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The short-term effects of cold spells on hospitalizations for chronic obstructive pulmonary disease: a time-series study in Beijing, China

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4 1 **The short-term effects of cold spells on hospitalizations for chronic obstructive**
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6 2 **pulmonary disease: a time-series study in Beijing, China**
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51
52 22 **Keywords:** cold spells, chronic obstructive pulmonary disease, hospitalizations, intensity
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54 23 and duration
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4 24 **ABSTRACT**

5
6 25 **Objectives:** Our work aimed at exploring the relationship between cold spells and chronic
7
8 26 obstructive pulmonary diseases (COPD) hospitalizations in Beijing, China, and assessing
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10 27 the moderating effects of the intensities and the durations of cold spells, as well as
11
12 28 identifying the vulnerable.

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15 29 **Design:** Time-series study.

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18 30 **Setting:** We obtained time-series data of COPD hospitalizations, meteorological
19
20 31 variables and air quality index in Beijing, China during 2012–2016.

21
22 32 **Participants:** All COPD hospitalizations among permanent residents in Beijing, China
23
24 33 in cold seasons (November to March) during 2012-2016 were included. (n=84,571).

25
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27 34 **Primary and secondary outcome measures:** A quasi-Poisson regression with a
28
29 35 distributed lag model was fitted to investigate the short-term effects of cold spells on
30
31 36 COPD hospitalizations by comparing the counts of COPD admissions during cold
32
33 37 spell days with those during non-cold spell days.

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35
36 38 **Results:** Cold spells under different definitions were associated with increased risks of
37
38 39 COPD hospitalizations, with the maximum cumulative relative risk (CRR) over three
39
40 40 weeks (lag0-21). The cumulative effects at lag0-21 increased with the intensities and the
41
42 41 durations of cold spells. Under the optimal definition, the most significant single-day
43
44 42 relative risk (RR) was found on the days of cold spells (lag0) with RR=1.042 (95%CI:
45
46 43 1.013, 1.072), and the CRR at lag0-21 was 1.394 (95%CI: 1.193, 1.630). The elderly
47
48 44 (aged≥65) were more vulnerable to the effects of cold spells on COPD hospitalizations.

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50
51 45 **Conclusion:** Cold spells are associated with increased COPD hospitalizations in Beijing,
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53 46 with the cumulative effects increased with their intensities and durations. The elderly are
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55 47 at particular risk of COPD hospitalizations triggered by cold spells.
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3 484 49 **Strengths and limitations of this study:**

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8 50 · This study was the first to examine the association between cold spells and COPD
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10 51 hospitalizations in China.
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12 52 · The study assessed the effects of cold spells under different definitions on COPD
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14 53 hospitalizations, thereby finding out a more reasonable cold spell definition on the
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16 54 issue.
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18 55 · The study identified more vulnerable subpopulation to COPD hospitalizations in
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20 56 response to cold spells, which guide more targeted prevention strategies.
21
22 57 · The ecological design cannot imply causality definitely, while limited information on
23
24 58 individual-level factors and inevitable exposure measurement errors may lead to
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26 59 bias.
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28 60 · The data from only one city limited the generalization of the study findings.
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35 62 **INTRODUCTION**

