

1 **Who is more Vulnerable to Death from Extremely Cold Temperatures?**
2 **A Case-Only Approach in Hong Kong with a Temperate Climate**

3
4 Hong Qiu ^a, Linwei Tian ^{a*}, Kin-fai Ho ^b, Ignatius T.S. Yu ^c, Thuan-Quoc Thach ^a, Chit-
5 Ming Wong ^a

6 ^a: School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong
7 Kong. ^b:The Jockey Club School of Public Health and Primary Care, The Chinese
8 University of Hong Kong. ^c: Hong Kong Occupational and Environmental Health
9 Academy.

10 **Type of manuscript:** Original Article

11 **Running Title:** Effect Modification on Extreme Cold Associated Mortality

12 *** Corresponding author:**

13 Dr. Linwei Tian, School of Public Health, Li Ka Shing Faculty of Medicine, The University
14 of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong. Phone: (+852)2831 5071; Fax:
15 (+852) 2855 9528 Email: linweit@hku.hk.

16 **The authors declare that they have no competing interests.**

17 **Funding support:** None

18 **Key Words:**

19 Case-Only Study; Cause of Death; Effect Modifiers; Extreme Cold; Mortality

20 **Acknowledgements:**

21 The authors thank the Census and Statistical Department of Hong Kong for providing
22 mortality data, the Hong Kong Observatory for providing temperature data, and the Hong
23 Kong Environmental Protection Department for providing air pollution data.

24 **Authors' contributions:**

25 HQ, LWT, and ITY defined the research theme. HQ, LWT and KFH analyzed the data,
26 interpreted the results and wrote the paper. TQT and CMW co-worked on associated data
27 collection and their interpretation.

28

29 **Abstract**

30 Short-term effects of ambient cold temperature on mortality have been well documented in
31 the literature worldwide. However, less is known about which subpopulations are more
32 vulnerable to death related to extreme cold. We aimed to examine the personal
33 characteristics and underlying causes of death that modified the association between
34 extreme cold and mortality in a case-only approach. Individual information of 197,680
35 deaths of natural causes, daily temperature and air pollution concentrations in cool season
36 (November ~ April) during 2002 - 2011 in Hong Kong were collected. The extreme cold
37 was defined as those days with preceding week with a daily maximum temperature at or
38 less than the 1st percentile of its distribution. Logistic regression models were used to
39 estimate the effects of modification, further controlling for age, seasonal pattern and air
40 pollution. Sensitivity analyses were conducted by using the 5th percentile as cutoff point to
41 define the extreme cold. Subjects with age of 85 and older were more vulnerable to
42 extreme cold, with odds ratio (OR) of 1.33 (95%CI: 1.22-1.45). The greater risk of extreme
43 cold related mortality was observed for total cardiorespiratory diseases and several specific
44 causes including hypertensive diseases, stroke, congestive heart failure, COPD and
45 pneumonia. Hypertensive diseases exhibited the greatest vulnerability to extreme cold
46 exposure, with OR of 1.37 (95%CI: 1.13-1.65). Sensitivity analyses showed the robustness
47 of these effect modifications. This evidence on which sub-populations are vulnerable to the
48 adverse effects of extreme cold is important to inform public health measures to minimize
49 those effects.

50

51 **Key Words:**

52 Case-Only Study; Cause of Death; Effect Modifiers; Extreme Cold; Mortality

53 **Introduction**

54 Studies on the associations between extreme cold/hot temperatures and daily mortality have
55 been well documented in the literature (Curriero et al. 2002; Hajat et al. 2007; Analitis et
56 al. 2008; Basagaña et al. 2011; Chen et al. 2013; Guo et al. 2014). Researchers have found
57 that both cold and hot temperatures are associated with increased risk of mortality. In
58 general, cold effects are delayed and last for more than a few days, whereas heat effects
59 appear quickly and do not last long. At the same time, identification of factors that modify
60 the effects of extreme temperatures on mortality is also an issue of interest in the scientific
61 community. A greater susceptibility has been reported for the elderly and female (Hajat et
62 al. 2007; Analitis et al. 2008; Zhou et al. 2014; Zeng et al. 2014), and for those with lower
63 socioeconomic status (Armstrong 2003; Hajat et al. 2007; Xu et al. 2013). Regarding the
64 medical conditions and preexisting diseases that may confer susceptibility, results of
65 previous studies from different regions are geographically heterogeneous (Schwartz 2005;
66 Medina-Ramón et al. 2006; Madrigano et al. 2013; Zanobetti et al. 2013; Zhou et al. 2014).

