

1 **The influence of pre-existing health conditions on short-term mortality risks of**
2
3 **temperature:**
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6 **evidence from a prospective Chinese elderly cohort in Hong Kong**
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2
3 **Abstract (word: 242)**
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6 **Background:**
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8 Both cold and hot temperatures are associated with adverse health outcomes. Less is known
9 about the role of pre-existing medical conditions to confer individual's susceptibility to
10 temperature extremes.
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16 **Methods:**
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18 We studied 66,820 subjects aged ≥ 65 who were enrolled and interviewed in all the 18
19 Elderly Health Centers of Department of Health, Hong Kong from 1998 to 2001, and
20 followed up for 10-13 years. The distributed lag nonlinear model (DLNM) combined with a
21 nested case-control study design was applied to estimate the nonlinear and delayed effects of
22 cold or hot temperature on all natural mortality among subjects with different pre-existing
23 diseases.
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36 **Results:**
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38 The relative risk of all natural mortality associated with a decrease of temperature from 25th
39 percentile (19.5 °C) to 1st percentile (11.3 °C) over 0-21 lag days for participants who reported
40 to have an active disease at the baseline was 2.21 (95% confidence interval (CI): 1.19, 4.10)
41 for diabetes mellitus (DM), 1.59 (1.12, 2.26) for circulatory system diseases (CSD), and 1.23
42 (0.53, 2.84) for chronic obstructive pulmonary disease (COPD), whereas 1.04 (0.59, 1.85) for
43 non-disease group (NDG). Compared with NDG, elders with COPD had excess risk of
44 mortality associated with thermal stress attributable to hot temperature, while elders with DM
45 and CSD were vulnerable to both hot and cold temperatures.
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1 **Conclusions:**

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3 Elders with pre-existing health conditions were more vulnerable to excess mortality risk to
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6 hot and/or cold temperature. Preventative measures should target on elders with chronic
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9 health problems.
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14 **Keywords:** Distributed lag nonlinear model; Elders; Medical condition; Mortality;
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17 Temperature; Nested case-control study
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1 **List of abbreviations and their full forms**
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5 Abbreviations	6 Full form
7 DLNM	8 The distributed lag nonlinear model
9 CI	10 Confidence interval
11 COPD	12 Chronic obstructive pulmonary disease
13 BMI	14 Body mass index
15 ICD-9	16 Ninth revision of the international classification of diseases
17 PM _{2.5}	18 Particulate matter with aerodynamic diameter less than or equal to 2.5 μm
19 TPU	20 Tertiary planning unit
21 AIC	22 Akaike information criterion
23 DM	24 Diabetes mellitus
25 CSD	26 Circulatory system diseases
27 NDG	28 Non-disease group
29 SD	30 Standard deviation
31 RR	32 Relative risk

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1 **List of Tables and Figures**
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4 **Table 1.** Baseline characteristics of the participants, according to pre-existing health
5 conditions in the prospective Chinese elderly cohort in Hong Kong (n=61,441).
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8 **Table 2.** All natural mortality after 10-13 years of following up at the end of study in 2011 by
9 pre-existing health conditions.
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12 **Table 3.** The cumulative relative risks of cold and hot effects on all natural mortality in elders
13 with pre-existing diseases along lag days.
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16 **Fig. 1.** The estimated relative risk of temperature centered at median (24.7 °C) on all natural
17 mortality over 21 days for subjects with different pre-existing diseases. NDG: non-disease
18 group; DM: diabetes mellitus; CSD: circulatory system diseases; COPD: chronic obstructive
19 pulmonary disease.
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23 **Fig. 2.** The estimated relative risk of cold temperature effects [a decrease from 25th percentile
24 of temperature (19.5 °C) to 10th percentile of temperature (16.2 °C)] and hot effects [an
25 increase from 75th percentile of temperature (27.8 °C) to 90th percentile of temperature (29.4
26 °C)] on all natural mortality over 21 days of lag. NDG: non-disease group; DM: diabetes
27 mellitus; CSD: circulatory system diseases; COPD: chronic obstructive pulmonary disease.
28 The solid lines are mean relative risks, and grey regions are 95% CIs.
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1 **1. Introduction**

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3 Climate change is likely to bring extreme temperature events more frequently with increased
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6 intensity and widespread distribution. It was observed that global warming not only increased
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9 the frequency of heat waves, but also led to increase in cold spells with a steeper rate than in
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11 hot spells from 1981 to 2010 worldwide (Song et al., 2013). Temperature extremes had short-
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13 term adverse impacts on health in that heat waves were associated with increased mortality,
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15 hospital admissions, and emergency room visits (Astrom et al., 2011; Khalaj et al., 2010;
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17 Knowlton et al., 2009; Williams et al., 2012). However, only a few studies have assessed the
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20 effects of cold temperature (Medina-Ramon and Schwartz, 2007; Medina-Ramon et al., 2006;
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23 Ou et al., 2013; Rocklov et al., 2014).
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31 Extreme temperature events affect vulnerable populations most, amplifying social disparities
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33 in health, both within and between countries (Meehl and Tebaldi, 2004). Understanding
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35 susceptibility to extreme temperature is of importance in environmental public health
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38 researches (Anderson and Bell, 2009; Gasparrini, 2014). However, there were few studies for
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40 effects of thermal stress on susceptible subgroups (Astrom et al., 2015; Bateson and Schwartz,
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42 2004; Ma et al., 2015), fewer were studies for effects of cold temperature and in persons with
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45 medical conditions. This may be due to: a lack of personal information to define susceptible
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48 groups in conventional studies with ecological designs (e.g. time-series, case-crossover, or
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51 case-only approaches); a lack of suitable statistical methods to assess effect modifiers of
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54 time-varying exposure in studies with cohort design; also the difficulties encountered in
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57 analyzing nonlinear and delayed effects for the relationship between temperature and
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1 mortality.