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38 63 The Intergovernmental Panel on Climate Change (IPCC) has predicted that human
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40 64 activities and global climate change cause variations in frequency, intensity and duration
41
42 65 of many extreme weather events, including heatwaves and cold spells.[1] Although the
43
44 66 amount of cold spells may decrease over most land areas due to global warming, a few
45
46 67 recent studies found that the persistent shift of the Arctic polar vortex and Arctic
47
48 68 amplification associated with global warming could lead to increased extremely cold
49
50 69 events in mid-latitudes.[2, 3] Over the last few years, the impacts of cold spells on human
51
52 70 health have gained growing attention from the public. Many studies have reported
53
54 71 positive relationships between cold spells and mortality[4-6] while the impacts of cold
55
56 72 spells on hospital visits or admissions are under-examined.
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4 73 Chronic obstructive pulmonary disease (COPD) is one of the common respiratory
5
6 74 diseases characterized by poorly reversible limitation of airflow.[7] Owing to its high
7
8 75 prevalence, morbidity, mortality and economic burden globally, COPD has been an
9
10 76 important public health concern and will remain a huge challenge for healthcare
11
12 77 practitioners in the foreseeable future.[8] Thus, it is crucial to identify the risk factors of
13
14 78 COPD, to improve strategies on prevention and intervention. Given the projected climate
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16
17 79 change, extreme temperature events potentially pose threats to COPD patients. Many
18
19 80 epidemiological studies have indicated that COPD has higher rates of exacerbation and
20
21 81 hospitalization in cold seasons.[9-11] We hypothesized that cold spells, defined as
22
23 82 prolonged periods of extremely cold weather, may be more relevant to COPD
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26 83 hospitalizations. However, few studies have been carried out on the very issue.[12]
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29 84 As the world's largest country by population, China shoulders the enormous burden of
30
31 85 COPD. A national cross-sectional study from 2012 to 2015 showed that the prevalence of
32
33 86 COPD among Chinese adults aged 20 years and older was 8.6% (99.9 million
34
35 87 patients).[13] On the other hand, with most areas located in mid-latitudes, China has
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37
38 88 experienced several severe cold spells in recent years. The cold spells in 2008 resulted
39
40 89 in a significantly higher all-cause mortality in subtropical China and estimated losses
41
42 90 exceeding \$22.3 billion.[14, 15] Moreover, the public now has a better perception of the
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44 91 potential risks of extreme temperatures in China, especially those with chronic
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46
47 92 conditions.[16] So it is of great value to assess the association between cold spells and
48
49 93 COPD hospitalizations to build prevention and adaption strategies in China.
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51 94 Cold spells have been defined differently due to the heterogeneity of climate and
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53 95 people's adaptive capacities in different regions. Previous studies suggested that the
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55 96 effects of cold spells varied by different cold spell characteristics and individual-specific
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57 97 factors.[17, 18] We have three main objectives in this work: (1) to illuminate the short-
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3 98 term effects of cold spells on the risk of hospitalizations for COPD with time-series
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5 99 methods. (2) to investigate the modification effect of cold spell intensities and durations
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8 100 by fitting different definitions. (3) to identify potentially vulnerable populations through
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10 101 stratified analyses. The results could help better understand the relationship between
11
12 102 extremely cold events and COPD hospitalizations, and provide scientific evidence in
13
14 103 policymaking for the prevention and the intervention of COPD.
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18 105 **MATERIALS AND METHODS**

19 106 **Data collection**

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22 107 Beijing, the capital of China, is located in the northern part of China (39°56'N,
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24 108 116°20'E). The area covers 16410.54 km², with more than 21 million population in 2016.
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26 109 Beijing has a typical semi-humid continental monsoon climate with four distinctive
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28 110 seasons.
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32 111 Daily hospitalizations for COPD from January 1, 2012, to December 31, 2016, were
33
34 112 collected from Beijing Municipal Health Commission Information Center covering all the
35
36 113 secondary and tertiary hospitals in Beijing. All case files consisted of the following
37
38 114 information: admission date, discharge date, age, gender, address, diagnosis and
39
40 115 International Classification of Diseases 10th revision (ICD-10) diagnostic code. Those
41
42 116 among Beijing residents with COPD as the primary discharge diagnosis (coded as J44)
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44 117 were included in the study. The study was approved by the ethical committee of Peking
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46 118 Union Medical College Hospital. All the data for the analysis were anonymous at
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48 119 collection.
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52 120 We collected the daily 2012–2016 meteorological data in Beijing from the China
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54 121 Meteorological Data Sharing Service System, including daily mean temperature (°C),
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56 122 daily mean relative humidity (%) and daily mean air pressure (hPa). For the same period,
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3 123 the daily air quality index (AQI) was obtained from the China National Environmental
4
5 124 Monitoring Centre. The AQI value denotes the maximum value of individual air quality
6
7
8 125 indexes (IAQI) of six monitored air pollutants (particulate matter with aerodynamic
9
10 126 diameter<2.5µm, particulate matter with aerodynamic diameter<10µm, nitrogen dioxide,
11
12 127 sulfur dioxide, carbon monoxide, and ozone). Considering the impact of influenza on
13
14 128 COPD exacerbations,[19] we also accessed the data on influenza isolates from the
15
16 129 Chinese National Influenza Center. Influenza epidemics (a binary variable representing
17
18 130 days with relatively high influenza incidence) were defined when the proportion of
19
20 131 isolates positive for influenza exceeded 30% of the maximum seasonal level (Influenza
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22 132 surveillance season was defined from the 27th week of the previous year to the 26th week
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24 133 of the following year).[20]
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135 **Cold spell definitions**