67 Hong Kong is a subtropical city located on the southern coast of China, with hot summer
68 and milder winter. The associations of extremely cold and hot temperatures with the
69 increased risk of mortality (Chan et al. 2012; Goggins et al. 2013; Yi and Chan 2015) have
70 been studied. Authors found the heat-related mortality varied with sociodemographic
71 characteristics (Chan et al. 2012), and the cold-related mortality was greater among elders
72 and non-cancer patients (Goggins et al. 2013). However in these studies, researchers used
73 time series Poisson model to estimate the main temperature effect and stratified subgroup
74 analyses to assess the potential modification, where the comparisons among subgroups
75 were not conducted and the statistical power might have been reduced. As an alternative,
76 Armstrong BG in 2003 firstly proposed and applied the case-only approach to assess how
77 the fixed factors modified the effects of time varying factors in time series study
78 (Armstrong 2003). Being a simplified approach that reduces the vulnerability to model
79 miss-specification bias (Armstrong 2003; Zanobetti et al. 2013), case-only analysis has its
80 advantages over the conventional time series analysis on assessing the effect modification.

81 A greater effect of colder temperatures on mortality risk has been suggested in cities with
82 warmer winter (Curriero et al. 2002; Analitis et al. 2008), and studies conducted in warmer
83 areas with higher long-term mean temperatures tended more frequently to report
84 detrimental effects of cold (Bhaskaran et al. 2009). Hong Kong has hot summer and

85 temperate winter, with very high prevalence of air conditioner usage in summer but almost
86 no house heating in winter, so that the subjects might be more vulnerable to cold.
87 Identifying the most susceptible subpopulations would have great public health
88 implications in this region. In the current study, we aimed to use a case-only approach to
89 identify the time invariant individual factors that confer susceptibility to extreme cold
90 associated mortality, including personal social-demographic characteristics and specific
91 causes of death.

92

93 **Materials and Methods**

94 **Mortality Data**

95 Daily mortality data during the cool seasons (November-April) in 2002-2011 were obtained
96 from Census and Statistical Department of Hong Kong. Individual information included
97 personal characteristics such as age, sex, occupational status and marital status. Primary
98 causes of death were coded in *International Classification of Diseases, 10th version*. The
99 underlying causes of death examined in this study as potential modifiers included all
100 diseases of circulatory system (ICD-10: I00-I99), diseases of respiratory system (ICD-10:
101 J00-J99) and diabetes (ICD-10: E10-E14). Some specific causes of cardiorespiratory death
102 were also examined, including stroke (ICD-10: I60-I69), hypertensive diseases (HBP, ICD-
103 10: I10-I15), myocardial infarction (MI, ICD-10: I21, I22), congestive heart failure (CHF,
104 ICD-10: I50), cardiac arrest (ICD-10: I46), chronic obstructive pulmonary disease (COPD,
105 ICD-10: J40-J44, J47) and pneumonia (ICD-10: J12-J18).

106 **Temperature and Air Pollution Data**

107 The daily minimum, mean and maximum temperature from 2002 to 2011 was obtained
108 from the Hong Kong Observatory. The extremely cold days were defined as those days
109 with preceding week with a daily maximum temperature at or less than the 1st percentile of
110 its distribution in Hong Kong (Medina-Ramón et al. 2006). The calculation was based on
111 the temperature on the 7-day moving average of the day of death and the 6 preceding days
112 (lag06), as previous studies have suggested that mortality is more related to days following
113 a several days with on average low temperature than to a single day of cold (Saez et al.
114 1995), and the cold effect would last for longer days than hot effect (Guo et al. 2014).
115 Different cutoff point using daily maximum temperature at or less than the 5th percentile to
116 define the extremely cold days was also tried in the sensitivity analyses.

117 Air pollution concentrations in the same period were obtained from the Environmental
118 Protection Department of Hong Kong. We calculated the daily 24-hr mean concentrations
119 of PM₁₀ and NO₂, and daytime 8-hr (10:00-17:00) mean concentrations of O₃ for each
120 general monitoring, and then averaged them across the ten stations (Qiu et al. 2013). Air
121 pollutants would be acted as potential confounders in the data analysis.

122 **Analytic Method**

123 This is a case-only approach to assess how the association between extreme temperature
124 and mortality was modified by the personal characteristics and the specific primary causes
125 of death. The underlying idea behind this approach is that if a time invariant factor
126 increases the risk of dying on extremely cold (or hot) days, a greater proportion of people
127 who died during those periods would be expected to have this factor, compared with people
128 who died during milder weather conditions. Hence, if a characteristic is a risk modifier for
129 deaths during extremely cold days, then extreme cold exposure should be a predictor of the
130 occurrence of that characteristic on death certificates using logistic regression. Formal
131 proof of the approach was provided by Armstrong (Armstrong 2003). Several studies
132 followed this approach to identify the sensitive subpopulation who is more vulnerable to
133 die from extreme temperatures (Schwartz 2005; Medina-Ramón et al. 2006; Medina-
134 Ramón and Schwartz 2007; Zanobetti et al. 2013).