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6 Among studies to explore whether medical conditions may confer susceptibility to
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9 temperature, most of them did not directly assess effects in persons with pre-existing health
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11 problems but instead indirectly through assessing mortality outcomes for specific causes
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13 (Atsumi et al., 2013) . This approach is not appropriate, since the underlying cause of death
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15 may not necessarily provide the information of existing medical conditions before death. For
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17 example, people died from cardiovascular diseases may have diabetes mellitus and persons
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19 with diabetes mellitus not be reflected in the underlying cause. Thus vulnerability of persons
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21 with specific health problems cannot be assessed.
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31 In the study, we aimed to assess the nonlinear and delayed mortality effects of cold or hot
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33 temperature among elders in a prospective Chinese elderly cohort in Hong Kong, and to
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35 comparatively assess effect modification of pre-existing diseases.
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42 **2. Methods**

43 *2.1. Study subjects*

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45 We included a total of 66,820 adults aged 65 years or older (≥ 65 years), about 9 % of people
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47 aged ≥ 65 years in Hong Kong, who enrolled at one of the eighteen Elderly Health Centres of
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49 the Department of Health from 1998 to 2001 and followed up until 31st of December 2011.
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54 Body mass index (BMI) was collected by physical examinations, and socio-economic
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56 conditions, lifestyle characteristics (smoking, physical activity, education), and morbidity
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1 status were collected by face-to-face interview during enrolment and follow-up visits by
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3 registered nurses (Schooling et al., 2014; Wong et al., 2015). Ethics approval was obtained
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6 from the Ethics Committee of the Faculty of Medicine, The University of Hong Kong and of
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9 the Department of Health of Hong Kong.

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14 Self-reported active chronic disease was collected through face-to face interview, which
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17 included hypertension, heart diseases, stroke, diabetes mellitus, and COPD and/or asthma.

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20 Self-reports of chronic diseases were confirmed and supplemented by clinical diagnoses
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23 based on history (Schooling et al., 2006). All natural mortality was coded as 1-799 according
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26 to the International Classification of Diseases, Ninth revision (ICD-9) before 2001 or A00-
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29 R99 based on ICD-10 from 2001 by the Department of Health. Subjects who died within the
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31 first year after recruitment were excluded from our analysis.

32 33 34 35 36 *2.2. Air pollutants and meteorological data*

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39 We obtained air pollutants data of ten general monitoring stations from Environmental
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42 Protection Department of Hong Kong from 1999 to 2011. We took daily 24-hour average
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45 concentration of particulate matter with aerodynamic diameter less than or equal to 2.5 μm
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48 ($\text{PM}_{2.5}$) and nitrogen dioxide (NO_2), and daily 8-hour (10:00-18:00 hours) average
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51 concentration of ozone (O_3). Data were regarded as missing if numbers of hourly
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54 concentration for one particular day were less than 75 % (18 hours for $\text{PM}_{2.5}$ and NO_2 , and 6
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57 hours for O_3). Daily concentrations of air pollutants were evaluated by averaging the daily
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60 concentrations across all valid monitoring stations.

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3 Daily mean air temperature and relative humidity in percent were measured by digital
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6 thermometers with platinum resistance sensors at the Hong Kong Observatory. The historical
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9 temperature data have been used in the previous population studies of temperature effects in
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12 Hong Kong (Goggins et al., 2015; Yi and Chan, 2014).
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14 15 16 17 *2.3. Statistical analysis* 18

