eAppendix

Who is sensitive to extreme cold and hot temperatures in an Indigenous Australian population?

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MATERIALS AND METHODS

Data collection

A prospective cohort with 719 Indigenous people was initiated in a remote Aboriginal community in Australia's Northern Territory in 1997. A baseline examination was carried out between 1992 and 1995 which collected information on age, sex, body mass index (BMI) and other individual factors. Any hospitalisations (ICD-10: A00–R99) were recorded for every participant between 1997 and 2004.

We stratified age at hospitalisation into two groups: old (> 45 years) and young (≤ 45 years). We used this relatively young threshold because Indigenous Australians have a life expectancy twenty years shorter than non-Indigenous Australians [1]. We stratified BMI at baseline into three groups: overweight ($BMI \geq 25$ kg/m^2), normal weight ($18.5 \leq BMI < 25$ kg/m^2), and underweight ($BMI < 18.5$ kg/m^2), using standard WHO definitions.

Daily minimum, mean and maximum temperatures, and dew point temperature were acquired from the weather underground website (http://www.wunderground.com/) for 1997–2004. The monitoring site is located in the Indigenous community. The temperature data were linked to the hospitalisation data using the hospitalisation dates. We used minimum daily temperature, because it gave a better model fit than mean or maximum temperature as judged by the Akaike Information Criteria.

This study was approved by the Behavioural and Social Science Ethical Review Committee of the University of Queensland.

Data analysis

The association between temperature and hospitalisation

We used a time-stratified case-crossover analysis to examine if temperature was associated with hospitalisation[2]. For each participant, the hospitalisation day was defined as "case day". The same days of the week in the same calendar month were selected as "control days", giving 3–4 control days per case day. This type of case-crossover design avoids the "overlap bias" [3] and controls for confounders that change gradually such as season [4]. Each subject acts as their own control, so the design also controls for time-independent factors such as gender. Day of the week was controlled for by matching to avoid any potential confounding due to the strong weekly pattern in hospitalisations.

We used conditional logistic regression to compare temperature exposure on case and control days. We used a distributed lag non-linear model (DLNM) to allow for delayed effects of up to 21 days, and for a non-linear association between temperature and hospitalisation. We used a natural cubic spline with 4 degrees of freedom to capture the well-known U-shaped association between temperature and hospitalisation. A natural cubic spline with 3 degrees of freedom was used for the delayed association of up to 21 days. We used 21 days because previous studies have shown that the delayed effects of cold and hot temperatures have a maximum delay of weeks [5]. We controlled for dew point temperature using a DLNM with the same lag and degrees of freedom as for temperature, because dew point temperature incorporates the effect of humidity on morbidity [6].

To show the associations we plotted the estimated odds ratios (ORs) for hospitalisation against temperature by group. To give a numeric summary we examined the odds ratios at specific temperatures, and calculated the odds ratios for hospitalisation at a relatively cold temperature (17.5 °C, 5th percentile of minimum temperature) compared with the 10th percentile of temperature (18.8 °C); and compared an extreme hot temperature (27.1 °C, 95th percentile of minimum temperature) with the 90th percentile of temperature (26.2 °C).

Effect modifiers

We used a case-only analysis to examine whether particular groups were more susceptible to the effects of cold and hot temperatures [7,8]. We examined the odds ratios for: overweight versus normal weight and normal weight versus underweight; men versus women; and old versus young. A multivariate logistic regression model was used to compare overweight with normal weight people and compare normal weight with underweight people. Binary logistic regression models were used to compare men and women, and the old and the young. For our case-only approach, the individual characteristics (e.g., overweight, normal weight and underweight) were used as the dependent variable, and temperature was used as the independent variable.

The odds ratios for the subgroups might be non-linear, because the main effect of temperature on morbidity is non-linear [5]. To model this we combined the DLNM and the case-only approach. The same DLNM as used for the main association between temperature and hospitalisation was again used to examine the effect modification.

Three other independent variables were added to the model. We controlled for dew point temperature (using the same DLNM as for temperature), day of the week as a categorical variable, and season using a sinusoid/cosinusoid with an annual cycle [8].

Sensitivity analyses were performed by using maximum lags from 15 to 30 days. We changed the degrees of freedom for temperature and dew point temperature (3 to 6). We also changed the degrees of freedom for lags (3 to 6). All statistical tests were two-sided and *p*-values of less than 0.05 were considered statistically significant.

The R software (version 2.15.0, R Development Core Team 2009) was used to fit all models, with the "dlnm" package to create the DLNM [9].