135 The validity of this approach depends on the assumption that the modifier and exposure are
136 independent, that is, not associated in the base population that gave rise to the deaths.

137 Because the personal characteristics vary among individuals but not fluctuate from day to
138 day variation of temperature, this assumption is clearly met in studies of ambient
139 temperature. Armstrong also suggested that the assumption that modifiers are fixed in time
140 could be relaxed to allow modifiers that change in time much more slowly than does the
141 temperature, such as age, chronic diseases, and some long-term treatments (Armstrong
142 2003). The case-only approach was proposed to analyze the effect modification but not the
143 main effect, and the motivation is simplification of modeling and reduced vulnerability to
144 model miss-specification bias.

145 As the personal characteristics such as gender, non-married marital status, and
146 economically inactive were all associated with old age, and Armstrong noted that
147 "Interaction of the time-varying factor of interest with another time-fixed variable" was
148 "almost certain to confound" an interaction of interest in a case-only analysis, we tried the

149 analyses by including the potential confounding of age as a four-level categorical variable
150 (age<65, age of 65-74, age of 75-84 and age>=85) in order to get the age-controlled
151 estimates of modification. Considering the possible interaction of the putative modifier
152 under investigation with other time-varying factors such as air pollutants, which would
153 confound the modification of interest (Armstrong 2003), we also did sensitivity analysis by
154 including air pollutants (PM₁₀, NO₂ and O₃) as additional indicators in the logistic
155 regression model. Furthermore, because of the baseline seasonal pattern of mortality, the
156 additional non-temperature related modifiers of risk by predisposing condition might be
157 captured by a sine and cosine term with 365.24-day period (Schwartz 2005). We therefore
158 included an annual sine-cosine pair to sufficiently control for a seasonal component that
159 might plausibly confound the modifier of interest and extreme temperature.

160 Binary logistic regression was repeatedly used to examine the modifier with two levels
161 such as personal characteristics (gender, employment and marital status); multinomial
162 logistic regression was used to examine the modifier with several categories such as age
163 and specific causes of death. All analyses were conducted in SPSS version 20.0.

164

165 **Results**

166 We included a total of 197,680 natural causes of death in cool seasons in Hong Kong in
167 this case-only analysis. Most of deaths were age of 75 years and older (62.6%), and males
168 (55.4%), and around half were married (47.4%). The majority of the deaths was
169 economically inactive (90.7%). Diseases of circulatory and respiratory system accounted
170 for 28.8% and 20.4% of the total natural causes of death, respectively (Table-1). The
171 temporal distribution of daily minimum/mean/maximum temperature from 2002 to 2011
172 was displayed in time-series plots (Figure-1). The cutoff point used to define the extremely
173 cold days was 14.7°C for the maximum temperature of 7-day moving average (lag06), the
174 1st percentile of its distribution during the study period.

175 Table-2 shows the individual characteristics that modify the extremely cold temperature
176 related mortality. People aged >=75 years (compared with 'age<65yrs'), females
177 (compared with 'males'), those economically inactive (compared with 'with occupation'),
178 and those never married/widowed/divorced (compared with 'married') showed larger risk
179 estimates of extreme cold, with ORs of 1.06-1.33 for extreme cold. However, the age-
180 controlled estimates of modification for 'female', 'economically inactive' and 'never
181 married/widowed/divorced' decreased and lost statistical significance, which may probably

182 be due to their association with old age. Causes of cardiorespiratory diseases (compared
183 with other natural causes) had higher risks of death related to extremely cold temperature,
184 with OR of 1.17 (95%CI: 1.10-1.25) for total circulatory diseases and 1.13 (95%CI: 1.05-
185 1.22) for total respiratory diseases, respectively. Among the specific causes of death,
186 COPD, pneumonia, stroke, hypertensive diseases, and congestive heart failure showed
187 greater susceptibility to death on days following extremely cold periods (Table-3). The
188 greatest risk of cold related mortality was observed for hypertensive diseases, with OR of
189 1.37 (95%CI: 1.13-1.65). The modifications of the specific circulatory causes on cold
190 related mortality were robust after controlling for age, seasonal pattern (a sine and cosine
191 term with 365.24-day period) and air pollutants (PM₁₀, NO₂ and O₃).

192 Sensitivity analyses using the 5th percentile as the cutoff point to define the extremely cold
193 days got similar estimates, which appeared to result in a larger statistical power to capture
194 more personal characteristics and specific causes of death including diabetes and MI as the
195 modifiers for the cold associated mortality (Table-4).