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20 The nested case-control design employs a case-control approach within an established cohort
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23 to obtain estimates from a sample of the cohort that are similar to estimates obtained from
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26 analysis of the entire cohort (Goldstein and Langholz, 1992). This design has become popular
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29 because it allows for computationally efficient analysis of data from a cohort with substantial
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32 savings in cost and time; it is a useful alternative for cohort analysis with studying time-
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35 varying exposures (Essebag et al., 2005). The nested case-control design has already been
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38 used to studying time-varying exposure, such as PM_{2.5} (Beverland et al., 2012).
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42 In this study, we used nested case-control design to assess short-term effects of temperature.
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45 We constructed nested case-control data sets as follows: (1) controls selected randomly from
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48 among the cohort subjects whose follow-up time at least as long as the case for each death in
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51 the cohort; (2) the associated date of controls (the date when the control reached the exact
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54 follow-up time as the case) was in the same calendar year and month as the death date of case
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57 to control long-term trend and seasonality; (3) the date of birth of controls was within 1
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60 calendar year of the date of birth of the case. We excluded controls when associated date was
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1 outside the follow-up period of the cohort. We randomly selected 9 controls to each case from
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3 all eligible subjects in the cohort (Beverland et al., 2012). For all participants (including
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5 persons with and without morbidity status), about 98% of cases had the full complement of 9
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7 controls, and for diabetes mellitus (DM), circulatory system diseases (CSD), chronic
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9 obstructive pulmonary disease (COPD), and non-disease group (NDG), about 92%, 97%,
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11 80%, and 93.4% respectively.
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20 Temperature appears a nonlinear and delayed relationship with mortality (Guo et al., 2011). A
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22 distributed lag nonlinear model (DLNM) has been developed based on a “cross-basis”
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24 function, which allows simultaneously estimate the nonlinear and delayed effects of
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26 temperature on mortality or morbidity in time-series data, and this approach was expanded to
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28 apply to cohort study recently (Gasparrini, 2014).
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36 We used conditional logistic regression to incorporate a DLNM in a nested case-control study
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38 design to assess the nonlinear and delayed mortality effects of temperature among subjects in
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40 a prospective Chinese elderly cohort, and to comparatively examine the effect modification of
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42 morbidity status and the extent of mortality displacement related to high temperature.
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$$\text{logit } P = T_{t,l} + b_1 X_i + b_2 X_i(t) + \text{Strata}(\text{strata}) \quad (1)$$

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55 where t is the day of death for case or an associated day of each control; $T_{t,l}$ is a matrix
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57 obtained by applying the DLNM to temperature, and l is the number of lag days; X_i is the
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1 vector of time-independent variables, including individual-level factors: gender, BMI (three
2 levels), smoking (three levels), physical exercise (four levels), education (three levels),
3 tertiary planning unit (TPU)-level factors: proportion of the population ≥ 65 years of age,
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5 proportion with tertiary education, and the average monthly income in each TPU, and district
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7 level factor: proportion of smokers in each district; $X_i(t)$ is the vector of time-dependent
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9 variables, including dummy variable of day of the week on day t , and natural cubic B-splines
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11 with 3 d.f. for relative humidity (Guo et al., 2011; Stafoggia et al., 2008). β_1 and β_2 are
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13 vectors of coefficients for time-independent and time-dependent variables; *Strata* (*strata*) is a
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15 categorical variable of each risk set.
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28 $T_{t,l}$ in model (1) was the term to estimate both the nonlinear and delayed effects of
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30 temperature. In order to completely capture the overall effects of temperature, we extended
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32 lags up to 21 days. We placed knots of natural cubic B-splines at equal intervals on the log
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34 scale of lags. We placed knots of natural cubic B-splines at equal spaces in the range of
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36 temperature, which was from 1999 to 2011. Minimum Akaike Information Criterion (AIC)
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38 was used to guide selection of the d.f. (knots) for temperature and lag days (Gasparrini,
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40 2014). It was found that using one knot for temperature and one knot for lag days produced
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42 the best model fit for all disease categories in the present study.
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53 To examine the extreme cold effect, we calculated the relative risk of all natural mortality
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55 associated with a decrease from 25th percentile of temperature (19.5 °C) to 1st percentile of
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57 temperature (11.3 °C); and the relative risk associated with a decrease from 25th (19.5 °C) to
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1 10th (16.2 °C) was used to represent the moderate cold effect (Goldberg et al., 2011; Guo et al.,
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3 2012). Meanwhile, we calculated the relative risk of all natural mortality associated with
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5 temperature increased from 75th (27.8 °C) to 99th (30.4 °C), and from 75th (27.8 °C) to 90th
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7 (29.4 °C) to represent the extreme and moderate hot effect, respectively. Cumulative effects
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9 over 0-21 days and the relative risk along the lags for both cold and hot temperatures were
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11 examined and plotted, the mortality displacement was assessed as well.
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20 The following sensitivity analyses were conducted to examine the robustness of the effect
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22 estimates:
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25 1. Random selection of 5, 7, and 12 controls for each case from all eligible subjects in
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27 the cohort;
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31 2. Adjustment for each of the three air pollutants PM_{2.5}, NO₂, and O₃ in the main
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33 temperature model as a natural cubic B-splines function with 3 d.f. (Guo et al., 2011);
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37 3. Time-stratified case-crossover study design incorporated with DLNM to estimate
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39 temperature mortality effects, in that controls were selected with the same year, month,
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41 and weekday as the case.
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45 4. Increasing the number of knots for both temperature and lag days to 2;
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50 Mortality risks associated with temperature between subjects with pre-existing health
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52 conditions and NDG were compared based on calculated Z-score and corresponding one-
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54 sided *p*-Value (Altman and Bland, 2003). Other statistical tests were all two-sided, and values
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56 of *p*<0.05 were considered statistically significant. We used the SAS version 9.2 software
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1 package to construct the dataset of nested case-control study. We used R software (version
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3 3.1.2; R Development core team 2014) to fit all models, with its “dlnm” package (version
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5 2.1.3) to perform distributed lag nonlinear models (Gasparrini et al., 2010). The SAS and R
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8 code used are available in Supplementary Material.
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10 11 12 13 14 **3. Results** 15