RESULTS

Descriptive statistics for the participants at the baseline are in Table 1. There were 2,253 hospitalisations in total.

Table 1: Summary statistics for the cohort of a remote Aboriginal community in Australia's Northern Territory

Category	Baseline (*n*=719)	Hospitalisation (*n*=2253)
Female	425	1496
Elderly	161	571
Overweight	201	726
Underweight	263	696

The remote Aboriginal community in Australia's Northern Territory has a tropical climate with a relatively small range of temperatures (Table 2). There are only two seasons: dry (May to October) and wet (November to April). It has an average daily temperature of 32 °C, with high humidity in the wet season. The coldest days were not cold by usual standards, but the hottest days were extremely hot.

Table 2: Percentiles of minimum, mean and maximum temperature, and dew point temperature in a remote Aboriginal community in Australia's Northern Territory between 1997 and 2004

Variable	5%	10%	25%	50%	75%	90%	95%
Minimum temperature (°C)	17.5	18.8	21.5	23.8	25.2	26.2	27.1
Mean temperature (°C)	23.9	24.9	26.5	28.0	29.2	30.0	30.4
Maximum temperature (°C)	29.0	29.9	31.1	32.3	33.5	34.4	34.9
Dew point temperature (°C)	11	14	19	23	24	24	25

The associations between temperature and hospitalisation are shown in Figure 1. Hotter temperatures were associated with an increased risk of hospitalisation for all participants, overweight people and men. Colder temperatures were associated with an increased risk of hospitalisation for women. Both cold and hot temperatures were associated with an increased risk of hospitalisation in older people.

The estimated effects of extreme temperatures on group-specific hospitalisations are shown in Table 3. Overweight people and old people were significantly more vulnerable to extreme hot temperatures (27.1 °C versus 26.2 °C), with odds ratios of 1.60 (1.08, 2.36) and 1.73 (1.21, 2.48), respectively.

Table 3: The association between cold and hot temperatures and hospitalisations by subgroup using a case-crossover design. Estimates were calculated from the non-linear model (Figure 1).

Subgroup	Odds Ratios (95% CI)	
	Cold [a]	Hot [b]
All participants	1.29 (0.96, 1.74)	1.13 (0.78, 1.65)
Overweight	0.97 (0.58, 1.61)	1.60 (1.08, 2.36)
Normal weight	1.27 (0.83, 1.96)	1.14 (0.69, 1.88)
Underweight	1.01 (0.65, 1.57)	1.36 (0.76, 2.43)
Female	1.27 (0.89, 1.81)	1.14 (0.71, 1.82)
Male	1.34 (0.89, 2.02)	1.16 (0.73, 1.85)
Young	1.09 (0.78, 1.52)	1.13 (0.75, 1.72)
Old	1.12 (0.65, 1.94)	1.73 (1.21, 2.48)

[a] 5th percentile of temperature (17.5 °C) relative to 10th percentile of temperature (18.8 °C);

[b] 95th percentile of temperature (27.1 °C) relative to 90th percentile of temperature (26.2 °C).

Overweight people had a greater risk of hospitalisation during extreme hot temperatures than those with normal weight, but not during cold days (Figure 2). Men were at a greater risk of hospitalisation during hot days. The older group had a greater risk of hospitalisation during both cold and hot days.

The estimated effect modifications of the association between temperature and hospitalisation are shown in Table 4. Age was an important effect modifier. The older group had OR of 2.73 (95% CI: 1.70–4.38) for cold days and 1.31 (95% CI: 1.01–1.77) for hot days. Overweight people showed increased susceptibility to hot temperatures (OR: 1.63; 95% CI: 1.13–2.36), while men had greater susceptibility on hot days (3.30; 2.13–5.11).

Table 4: Effect modifiers of the association between cold and hot temperatures and hospitalisation using a case-only study. Estimates were calculated from the non-linear model (Figure 2).

Subgroup	Odds Ratios (95% CI)	
	Cold [a]	Hot [b]
Overweight VS Normal weight	0.91 (0.55, 1.51)	1.63 (1.13, 2.36)
Normal weight VS Underweight	0.90 (0.61, 1.33)	1.17 (0.70, 1.95)
Male VS Female	1.32 (0.95, 1.82)	3.30 (2.13, 5.11)
Old VS Young	2.73 (1.70, 4. 38)	1.31 (1.01, 1.77)

[a] 5^{th} percentile of temperature (17.5 °C) relative to 10^{th} percentile of temperature (18.8 °C);

[b] 95^{th} percentile of temperature (27.1 °C) relative to 90^{th} percentile of temperature (26.2 °C).