136 The definition of cold spells varied across the research field due to distinct climatic
137 features and temperature variations in different regions. As to the prior studies, cold
138 spells were usually defined based on their temperature thresholds and durations.[4, 12,
139 21] Instead of specific temperatures as thresholds, percentiles of temperature were
140 shown to have a better model fit according to quasi-Poisson Akaike Information Criterion
141 (Q-AIC).[4] Moreover, some researchers suggested that daily mean temperature is
142 superior to the minimum or maximum temperature as an indicator to define cold spells
143 because it reflects the exposure throughout the day rather than a short period.[17, 22]
144 Therefore, we defined cold spell episodes as days when daily mean temperature at or
145 below the 10th, 5th or 3rd percentile for at least 2, 3 or 4 consecutive days of the study
146 period.[18] To avoid the possible biases caused by a few extreme summer events, we
147 restricted the study period to the five coldest adjacent months (from November of the

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4 148 previous year to March of the following year)[6, 12, 17] The cold spell was
5
6 149 treated as a dichotomous variable, with a value of 1 during the cold spell period. The
7
8 150 statistical analyses were performed separately for each definition of cold spells.
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12 152 **Statistical methods**

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15 153 In the analyses, the dependent variable was the number of daily COPD
16
17 154 hospitalizations following a quasi-Poisson distribution. Hence, we adopted a distributed
18
19 155 lag model (DLM) [23] with a quasi-Poisson generalized linear regression model. To
20
21 156 investigate the effects of cold spells on COPD hospitalizations, we compared the counts
22
23 157 of COPD admissions during cold spell days with those during non-cold spell days, after
24
25 158 adjusting for relative humidity, atmospheric pressure, AQI, seasonality, long-term trends,
26
27 159 statutory holiday, influenza epidemics, and day of the week (DOW). The Q-AIC was
28
29 160 employed to choose the optimal cold spell definition and degrees of freedom (df). The
30
31 161 model was established as follows:
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33

34
35 162 $Y_t \sim \text{quasiPoisson}(\mu_t)$

36
37 163 $\text{Log}(\mu_t) = \alpha + \text{cb}(\text{CS}_t, \text{lag}, \text{df} = 3) + \text{ns}(\text{RH}_t, \text{df} = 3) + \text{ns}(\text{AP}_t, \text{df} = 3) + \text{ns}(\text{AQI}_t, \text{df} = 3)$
38
39 164 $+ \text{ns}(\text{Time}_t, \text{df} = 3/\text{per year}) + \gamma \text{DOW}_t + \delta \text{Holiday}_t + \nu \text{Influenza}_t,$