16 17 *3.1. Descriptive statistics* 18

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20 A total of 66,820 subjects were recruited in the prospective Chinese elderly cohort of Hong
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22 Kong. After excluding subjects who died within first year post recruitment and subjects with
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24 missing data, 61,441 were left in our final analysis. Table 1 shows the baseline characteristics
25
26 of participants, stratified according to pre-existing active diseases. The characteristics of the
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28 subjects were similar in most respects across pre-existing active disease groups. But subjects
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30 with COPD tended to be more smokers (quitted or current), older and less females when
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32 compared with other morbidity subgroups. Mean age at enrollment was 72 years. About two
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34 third (66%) of subjects were female; a major part of subjects had never smoked (71.3%), and
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36 did exercise more than six times per week (72.1%).
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53 Among 61,441 subjects at recruitment, 47.3% subjects reported to have CSD, 14.2% to have
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55 DM, 6.2% to have COPD, and 45.4% subjects reported they did not have those three diseases
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57 (NDG). After 10-13 years of following up till the end of the study on 31 December 2011,
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1 16,497 (26.9%) subjects died among which 1,855 were subjects with COPD, 3,024 were
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3 subjects with DM, 9,070 were with CSD, and 5,809 were NDG. The corresponding death
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5 rates were 48.4%, 34.6%, 31.2% and 20.8, respectively (Table 2).
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11 [Table 2 here]
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17 *3.2. Cumulative effects of cold and hot temperatures*

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19 Table 3 presents the cumulative relative risks of extreme cold effects (decreasing from 25th to
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21 1st percentile of mean temperature), moderate cold (decreasing from 25th to 10th percentile),
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23 moderate hot (increasing from 75th to 90th percentile), and extreme hot (increasing from 75th
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25 to 99th percentile) on all natural mortality for subjects with different pre-existing diseases.
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29 The cumulative effects of cold temperatures over longer lags were greater than effects over
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31 0-3 lag days for all subjects and subgroups with DM and CSD, while the cumulative effects
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33 of hot temperatures didn't vary much along the lags, except for subjects with DM.
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42 Compared with the temperature at 25th percentile (19.5 °C), the relative risks of extreme cold
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44 temperature (1st percentile of temperature, 11.3 °C) over lag 0-21 days were 2.21 (95% CI:
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46 1.19, 4.10) for DM, 1.59 (1.12, 2.26) for CSD, 1.23 (0.53, 2.84) for COPD, and 1.49 (1.15,
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48 1.93) for all subjects respectively, while 1.04 (0.59, 1.85) for NDG. Compared with the
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50 temperature at 75th percentile (19.5 °C), the relative risks associated with extreme hot
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52 temperature (99th percentile of temperature, 30.4 °C) over lag 0-3 days were 1.05 (95% CI:
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54 0.94, 1.17) for DM, 1.06 (0.99, 1.12) for CSD, 1.14 (0.98, 1.32) for COPD, and 1.01 (0.97,
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1 1.06) for all subjects respectively. We did not observe any significant association between
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3 cold/hot temperatures and all natural mortality in NDG.
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8 9 *3.3. Comparisons with NDG*

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11 When compared with NDG over the same lag periods, the cumulative cold effects over 0-13
12 lag days were significantly greater for elders with DM ($p<0.05$), for elders with CSD ($p<0.1$)
13 and for all subjects ($p<0.1$), while the cumulative hot effects over 0-3 lag days appeared
14 significant greater for subjects with COPD and CSD ($p<0.05$), and subjects with DM ($p<0.1$).
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16 Results showed that subjects with DM and CSD exhibited greater vulnerability to both cold
17 and hot weather, while subjects with COPD had excess mortality risk attributable to hot
18 temperature (Table 3).
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37 *3.4. Temperature-lag-mortality relationships*

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39 The 3-dimensional plots show the distributed lag and non-linear relationship between all
40 natural mortality and temperature for subjects with different morbidity status at all lag days
41 (see Supplementary Material, Fig. S1). The overall temperature-mortality relationships in
42 general were U-shaped over all 21 days with increased health effects in both cold and high
43 temperatures. Overall cold temperature effects were much higher than hot effects (Fig. 1).
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56 [Figure 1 here]
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1 Generally, cold temperature effects were delayed and lasted for about 20 days, while hot
2 effects were immediate and lasted for less than 5 days. Cold temperature effects were delayed
3 for subjects with COPD and CSD, but not for subjects with DM (Fig. 2). Furthermore,
4 mortality displacement related to hot temperature was not found in subjects with DM.
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17 [Figure 2 here]
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22 3.5. Sensitivity analysis

23 For results of sensitivity analysis, in general, the mortality effects of temperature become
24 stable when more than 7 controls were selected for each case (see Supplementary Material,
25 Table S1 to Table S3). When increasing number of knots for both temperature and lag days to
26 two, or controlling for each of the three air pollutants (PM_{2.5}, NO₂, and O₃) or using time-
27 stratified case-crossover study design to estimate temperature mortality effects, the effect
28 estimates remained similar (see Supplementary Material, Table S4 to Table S6).
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44 4. Discussion