196

197 **Discussion**

198 In this case-only study conducted in cool seasons in Hong Kong, we identified several sub-
199 populations that are particularly susceptible to extremely cold temperatures. Subjects with
200 hypertensive diseases were especially vulnerable to extreme cold. The increase in deaths on
201 days following extremely cold periods was higher also for stroke, MI, CHF, COPD and
202 pneumonia. Among the personal characteristics, only older age was clearly associated with
203 elevated risk of mortality from extremely cold temperatures.

204 **Chronic Diseases.** It is explicable that subjects with hypertensive diseases show the
205 greatest susceptibility to the effects of extremely cold temperature. Cold stress has been
206 found to result in raising blood pressure, increasing the blood viscosity and platelet counts
207 (Keatinge et al. 1984; Elwood et al. 1993). The cold effects on homeostasis system with
208 increased fibrinogen, together with the effect on blood pressure, could explain a large part
209 of the increase in myocardial infarction in the winter (Elwood et al. 1993). The marked
210 increase of deaths from stroke on extremely cold days may also relate to the higher blood
211 pressure in winter and increased levels of plasma cholesterol and fibrinogen (Keatinge et
212 al. 1984; Fröhlich et al. 1997) which could facilitate the formation of blood clots and lead
213 to thrombosis through haemoconcentration. It is interesting we found the higher risk of
214 dying from congestive heart failure on days following extremely cold periods, which was

215 not reported in previous studies (Schwartz 2005; Medina-Ramón et al. 2006). Congestive
216 heart failure would be a result of many cardiovascular diseases or occur when several
217 cardiovascular diseases/conditions are present at once. However, we did not found the
218 increased vulnerability for cardiac arrest on extremely cold days as a previous study
219 reported (Medina-Ramón et al. 2006), which could result from the small sample size in our
220 study. We only recorded 284 cardiac arrest cases during the ten years' study period,
221 accounting for 0.1 percent of the total deaths.

222 The increased susceptibility of causes of respiratory diseases especially COPD and
223 pneumonia are also noteworthy. The lungs of persons with COPD and pneumonia are
224 typically colonized by bacteria, and cold weather can easily exacerbate respiratory
225 infections (Burge 2006). In addition, cold can induce bronchospasm, as well as increase
226 platelet and red cell counts, and blood viscosity (Keatinge et al. 1984). Because persons
227 with COPD often have cardiovascular complications, these effects on blood components
228 may also play a role.

229 **Sociodemographic Factors.** Being consistent with the previous studies (Schwartz 2005;
230 Hajat et al. 2007; Analitis et al. 2008; Medina-Ramón and Schwartz 2008; Zhou et al.
231 2014; Yi and Chan 2015), we found a greater susceptibility of the elderly to extreme cold
232 related death. A reduced thermoregulatory capacity in the elderly, combined with a
233 diminished ability to detect changes in their body temperature, may partly explain their
234 increased susceptibility. A French three-city study found that outdoor temperature and
235 blood pressure are strongly correlated in the elderly (Alpérovitch et al. 2009). The elderly
236 may also have a higher prevalence of co-morbidities which would make them more
237 sensitive to cold effect.

238 The modification effects of other personal characteristics including 'female', 'economically
239 inactive' and 'never married/widowed/divorced' were less significant and less robust, and
240 the age-controlled estimates of modification disappeared. These characteristics and old age
241 were interrelated, so that their vulnerability may probably be explained by old age. The
242 susceptibility of females may be due to the fact that they live longer. The susceptibility of
243 those economically inactive may be due to the group of retired and again be explained by
244 age; and the susceptibility of those never married/widowed/divorced may be driven by the
245 widowed group and therefore be explained by age (or sex).

246 ***Advantages of case-only approach.*** The conventional approach to investigate the
247 modification of personal characteristics and pre-existing comorbidities is by inclusion of
248 interaction terms in the regression model of outcome on the exposure and modifier, or by
249 carrying out separate regressions on strata with different modifier status (Lipsett et al.
250 1997; Zanobetti et al. 2000; Zeka et al. 2006; Peel et al. 2007; Kan et al. 2008; Qian et al.
251 2013). However, the case-only approach provides important advantages over traditional
252 analyses in examining the effect modification, including reduction of potential confounding
253 by variables typically associated with mortality, simplification of modeling, and reduction
254 of results sensitivity to model misspecification bias (Armstrong 2003; Zanobetti et al.
255 2013). Of particular interest, the long term trend and periodicity in mortality whose
256 modeling is quite complex, drops out in case-only approach. It was encouraging that in this
257 study, seasonal pattern and air pollutants did not appear to confound the modification of
258 interested factors. Using the 5th percentile as the cutoff point to define the extremely cold
259 days seemed easier to identify the specific cardiorespiratory causes of death as the
260 modifiers for the cold associated mortality, which may be due to the larger statistical power
261 than the 1st percentile being used as the cutoff. Although such findings need to be
262 confirmed in more locations, including areas with different climates, they support the use
263 of the case-only approach to examine susceptibility.