40
41 165 where t is the day of observation; Y_t is the expected number of hospitalizations for COPD
42
43 166 on day t ; α is the intercept; CS_t denotes the cold spells on day t (0=non-cold spell days,
44
45 167 and 1=cold spell days); cb represents the cross-basis function, including a linear function
46
47 168 and a natural cubic spline function with 3 df to assess the linear and lagged effects of the
48
49 169 cold spells separately. We fitted a lag structure up to 21 days in the models to completely
50
51 170 capture the flexible lagged effects of cold spells exposure. ns refers to the natural cubic
52
53 171 spline function. ns with 3 df was applied for the mean relative humidity (RH_t), mean
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55 172 atmospheric pressure (AP_t) and air quality index (AQI_t), respectively. ns with 3 df per year
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3 173 was used to control the seasonality and long-term trends. DOW_t is a categorical variable
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6 174 indicating the day of the week on day t , and γ is the coefficient. $Holiday_t$ is a binary
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8 175 variable (0=non-statutory holiday, and 1=statutory holiday) and δ is the coefficient.
9
10 176 $Influenza_t$ is a dichotomous variable with the value of "1" for the influenza epidemic on
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12 177 day t , and ν is the coefficient. The statistical methods, maximum lag days and
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14 178 confounding factors included in the model were commonly utilized and described in
15
16
17 179 previous publications.[4, 14, 17, 18, 24, 25]

18
19 180 To observe the variation trend of lagged effects, we calculated the single-day lagged
20
21 181 effects (from lag0 to lag21) and cumulative effects (lag0, lag0–7, lag0–14 and lag0–21) of
22
23 182 cold spells on COPD hospitalizations, respectively. To identify the susceptible
24
25 183 subpopulations for more targeted public health interventions, we further conducted
26
27 184 subgroup analyses to investigate the potential modification effects by gender (male and
28
29 185 female) and age (0-64 years old and ≥ 65 years old) under the optimal definition of cold
30
31 186 spells. The statistical differences of the risk estimates between the subgroups were
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33 187 examined by the Z-test with the following equation:
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$$37 \quad 188 \quad Z = (E_1 - E_2) / \sqrt{(SE_1^2 + SE_2^2)}$$

38
39 189 where Z represents the Z-test value; E_1 and E_2 denote the effect estimates of two
40
41 190 categories; SE_1 and SE_2 are corresponding standard errors of E_1 and E_2 .
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46 192 **Sensitivity analysis**

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48
49 193 We performed the sensitivity analyses by altering the df with 3–5 df per year of the
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51 194 long-term trend, 3–5 df of the relative humidity, 3-5 df of the air pressure, 3-5 df of the
52
53 195 AQI and 3–5 df of the lag dimension in the DLM under the optimal definition of cold
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55 196 spells. We used R software version 3.6.1 with the “dlnm” and “splines” packages to run
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57 197 the analyses. All statistical tests were two-sided and values of $p < 0.05$ were considered
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3 198 statistically significant.
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8 200 **Patient and public involvement**

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10 201 Patients were not involved in development of the research question and outcome

11 202 measures, study design or conduct of this study.
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17 204 **RESULTS**

18 205 **Data description**

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22 206 Table 1 shows the descriptive statistics of the study population, meteorological
23
24 207 variables and AQI during the cold seasons (November to March) from 2012 to 2016 in
25
26 208 Beijing. There was a total of 84,571 COPD hospitalizations throughout the study period.
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28 209 Among these cases, 63.6% were males and 36.4% were females. 83.9% of all patients
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30 210 were aged 65 years and above. The average of daily mean temperature, relative
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32 211 humidity, air pressure, and AQI were 0.9°C (range, -16.0-18.0°C), 46.6% (range, 8.0-
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34 212 98.0%), 1025.3hPa (range, 1005.0-1044.0hPa) and 126.3 (range, 17.0-485.0),
35
36 213 respectively.
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40 214 Table 2 shows the overview information of cold spells under different definitions. More
41
42 215 days were defined as cold spell days with higher temperature thresholds and shorter
43
44 216 duration. We observed the most cold spell episodes and days in four years with the
45
46 217 definition of periods for at least 2 days and daily mean temperature below or at the 10th
47
48 218 percentile (-6°C). In contrast, there were only 2 cold spell episodes and 10 cold spell days
49
50 219 if we defined cold spells as periods for 4 or more consecutive days when daily mean
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52 220 temperature was below or at the 3rd percentile (-8°C).
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58 222 **Effects of cold spells under different definitions**