45 To the best of our knowledge, this is the first study to assess the nonlinear and delayed
46 mortality effects of cold or hot temperature for persons with baseline existing health problem
47 in a cohort. The major findings of this study are: (1) persons with pre-existing disease are
48 more vulnerable to hot and/or cold temperature; (2) cold temperature effects are more
49 pronounced than hot temperature effects; and (3) cold temperature effects are delayed and
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1 persist for about 20 days, while hot effects are immediate and last for shorter period.
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6 *4.1. Mortality risks of temperature* 7

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9 To date several studies have examined the temperature-mortality relationship worldwide
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11 (Basu, 2009; Gasparrini et al., 2012; Hajat et al., 2005; Hajat et al., 2010; Nordio et al., 2015),
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13 but few focused on persons with pre-existing active diseases were based on case-only study
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15 design (Khalaj et al., 2010; Medina-Ramon et al., 2006; Schwartz, 2005; Zanobetti et al.,
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17 2013). The major disadvantage of case-only study to identify susceptible subgroups is that the
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19 excess risk of mortality associated with extreme temperatures in each subpopulation cannot
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21 be estimated on its own, but only relative to other subpopulations. Consequently, we cannot
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23 obtain absolute effects of extreme temperature in a susceptible subgroup.
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33 Indeed we did not find any studies that assessed absolute mortality effects of temperature for
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35 persons with existing diseases directly. In addition, the magnitude of temperature effects
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37 varies greatly by climate, region, and population (Curriero et al., 2002). To avoid these
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39 variations, we compared temperature mortality effects for all subjects (including persons with
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41 or without morbidity) with previous studies conducted in Hong Kong. We compared with the
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43 study of Xu et al. (2013), who used the same cohort data, and reported that hot temperature
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45 effects were non-significant ($p < 0.05$) at lag 0-1 for all natural mortality, which were
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47 consistent with our results. Cold temperature effects are usually delayed and lasting for a few
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49 weeks, thus we compared our results with the study of Yi and Chan (2014), who used quasi-
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51 Poisson model combined with a DLNM in time-series study design, and reported that cold
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1 effects in terms of relative risk for decrease in temperature from 1st to 25th percentile at lag 0-
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3 13 and lag 0-21 for subjects aged older than 75 years was 1.37 (1.26, 1.47) and 1.41 (1.35,
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5 1.51), respectively. These results were comparable with results of our study (mean age of
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7 subjects at baseline was 72 years, and followed up for 10 to 13 years).
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12 Our results suggest that persons with DM increase susceptibility to both cold and hot
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14 temperature. These findings agree with study conducted in two Chinese cities (Harbin and
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16 Chongqing), which showed significant associations between both extreme hot and cold
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18 temperatures and DM mortality (Li et al., 2014). Most studies reported that people with DM
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20 have a high risk of death (Medina-Ramon et al., 2006; Schwartz, 2005; Zanobetti et al., 2013),
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22 hospitalizations (Knowlton et al., 2009), and emergency department visits (Khalaj et al., 2010)
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24 during heat wave or in high temperature, but few have indicated that persons with DM are
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26 sensitive to cold temperature (Li et al., 2014). Mortality displacement is of public health
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28 importance, and it has been well documented in the literature that hot effects appear more
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30 acute and followed by harvesting (Hajat et al., 2005; Qiao et al., 2015). A novel finding of our
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32 study is that mortality displacement related to hot temperature was not found in subjects with
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34 DM, which suggests that persons with DM are at risk of premature death associated with
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36 hotter temperature. Temperature not only can have an impact on very frail individual but also
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38 on relatively healthy persons who have DM.
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56 DM is characterized by a chronic state of low-grade inflammation, endothelial dysfunction,
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58 and hypercoagulability (Luchsinger et al., 2001), and it has already been reported that several
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1 factors, such as oxidative stress and protein kinase C, may contribute to macrovascular injury
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3 from hyperglycemia. When exposed to extreme temperatures, blood vessels dilate or constrict
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5 in order to maintain body temperature. The increased demands on the circulatory system
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7 interact with those injured vasculature would increase risk of fatal events (Hajat et al., 2005;
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9 Idris et al., 2006). Thus, it is biological plausible that persons with DM may increase
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11 susceptibility to both cold and hot temperature.
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20 Our results showed that subjects with CSD were at higher risk of death from hot temperature,
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22 and also suggested higher mortality risk from cold temperature, which have been consistently
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24 confirmed by previous studies using cause-specific mortality (Gasparri et al., 2012; Ma et
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26 al., 2011; Ma et al., 2013; Medina-Ramon et al., 2006). In order to adapt to heat when
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28 exposed to hot temperature, cardiac output shapely increased primarily by increased heart
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30 rate, which put a great burden to heart (Rowell, 1974). Cold temperature can increase heart
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32 rate, blood pressure, peripheral vasoconstriction, plasma fibrinogen concentration, blood
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34 cholesterol level, platelet viscosity, and red cell count (Keatinge et al., 1984), which changes
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36 may predispose the subjects to arterial thrombosis and lead to heart attack and stroke or even
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38 death (Atsumi et al., 2013; Mercer, 2003; Nayha, 2002).
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50 In our study, we found mortality displacements related to hot effects for subjects with CSD
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52 and COPD, but they were not statistically significant. Previous studies have indicated that
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54 mortality displacement related to hot stress was more strongly associated with deaths from
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56 cardiovascular and respiratory diseases than all natural mortality (Goodman et al., 2004;
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1 Hajat et al., 2005). Qiao et al. (2015) reported mortality displacement for respiratory deaths
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3 was more immediate and greater than cardiovascular deaths, which were also similarly shown
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6 in our findings.
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11 We found persons with COPD were susceptible to increased risk of mortality when exposed
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13 to hot temperature, but not to cold temperature. This findings are consistent with findings of
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15 Schifano et al. (2009) and Michelozzi et al. (2009) who reported that people with COPD have
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17 increased mortality and hospital admissions when exposed to high temperature, and
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20 consistent with findings of Medina-Ramon et al. (2006), Ma et al. (2013), and Astrom et al.
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22 (2015) who did not find higher mortality risks when exposed to cold temperature. But our
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24 results are conflict with findings of Schwartz (2005) who showed that persons with COPD
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26 had higher mortality risks attributable to extreme cold temperature than persons did not have
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28 that condition in a case-only study. One possible explanation might be that persons with
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30 COPD were more likely to confine to bed or stay in homes during cool seasons.
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42 *4.2. The nested case-control study design and DLNM*

