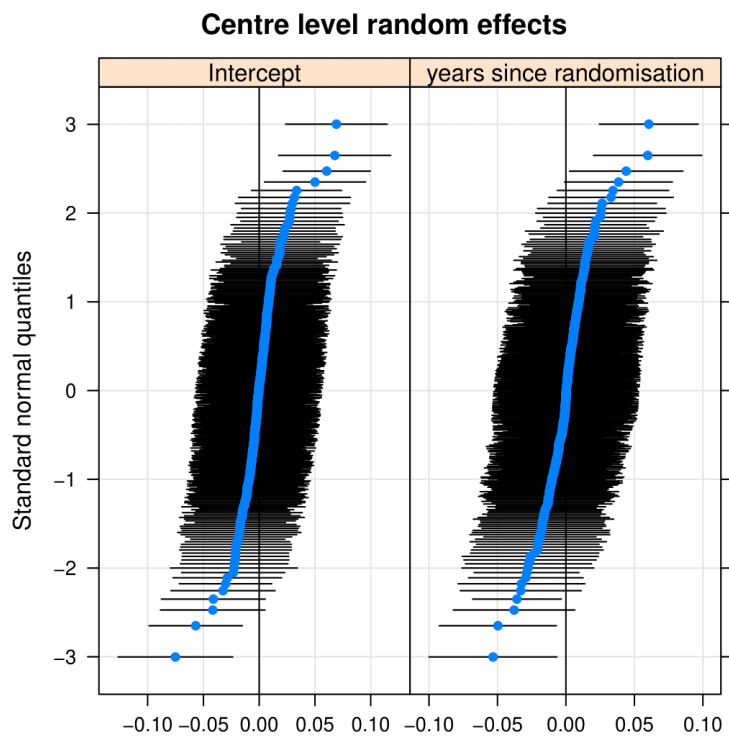|	**Item No.**	**Recommendation**	**Page No.**	**Relevant text from manuscript**
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	
Methods				
Study design	4	Present key elements of study design early in the paper	5 - 8	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5 - 8	

Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	
		Case-control study—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 - 6

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 - 6	
Bias	9	Describe any efforts to address potential sources of bias	4 - 5	use of RCT data
Study size	10	Explain how the study size was arrived at	5	

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5 - 6	linear mixed model, case-time series
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6 – 7	
		(*b*) Describe any methods used to examine subgroups and interactions	7	
		(*c*) Explain how missing data were addressed	28	Supplementary Figure 1
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed		Minimal loss to follow-up
		Case-control study—If applicable, explain how matching of cases and controls was addressed		
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy		
		(*e̲*) Describe any sensitivity analyses	7 – 8	

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	28	Supplementary Figure 1
		(b) Give reasons for non-participation at each stage	28	Supplementary Figure 1
		(c) Consider use of a flow diagram	28	Supplementary Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	16 - 17	Tables 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	28	Supplementary Figure 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8 – 9; 19; 29	Results; Figure 1; Supplementary Figure 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		

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		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results - 5	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8 – 9; 20	Results; Figure 2; Supplementary Tables 1 - 5
		(*b*) Report category boundaries when continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8 – 9; 21	Results; Figure 3

Discussion

Key results	18	Summarise key results with reference to study objectives	9 – 10	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	11	Discussion

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8	End of methods section

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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.