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4 223 Figure 1 depicts the lag structures of associations between cold spells under 9 different
5
6 224 definitions and COPD hospitalizations of the total population. All cold spells had impacts
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8 225 on the risks of hospitalizations for COPD and most trends of their lagged effects were
9
10 226 non-linear with two patterns. One was that the relative risk (RR) of hospitalizations for
11
12 227 COPD reached maximum on the days (lag0) of cold spells, then decreased and
13
14
15 228 remained significant for 10-16 days (lag10-lag16). The other one was that the RR
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17 229 became significant on the 3rd or 4th day (lag3 or lag4) after exposure to cold spells, then
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19 230 gradually reached the maximum at about the 8th day (lag8) and lasted till the 15th-17th
20
21 231 days (lag15-lag17).

22
23
24 232 Table 3 shows the cumulative effects of cold spells on COPD hospitalizations under
25
26 233 different definitions. For each definition, the cumulative relative risk (CRR) increased with
27
28 234 longer cumulative lags, with the highest CRR at lag0-21. Among 9 different definitions,
29
30 235 the CRRs of cold spells at lag0-21 increased as the definition had a longer duration or
31
32 236 lower temperature threshold. The maximum CRR over lag0-21 when the temperature
33
34 237 threshold was set at the 10th percentile appeared at the duration \geq 4 consecutive days. In
35
36 238 comparison, the CRR values of the duration \geq 3 consecutive days and \geq 2 consecutive
37
38 239 days were lower. Likewise, when the duration was set for at least 4 consecutive days, the
39
40 240 maximum CRR over lag0-21 appeared at the temperature range defined as \leq 3rd
41
42 241 percentile, while the CRR of temperature threshold at the 5th and 10th percentile were
43
44 242 lower. The lowest Q-AIC value (7769.8) indicating the best model fit was observed in
45
46 243 Model 3 (Table 2). Hence, the optimal cold spell definition was daily mean temperature
47
48 244 \leq 10th percentile (-6°C) with at least 4 consecutive days during the study period. The
49
50 245 optimal model was able to find the most significant single-day lagged effect earliest (lag0)
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52 246 and remained significant till the 14th day (lag14) (Figure 1).

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58 247 Table 4 and Figure 2 reveal the results for the subgroup analyses of gender and age
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3 248 based on the optimal cold spell definition. The effects of cold spells were similar between
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5 249 males and females, with the most significant single-day lagged effect both occurred at
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7
8 250 lag0 ($Z=0.041$, $P=0.48$). The cumulative effects at lag0-21 of two genders also differed
9
10 251 slightly ($Z=-0.730$, $P=0.23$). Additionally, in the subgroups stratified by the age, the most
11
12 252 significant single-day lagged effect and cumulative effect for people aged ≥ 65 years were
13
14 253 at lag0 and at lag0-21, respectively. However, no significant effect of cold spells was
15
16 254 observed in those aged 0-64 years. The results of sensitivity analyses indicated that the
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18 255 effect estimates of cold spells under the optimal definition on COPD hospitalizations were
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20 256 still robust. (See Supplementary Materials, Tables S1–S5).
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26 258 **DISCUSSION**

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28
29 259 In this study, we showed that cold spells were associated with increase hospitalizations
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31 260 for COPD. The adverse impacts of cold spells varied with their durations and intensities.
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33 261 Based on the statistical model fit, the optimal definition of cold spells was daily mean
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35 262 temperature less than or equal to the 10th percentile lasting for at least 4 consecutive
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37 263 days during the study period. The elderly seemed more sensitive to cold spells than the
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39 264 younger, while the susceptibility difference between genders was not noticeable.
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41