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44 Many study designs have been used in assessing health effects of temperature on mortality
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46 and morbidity, such as case-crossover (Guo et al., 2011; Medina-Ramon and Schwartz, 2007),
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48 time-series (Anderson and Bell, 2009; Wu et al., 2013), and Bayesian hierarchical models
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50 (Anderson et al., 2013; Bobb et al., 2014). Generally, these study designs are using
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52 aggregated data with the limitation of not being able in identifying more potential modifiers
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54 of exposures (e.g. temperature, air pollutants). However, cohort study can record detailed
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1 individual information (e.g. demographic characteristics, socioeconomic position, lifestyle,
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3 social functional status), and has a great potential to thoroughly explore modifiers of
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5 exposure effects. Basically, nested case-control design is a type of case-control design nested
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7 in a cohort study. This study design has been widely used (Lin et al., 2015; Olsson et al.,
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9 2010; Sawada et al., 2010) due to its being able to control for long-term trend and seasonality
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11 by study design through matching, which is particular useful when studying time-varying
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13 exposure. The nested case-control design is a useful alternative to Cox regression to analyze
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15 time-varying exposure, due to similar risk estimates with superior computational efficiency
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17 (Essebag et al., 2005).
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28 One of the main advantages of DLNM is that it allows the model to contain detailed
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30 representation of exposure-response relationship. This in turn provides an estimate of the
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32 overall effect in the presence of delayed contributions or harvesting with constraint on lag
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34 days to resolve the high correlation between exposures in adjacent days and the resulting
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36 collinearity in the model (Gasparrini et al., 2010; Zanobetti et al., 2002). Therefore, applying
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38 DLNM in a nested case-control is applicable to estimate health effects of time-varying
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40 exposure as well as mortality displacement in a cohort.
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50 This is the first attempt to assess mortality effects of temperature after incorporating DLNM
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52 to a nested case-control study design. This method has potential applications to identify
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54 modifiers of time-varying exposure (e.g. temperature, air pollutants) on morbidity and
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56 mortality. For instance, our approach can be applied to explore whether people living in high-
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1 polluted areas has a higher risk to thermal stress than people living in low-polluted areas.
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6 Our study has some limitations. First, medical conditions were self-reported, thus it is subject
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9 to misclassification. Second, our cohort subjects being older than 65 years at recruitment may
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12 have multiple health problems, which may not reflect the specific modifying effect of certain
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15 existing disease. However, subjects with DM may probably comorbid with CSD or
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18 respiratory diseases, the higher cold risk in this group confirms that persons with diabetes
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21 mellitus may be susceptible to excess mortality risk associated with temperature stress. Last
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24 but not least, the subjects were volunteers; however, in Hong Kong, the enrolment to the
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27 Elderly Health Service is free and open to all residents who are 65 years or older. Thus, the
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30 sample would be representative of the elderly population in Hong Kong (Schooling et al.,
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33 2006). Even if the enrolment is subject to volunteer bias, that bias is towards those who are
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36 health conscious, our results tend to be conservative.
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39 **5. Conclusions**

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42 DLNM can be applied in a nested case-control study design in a cohort to estimate nonlinear
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45 and delayed effects of time-varying exposure (e.g. temperature). Mortality effects of cold
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48 temperature may be more pronounced than hot temperature. Elders with pre-existing health
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51 conditions are more vulnerable to excess mortality risk at short-term exposure to hot and/or
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54 cold temperature. Our study provides evidence to enhance protection of the vulnerable ones.
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1 **Conflicts of interest**

2
3 The authors declare no conflicts of interest.
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Table 1. Baseline characteristics of the participants, according to pre-existing health conditions in the prospective Chinese elderly cohort in Hong Kong (n=61,441).