264 ***Limitations of this study.*** One limitation of this study is that we could not link the death
265 data to the previous medical records of the decedents, so that we were unable to abstract the
266 pre-existing comorbidities for each subject. Although the subjects who died of
267 cardiorespiratory diseases might have had pre-existing chronic cardiorespiratory diseases,
268 modification of the specific primary causes of death identified in this study could not
269 exactly represent the modification of the pre-existing comorbidities. Second, air pollution
270 concentrations averaged from general monitoring stations were assigned to all the
271 decedents. This may introduce some misclassification of the pollution exposure although
272 the potential error can be non-differential. Another limitation came from the case-only
273 study design itself, which cannot estimate the main effect of the extreme cold but only the
274 effect modification by certain characteristics. With the main effects of cold temperature on
275 mortality in Hong Kong been well studied previously (Goggins et al. 2013; Guo et al. 2014;
276 Yi and Chan 2015), however, examining the effect modification was the main purpose of
277 the current study.

278

279 **Conclusions**

280 We identified old age and some specific cardiorespiratory causes including hypertensive
281 diseases, stroke, congestive heart failure, COPD and pneumonia that are particularly
282 susceptible to extreme cold related mortality. Understanding who is susceptible to the
283 extreme events will be important in minimizing their public health impact. The vulnerable
284 subpopulations identified in this study may use central heating to mitigate the cold effect
285 on days following extremely cold periods.

286 **References:**

- 287 Alperovitch A, Lacombe J, Hanon O, et al (2009) Relationship Between Blood Pressure
288 and Outdoor Temperature in a Large Sample of Elderly Individuals: The Three-City
289 Study. *Arch Intern Med* 169:75–80.
- 290 Analitis A, Katsouyanni K, Biggeri A, et al (2008) Effects of cold weather on mortality:
291 Results from 15 European cities within the PHEWE project. *Am J Epidemiol*
292 168:1397–1408.
- 293 Armstrong BG (2003) Fixed factors that modify the effects of time-varying factors:
294 applying the case-only approach. *Epidemiology* 14:467–72.
- 295 Basagaña X, Sartini C, Barrera-Gómez J, et al (2011) Heat waves and cause-specific
296 mortality at all ages. *Epidemiology* 22:765–72.
- 297 Bhaskaran K, Hajat S, Haines a, et al (2009) Effects of ambient temperature on the
298 incidence of myocardial infarction. *Heart* 95:1760–9.
- 299 Burge P (2006) Prevention of exacerbations: how are we doing and can we do better? *Proc*
300 *Am Thorac Soc* 3:257–61.
- 301 Chan EYY, Goggins WB, Kim JJ, Griffiths SM (2012) A study of intracity variation of
302 temperature-related mortality and socioeconomic status among the Chinese population
303 in Hong Kong. *J Epidemiol Community Health* 66:322–7.
- 304 Chen R, Wang C, Meng X, et al (2013) Both low and high temperature may increase the
305 risk of stroke mortality. *Neurology* 81:1064–70.
- 306 Curriero FC, Heiner KS, Samet JM, et al (2002) Temperature and mortality in 11 cities of
307 the eastern United States. *Am J Epidemiol* 155:80–7.
- 308 Elwood PC, Beswick A, Brien JRO, et al (1993) Temperature and risk factors for
309 ischaemic heart disease in the Caerphilly prospective study. *Br Heart J* 70:520–523.
- 310 Fröhlich M, Sund M, Russ S, et al (1997) Seasonal variations of rheological and hemostatic
311 parameters and acute-phase reactants in young, healthy subjects. *Arterioscler Thromb*
312 *Vasc Biol* 17:2692–2697.