42 265 Our finding is in accordance with previous studies reporting an excess of COPD
43
44 266 hospitalizations,[12] emergency visits[26] and mortality[4, 6, 26] associated with cold
45
46 267 spells. For instance, Monteiro et al. reported significant effects of cold spells identified by
47
48 268 various indices on COPD hospitalizations with a lagged effect of at least two weeks.[12]
49
50 269 Several underlying mechanisms may explain for elevated COPD morbidity and mortality
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52 270 attributable to extremely cold events. Firstly, cold exposure has been found to be related
53
54 271 to a decline in lung function (FEV_1 , FVC and PEF) among COPD patients.[27, 28]
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56 272 Secondly, Koskela et al. reported that cold air could directly induce bronchoconstriction,
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3 273 leading to excessive dyspnea in patients with COPD.[29] Thirdly, cold exposure may
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5 274 suppress the immune response and increase susceptibility to viral infections in
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8 275 humans.[30] Meanwhile, the transmission efficiency of the influenza virus is inversely
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10 276 correlated with ambient temperature.[31] Fourthly, the cold temperature may provoke
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12 277 airway inflammation and mucin hypersecretion in airway epithelium, which results in
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15 278 COPD morbidity and mortality by blocking airways and causing recurrent infections.[32,
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17 279 33]

18
19 280 We found that the CRR values of COPD hospitalizations increased with longer duration
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21 281 and higher intensity of cold spells. Some prior studies have similar findings,[17, 18]
22
23 282 indicating that both the duration and the intensity affect the health risks of cold spells.
24
25 283 According to the minimum Q-AIC value criterion, the optimal definition of cold spells was
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27 284 the daily average temperature at or below the 10th percentile with 4 or more consecutive
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29 285 days. Compared with other definitions, this one had a lower intensity and longer duration,
30
31 286 and the most significant single-day lagged effect of cold spells on COPD hospitalizations
32
33 287 appeared earliest (lag0). Our results agree with a study in Porto showing that the
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35 288 moderately low temperature with long periods contributed greater to COPD exacerbation
36
37 289 than extremely low temperature with shorter-lasting days.[12] However, studies on some
38
39 290 other diseases defined the optimal cold spell definitions with a threshold at the 5th
40
41 291 percentile or at least 2 days duration,[18, 24] indicating different definitions may apply to
42
43 292 different outcomes. In addition, some studies reported the temporal changes of people's
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45 293 adaption capacities to cold spells during recent decades under climate change.[5, 34]
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47 294 Overall, more effective cold spell definitions and warning systems adapted to regional
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49 295 climate, specific diseases, and dynamic changes of the population's sensitivity should be
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51 296 further studied and implemented in the future.

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53 297 In the subgroup analyses based on the optimal cold spell definition, we found that the
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3 298 effects of cold spells on COPD hospitalizations were more significant in the elderly (aged
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5 299 ≥65 years) than people aged 0–64 years. This finding is consistent with previous
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8 300 studies.[4, 35, 36] The reasons may point to reduced thermoregulatory ability, higher
9
10 301 prevalence of chronic diseases[17, 26] and impaired immunity[37] in the elderly. Note
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12 302 that since aging is one of the risk factors of COPD, most patients in our study were over
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14 303 64, giving more power to achieve statistical significance. However, some studies showed
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16 304 the opposite results.[6] It was speculated that the younger tend to spend more time
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18 305 outdoors, which increase opportunities for exposure to extremely cold temperature. In
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20 306 terms of gender, we found similar impacts of cold spells among males and females,
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22 307 which corresponds with previous studies.[4, 35, 36]

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26 308 Our study showed substantial effects of cold spells on the risk of COPD
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28 309 hospitalizations with a lagged effect of about 3 weeks. As a result, it is meaningful and
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30 310 urgent to provide effective and practical guidelines for preventions, particularly for COPD
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32 311 patients in response to cold spells in China. Both the government and individuals should
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34 312 take practical actions. The meteorological departments should improve early warning
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36 313 systems with timely forecast and publication of extremely cold events. Moreover, the
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38 314 government should exert great efforts to raise public awareness of the health hazards of
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40 315 cold spells and ensure adequate public and medical services coping with cold spells.[4]
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42 316 As for individuals, it has been reported that staying indoor and wearing warm clothing
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44 317 could reduce mortality in extremely cold weather.[38] Tseng et al. suggested that COPD
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46 318 patients who received inhaled medicine were less affected by cold temperature-related
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48 319 COPD exacerbation.[36] Therefore, keeping warm, minimizing the outdoor activities and
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50 320 taking medication regularly are vital measures to fight against cold spells for individuals
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52 321 with COPD.