Characteristic	Pre-existing diseases				
	NDG	DM	CSD	COPD	All subjects
Individual-level					
Age in year (mean ± SD)	71.5 ± 5.5	71.9 ± 5.2	72.4 ± 5.6	73.3 ± 5.7	72.0 ± 5.6
Sex (%)					
Male	33.2	33.0	33.3	49.3	33.9
Female	66.8	67.0	66.7	50.7	66.1
BMI (%)					
1 st (<21.6)	50.6	52.7	51.2	45.3	50.8
2 nd - 3 rd (21.6-26.3)	28.5	15.2	16.5	31.2	22.8
4 th (>26.3)	20.9	32.0	32.3	23.5	26.3
Smoking (%)					
Never	71.7	72.9	72.9	43.7	71.3
Quitted	17.2	19.5	19.8	37.9	19.2
Current	11.1	7.5	7.2	18.3	9.5
Exercise (%)					
Never	16.5	13.3	14.0	16.7	15.2
<4	7.3	6.8	6.7	6.8	7.0
4-6	5.7	5.7	5.6	5.8	5.7
>6	70.4	74.2	73.7	70.7	72.1
Education (%)					
Post-secondary	3.8	3.6	3.7	3.1	3.7
Secondary	13.3	13.6	13.7	11.7	13.5
Primary	37.0	35.8	36.5	39.5	36.9
Below primary	45.8	47.0	46.1	45.7	46.0
TPU-level					
Age ≥ 65 (%)	12.1	12.2	12.2	12.1	12.1
Tertiary education (%)	12.9	12.9	13.1	12.2	13.0
Income ≥ US\$1,923/m (%)	59.5	59.5	59.6	58.6	59.5
District-level					
Smoking rate (%)	11.5	11.6	11.6	11.6	11.6

Abbreviations: BMI, body mass index; TPU, tertiary planning unit; NDG: non-disease group; DM: diabetes mellitus; CSD, circulatory system diseases; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Table 2. All natural mortality after 10-13 years of following up at the end of study in 2011 by pre-existing health conditions.

Morbidity status	No. of subjects	No. of death	%
NDG	27890	5809	20.8
DM	8752	3024	34.6
CSD	29081	9070	31.2
Hypertension	25154	7712	30.7
Heart	8164	2899	35.5
Stroke	1745	764	43.8
COPD	3829	1855	48.4
All subjects	61441	16497	26.9

Abbreviations: NDG: non-disease group; DM: diabetes mellitus; CSD, circulatory system diseases; COPD, chronic obstructive pulmonary disease.

Table 3. The cumulative relative risks of cold and hot effects on all natural mortality in elders with pre-existing diseases along lag days.

Pre-existing disease	Lag (day)	Extreme cold ^a	Moderate cold ^b	Moderate hot ^c	Extreme hot ^d
NDG	0-1	0.98 (0.84, 1.13)	1.00 (0.95, 1.05)	0.98 (0.95, 1.02)	0.97 (0.91, 1.04)
	0-3	0.96 (0.76, 1.22)	1.00 (0.92, 1.08)	0.97 (0.91, 1.03)	0.95 (0.86, 1.06)
	0-13	0.97 (0.64, 1.49)	1.01 (0.88, 1.15)	0.96 (0.87, 1.05)	0.93 (0.79, 1.09)
	0-21	1.04 (0.59, 1.85)	1.02 (0.86, 1.22)	0.97 (0.86, 1.10)	0.96 (0.78, 1.17)
DM	0-1	1.11 (0.95, 1.29)	1.03 (0.98, 1.08)	1.02 (0.98, 1.06) [#]	1.03 (0.96, 1.11)
	0-3	1.22 (0.95, 1.56) [#]	1.06 (0.98, 1.14)	1.03 (0.96, 1.10)	1.05 (0.94, 1.17) [#]
	0-13	1.77 (1.12, 2.80)[*]	1.20 (1.04, 1.38)[*]	1.03 (0.93, 1.14)	1.06 (0.89, 1.25)
	0-21	2.21 (1.19, 4.10)[*]	1.25 (1.03, 1.51)[#]	1.12 (0.99, 1.27) [#]	1.22 (0.98, 1.50) [#]
CSD	0-1	1.05 (0.96, 1.14)	1.01 (0.98, 1.04)	1.02 (1.00, 1.05) [*]	1.04 (1.00, 1.08) [*]
	0-3	1.09 (0.95, 1.26)	1.02 (0.97, 1.07)	1.03 (0.99, 1.07) [#]	1.06 (0.99, 1.12) [*]
	0-13	1.34 (1.04, 1.74)[#]	1.11 (1.02, 1.20)[*]	0.99 (0.93, 1.05)	0.99 (0.89, 1.09)
	0-21	1.59 (1.12, 2.26)[*]	1.16 (1.04, 1.29)[*]	1.02 (0.95, 1.10)	1.03 (0.91, 1.17)
COPD	0-1	1.08 (0.88, 1.31)	1.01 (0.94, 1.07)	1.05 (1.00, 1.11) [*]	1.09 (0.99, 1.20) [*]
	0-3	1.15 (0.84, 1.58)	1.02 (0.92, 1.13)	1.08 (0.99, 1.18) [*]	1.14 (0.98, 1.32) [*]
	0-13	1.37 (0.76, 2.48)	1.10 (0.91, 1.32)	1.03 (0.89, 1.18)	1.05 (0.82, 1.33)
	0-21	1.23 (0.53, 2.84)	1.04 (0.81, 1.35)	1.07 (0.90, 1.28)	1.12 (0.83, 1.52)
All subjects	0-1	1.02 (0.96, 1.09)	1.00 (0.98, 1.03)	1.01 (0.99, 1.02) [#]	1.01 (0.98, 1.04)
	0-3	1.05 (0.95, 1.17)	1.01 (0.98, 1.05)	1.01 (0.98, 1.03)	1.01 (0.97, 1.06)
	0-13	1.30 (1.07, 1.57)[#]	1.10 (1.03, 1.17)[*]	0.98 (0.94, 1.02)	0.97 (0.90, 1.04)
	0-21	1.49 (1.15, 1.93)[*]	1.14 (1.06, 1.24)[*]	1.00 (0.95, 1.06)	1.00 (0.92, 1.10)