The results did not change when we changed the: lag days from 15 to 30 days, degrees of freedom for temperature and relative humidity from 3 to 6, and degrees of freedom for lags from 3 to 6.

We used normal BMI cut-offs to define overweight, normal weight and underweight. However, optimal BMI cut-offs are still uncertain for the Indigenous Australians due to differences in body shape and other physiological factors. Studies have suggested that a lower BMI cut-off for overweight of 22 kg/m^2 might be more appropriate than 25 kg/m^2 [1]. We conducted a sensitivity analysis to check this issue. When we defined overweight using BMI $\geq$ 22 kg/m^2, the effect modification was only slightly higher than using BMI $\geq$ 25 kg/m^2 (results not shown).

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Figures

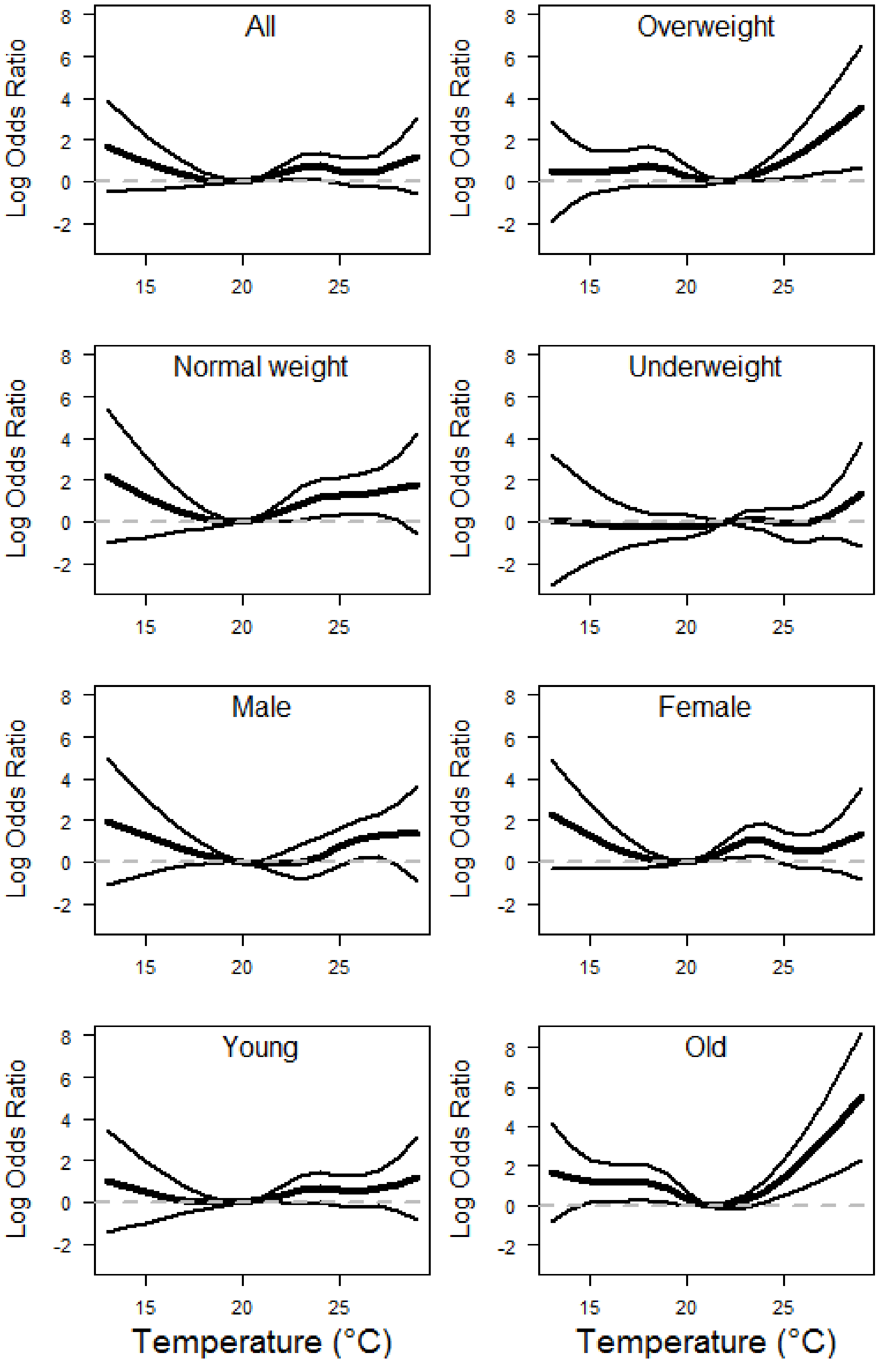

Figure 1: The non-linear associations between temperature and hospitalisation using a case-crossover model. Temperature has a lag of 0–21 days and 4 degrees of freedom natural cubic spline. The thick lines are log odds ratios, the thin lines are 95% confidence intervals. The dotted horizontal line represents no change in risk.