- 313 Goggins WB, Chan EYY, Yang C, Chong M (2013) Associations between mortality and
314 meteorological and pollutant variables during the cool season in two Asian cities with
315 sub-tropical climates: Hong Kong and Taipei. *Environ Health* 12:59.
- 316 Guo Y, Gasparini A, Armstrong B, et al (2014) Global variation in the effects of ambient
317 temperature on mortality: a systematic evaluation. *Epidemiology* 25:781–9.
- 318 Hajat S, Kovats RS, Lachowycz K (2007) Heat-related and cold-related deaths in England
319 and Wales: who is at risk? *Occup Environ Med* 64:93–100.
- 320 Kan H, London SJ, Chen G, et al (2008) Season, sex, age, and education as modifiers of the
321 effects of outdoor air pollution on daily mortality in Shanghai, China: The Public
322 Health and Air Pollution in Asia (PAPA) Study. *Environ Health Perspect* 116:1183–8.
- 323 Keatinge WR, Coleshaw SRK, Cotter F, et al (1984) Increases in platelet and red cell
324 counts , blood viscosity , and arterial pressure during mild surface cooling : factors in
325 mortality from coronary and cerebral thrombosis in winter. *Br Med J* 289:1405–8.
- 326 Lipsett M, Hurley S, Ostro B (1997) Air pollution and emergency room visits for asthma in
327 Santa Clara County, California. *Environ Health Perspect* 105:216–22.
- 328 Madrigano J, Mittleman M a, Baccarelli A, et al (2013) Temperature, myocardial
329 infarction, and mortality: effect modification by individual- and area-level
330 characteristics. *Epidemiology* 24:439–46.
- 331 Medina-Ramón M, Schwartz J (2007) Temperature, temperature extremes, and mortality: a
332 study of acclimatisation and effect modification in 50 US cities. *Occup Environ Med*
333 64:827–33.
- 334 Medina-Ramón M, Schwartz J (2008) Who is more vulnerable to die from ozone air
335 pollution? *Epidemiology* 19:672–9.
- 336 Medina-Ramón M, Zanobetti A, Cavanagh DP, Schwartz J (2006) Extreme Temperatures
337 and Mortality: Assessing Effect Modification by Personal Characteristics and Specific
338 Cause of Death in a Multi-City Case-Only Analysis. *Environ Health Perspect*
339 114:1331–1336.
- 340 Peel JL, Metzger KB, Klein M, et al (2007) Ambient air pollution and cardiovascular
341 emergency department visits in potentially sensitive groups. *Am J Epidemiol*
342 165:625–33.

- 343 Qian Y, Zhu M, Cai B, et al (2013) Epidemiological evidence on association between
344 ambient air pollution and stroke mortality. *J Epidemiol Community Health* 67:635–40.
- 345 Qiu H, Yu IT-S, Wang X, et al (2013) Cool and dry weather enhances the effects of air
346 pollution on emergency IHD hospital admissions. *Int J Cardiol* 168:500–5.
- 347 Saez M, Sunyer J, Castellsague J, Murillo C (1995) Relationship between Weather
348 Temperature and Mortality : A Time Series Analysis Approach in Barcelona. *Int J*
349 *Epidemiol* 24:576–582.
- 350 Schwartz J (2005) Who is Sensitive to Extremes of Temperature? *Epidemiology* 16:67–72.
- 351 Xu Y, Dadvand P, Barrera-Gómez J, et al (2013) Differences on the effect of heat waves on
352 mortality by sociodemographic and urban landscape characteristics. *J Epidemiol*
353 *Community Health* 67:519–25.
- 354 Yi W, Chan APC (2015) Effects of temperature on mortality in Hong Kong: a time series
355 analysis. *Int J Biometeorol* 59:927–936.
- 356 Zanobetti a, Schwartz J, Gold D (2000) Are there sensitive subgroups for the effects of
357 airborne particles? *Environ Health Perspect* 108:841–5.
- 358 Zanobetti A, O’Neill MS, Gronlund CJ, Schwartz JD (2013) Susceptibility to mortality in
359 weather extremes: effect modification by personal and small-area characteristics.
360 *Epidemiology* 24:809–19.
- 361 Zeka A, Zanobetti A, Schwartz J (2006) Individual-level modifiers of the effects of
362 particulate matter on daily mortality. *Am J Epidemiol* 163:849–59.
- 363 Zeng W, Lao X, Rutherford S, et al (2014) The effect of heat waves on mortality and effect
364 modifiers in four communities of Guangdong Province, China. *Sci Total Environ* 482-
365 483:214–21.
- 366 Zhou MG, Wang LJ, Liu T, et al (2014) Health impact of the 2008 cold spell on mortality
367 in subtropical China: the climate and health impact national assessment study
368 (CHINAs). *Environ Health* 13:60.
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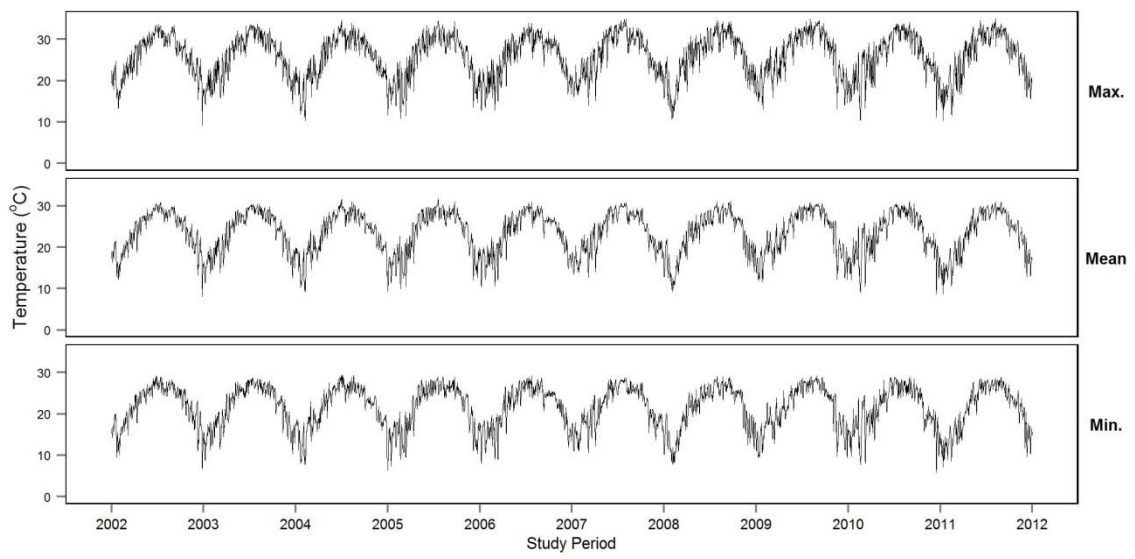
372