Abbreviations: NDG: non-disease group; DM: diabetes mellitus; CSD, circulatory system diseases; COPD, chronic obstructive pulmonary disease.

^a A decrease from 25th percentile of temperature (19.5 °C) to 1st percentile of temperature (11.3 °C);

^b A decrease from 25th percentile of temperature (19.5 °C) to 10th percentile of temperature (16.2 °C);

^c An increase from 75th percentile of temperature (27.8 °C) to 90th percentile of temperature (29.4 °C);

^d An increase from 75th percentile of temperature (27.8 °C) to 99th percentile of temperature (30.4 °C).

^{*}: Compared with NDG in the same lag period, p -Value < 0.05;

[#]: Compared with NDG in the same lag period, $0.05 \leq p$ -Value < 0.1.

Figure legends

Fig. 1. The estimated relative risk of temperature centered at median (24.7 °C) on all natural mortality over 21 days for subjects with different pre-existing diseases. NDG: non-disease group; DM: diabetes mellitus; CSD: circulatory system diseases; COPD: chronic obstructive pulmonary disease.

Fig. 2. The estimated relative risk of cold temperature effects [a decrease from 25th percentile of temperature (19.5 °C) to 10th percentile of temperature (16.2 °C)] and hot effects [an increase from 75th percentile of temperature (27.8 °C) to 90th percentile of temperature (29.4 °C)] on all natural mortality over 21 days of lag. NDG: non-disease group; DM: diabetes mellitus; CSD: circulatory system diseases; COPD: chronic obstructive pulmonary disease. The solid lines are mean relative risks, and grey regions are 95% CIs.

Figure1

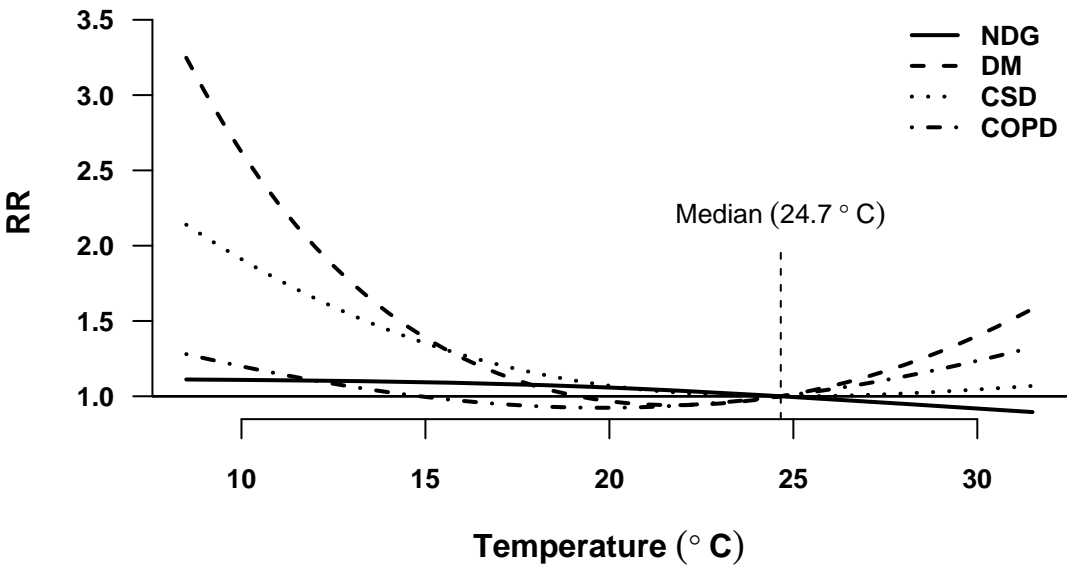


Figure 2