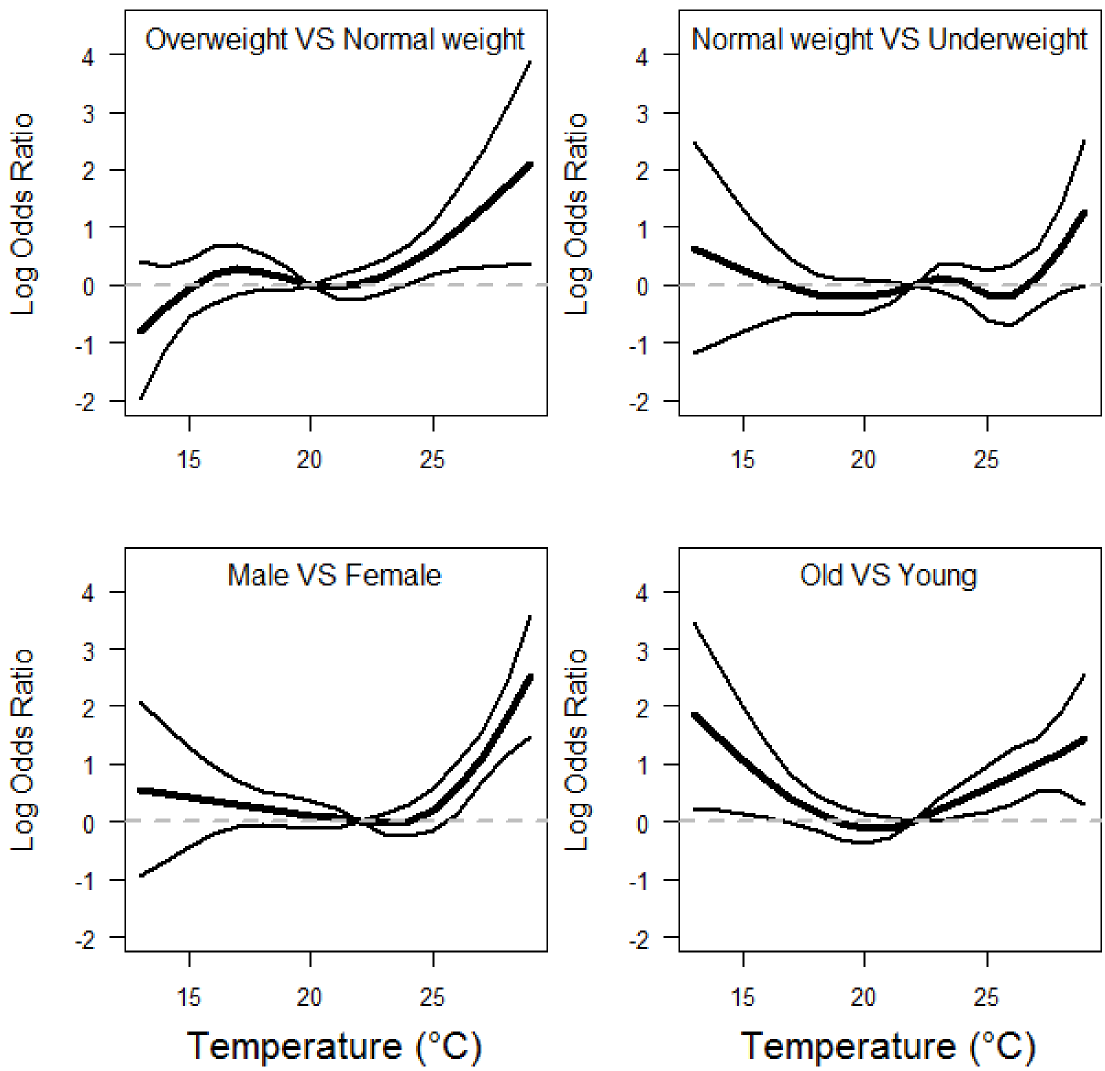

Figure 2: Non-linear effect modifications of the association between temperature and hospitalisation using a case-only study. Temperature has a lag of 0–21 days and 4 degrees of freedom natural cubic spline. The think lines are log odds ratios, the thin lines are 95% confidence intervals.