**Table-1 Descriptive Statistics for Natural Causes of Death in Cool Seasons
in Hong Kong (November-April, 2002-2011)**

Category	Number	Percentage (%)
Total	197,680	100.0
Age		
<65 yrs	36,570	18.5
65-74 yrs	37,425	18.9
75-84 yrs	66,103	33.4
>=85 yrs	57,582	29.1
Sex		
Male	109,505	55.4
Female	88,175	44.6
Occupational Status		
With occupation	18,402	9.3
Economically inactive	179,278	90.7
Married Status		
Married	93,775	47.4
Never married/Widowed/Divorced	75,585	38.2
Unknown	28,320	14.3
Cause of death		
Diabetes	3,209	1.6
All cardiovascular diseases	57,024	28.8
Stroke	18,657	9.4
Hypertensive Diseases	3,720	1.9
Myocardial Infarction	10,550	5.3
Congestive Heart Failure	4,283	2.2
Cardiac Arrest	158	0.1
All respiratory diseases	40,310	20.4
COPD	10,092	5.1
Pneumonia	25,808	13.1

373

374 **Figure-1** The temporal distribution of daily maximum/mean/minimum temperature (°C) in
375 Hong Kong, 2002-2011



376

377

378

Table-2 Modification by Personal Characteristics of the Effect of Extremely Cold

379

Temperatures on Mortality in Cool Seasons in Hong Kong, 2002-2011 (OR (95%CI))*

380

Characteristics	Model 1 ^a	Model 2 ^b	Model 3 ^c
Age of 65-74yrs	1.05 (0.95, 1.15)	-	1.04 (0.95, 1.15)
Age of 75-84yrs	1.19 (1.10, 1.30)	-	1.19 (1.10, 1.30)
Age of 85yrs and older	1.33 (1.22, 1.45)	-	1.33 (1.22, 1.45)
Female	1.06 (1.00, 1.12)	1.01 (0.96, 1.07)	1.06 (1.00, 1.12)
Economically Inactive	1.11 (1.00, 1.23)	1.02 (0.92, 1.14)	1.09 (0.98, 1.20)
Never married/Widowed /Divorced	1.08 (1.01, 1.15)	1.02 (0.96, 1.09)	1.08 (1.01, 1.15)

381

*: Estimates represent the ratio of relative risk associated with extreme cold in persons who have the condition (e.g. being female) relative to that ratio in other persons. For the age groups, all compared with the age less than 65yrs group. The extremely cold days were defined as those with a daily maximum temperature at or less than the 1st percentile of its distribution in Hong Kong during 2002-2011, based on the temperature on the 7-day moving average of same day of death and the 6 preceding days.

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^a: single factor model with extreme cold only; ^b: model 1 further controlling for confounding from age as a four-level categorical factor; ^c: model 1 further controlling for confounding from seasonal pattern (captured by an annual sine-cosine pair with 365.24-day period) and air pollutants (PM₁₀, NO₂ and O₃).

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Table-3 Primary Causes of Death as Modifiers of the Effect of Extremely Cold

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Temperatures on Mortality in Cool Seasons in Hong Kong, 2002-2011 (OR (95%CI))*

Cause of Death	Model 1 ^a	Model 2 ^b	Model 3 ^c
Diabetes	1.19 (0.96, 1.48)	1.17 (0.94, 1.45)	1.19 (0.96, 1.48)
All Circulatory Diseases	1.17 (1.10, 1.25)	1.13 (1.06, 1.21)	1.17 (1.10, 1.25)
Stroke	1.14 (1.03, 1.26)	1.10 (1.00, 1.22)	1.14 (1.03, 1.26)
Hypertensive Diseases	1.37 (1.13, 1.65)	1.31 (1.08, 1.58)	1.37 (1.13, 1.66)
Myocardial Infarction	1.09 (0.96, 1.24)	1.07 (0.94, 1.21)	1.09 (0.96, 1.24)
Congestive Heart Failure	1.25 (1.04, 1.50)	1.16 (0.96, 1.39)	1.25 (1.04, 1.50)
Cardiac Arrest	1.10 (0.41, 2.96)	1.06 (0.39, 2.87)	1.02 (0.38, 2.77)
All Respiratory Diseases	1.13 (1.05, 1.22)	1.06 (0.99, 1.15)	1.13 (1.05, 1.22)
COPD	1.14 (1.00, 1.29)	1.09 (0.95, 1.24)	1.12 (0.99, 1.28)
Pneumonia	1.16 (1.06, 1.26)	1.08 (0.98, 1.18)	1.16 (1.06, 1.26)

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*: Estimates represent the ratio of relative risk associated with extreme cold in persons who die from a specific cause of death (e.g. stroke) relative to that ratio in persons dying from other non-cardiorespiratory and non-diabetes causes. The extremely cold days were defined as those with a daily maximum temperature at or less than the 1st percentile of its distribution in Hong Kong during 2002-2011, based on the temperature on the 7-day moving average of same day of death and the 6 preceding days.

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^a: single factor model with extreme cold only; ^b: model 1 further controlling for confounding from age as a four-level categorical factor; ^c: model 1 further controlling for confounding from seasonal pattern (captured by an annual sine-cosine pair with 365.24-day period) and air pollutants (PM₁₀, NO₂ and O₃).

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402 **Table-4 Sensitivity Analysis using the 5th percentile as the cutoff to define the extreme**
 403 **cold (OR (95%CI))***

Condition	Model 1^a	Model 2^b	Model 3^c
Characteristics			
Age of 65-74yrs	1.01 (0.97, 1.06)	-	1.00 (0.96, 1.05)
Age of 75-84yrs	1.08 (1.04, 1.13)	-	1.08 (1.04, 1.13)
Age of 85yrs and older	1.17 (1.12, 1.22)	-	1.17 (1.13, 1.22)
Female	1.03 (1.00, 1.06)	1.00 (0.97, 1.03)	1.03 (1.00, 1.06)
Economically Inactive	1.01 (0.97, 1.06)	0.97 (0.92, 1.02)	0.98 (0.94, 1.03)
Never married/Widowed /Divorced	1.06 (1.03, 1.09)	1.02 (0.99, 1.06)	1.06 (1.03, 1.10)
Cause of death			
Diabetes	1.20 (1.08, 1.33)	1.19 (1.07, 1.32)	1.17 (1.05, 1.30)
All Circulatory Diseases	1.17 (1.14, 1.21)	1.15 (1.12, 1.19)	1.16 (1.12, 1.20)
Stroke	1.16 (1.10, 1.21)	1.14 (1.09, 1.20)	1.15 (1.10, 1.21)
Hypertensive Diseases	1.31 (1.19, 1.44)	1.29 (1.17, 1.41)	1.30 (1.18, 1.44)
Myocardial Infarction	1.11 (1.04, 1.18)	1.10 (1.03, 1.17)	1.09 (1.02, 1.16)
Congestive Heart Failure	1.19 (1.09, 1.31)	1.15 (1.05, 1.26)	1.20 (1.09, 1.32)
Cardiac Arrest	1.31 (0.83, 2.06)	1.29 (0.82, 2.03)	1.25 (0.79, 1.97)
All Respiratory Diseases	1.11 (1.07, 1.15)	1.08 (1.04, 1.12)	1.11 (1.07, 1.16)
COPD	1.12 (1.05, 1.20)	1.10 (1.03, 1.17)	1.11 (1.04, 1.18)
Pneumonia	1.12 (1.07, 1.17)	1.08 (1.03, 1.13)	1.13 (1.09, 1.18)

404 *: Estimates represent the ratio of relative risk associated with extreme cold in persons with
 405 sociodemographic characteristic or dying from a specific cause of death relative to that ratio in other persons.
 406 The extremely cold days were defined as those with a daily maximum temperature at or less than the 5th
 407 percentile of its distribution in Hong Kong during 2002-2011, based on the temperature on the 7-day moving
 408 average of same day of death and the 6 preceding days.
 409 ^a: single factor model with extreme cold only; ^b: model 1 further controlling for confounding from age as a
 410 four-level categorical factor; ^c: model 1 further controlling for confounding from seasonal pattern (captured by an
 411 annual sine-cosine pair with 365.24-day period) and air pollutants (PM₁₀, NO₂ and O₃).