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58 322 The main strengths of our study are as follows: Firstly, to the best of our knowledge,
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3 323 this is the first study to investigate the relationship between cold spells and COPD
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6 324 hospitalizations in China. Secondly, we controlled the confounding factors of air pollution
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8 325 and influenza infections, which were not considered by some previous studies. Existing
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10 326 literature has shown that both air pollutants and influenza may influence the health
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12 327 effects of low temperatures.[38, 39] Thirdly, we identified the elderly more vulnerable to
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15 328 cold spells by stratified analyses, which guide more targeted prevention strategies.
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17 329 Meanwhile, the study also has several limitations: Firstly, as an ecological study, the
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19 330 association between cold spells and COPD hospitalizations does not imply causality.
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21 331 Secondly, different socio-economic status or other factors on an individual level might be
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23 332 confounding factors and were not considered in the association. Thirdly, the
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25 333 meteorological variables and AQI were all from monitoring stations, not reflecting the
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27 334 individual level of exposures. Moreover, people are more likely to stay indoors with
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29 335 heating system during extremely cold days in northern China, so inevitable exposure
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31 336 measurement errors may lead to bias. Lastly, the data from only one city weakens the
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33 337 extrapolation validity of the study.
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40 339 **CONCLUSION**

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42 340 Our study demonstrates that short-term exposure to cold spells is associated with an
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44 341 increased risk of COPD hospitalizations. The cumulative effects increased with the
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46 342 intensities and the durations of cold spells. The elderly are more vulnerable to COPD
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48 343 hospitalizations during cold spell periods. These findings provide scientific foundations for
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50 344 comprehensive public health strategies to reduce cold spell-related COPD
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52 345 hospitalizations in Beijing, China.
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58 347 **Contributors:** YL and YC are joint first author and designed the study. ZF obtained the
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3 348 original data and funding. DK, XL, JF, YZ and ZC preprocessed the data. YL, YC, and YZ
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5 349 analyzed the data. YL and YC drafted the manuscript. XZ, KX, CJ and ZF reviewed and
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8 350 edited the manuscript. All authors have read and approved the final manuscript. ZF is the
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10 351 study guarantor.

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20 356 **Competing interests:** None declared.

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22 357 **Ethical approval:** This study was approved by the ethical review committee of Peking
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24 358 Union Medical College Hospital.

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26 359 **Data sharing statement:** No additional data are available.
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360 **REFERENCES**

- 361 1 IPCC, 2014. *Climate Change 2014: Synthesis Report. Contribution of Working Groups I,*
362 *II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change*
363 [Core Writing Team, R.K. Pachauri and L.A. Meyer (eds.)]. IPCC, Geneva, Switzerland, 151
364 pp.
- 365 2 Cohen J, Screen JA, Furtado JC, *et al.* Recent Arctic amplification and extreme mid-
366 latitude weather. *Nature Geoscience* 2014;**7**:627-37.
- 367 3 Zhang J, Tian W, Chipperfield MP, *et al.* Persistent shift of the Arctic polar vortex towards
368 the Eurasian continent in recent decades. *Nature Climate Change* 2016;**6**:1094-9.
- 369 4 Chen J, Yang J, Zhou M, *et al.* Cold spell and mortality in 31 Chinese capital cities:
370 Definitions, vulnerability and implications. *Environment international* 2019;**128**:271-8.
- 371 5 Lee W, Choi HM, Lee JY, *et al.* Temporal changes in mortality impacts of heat wave and
372 cold spell in Korea and Japan. *Environment international* 2018;**116**:136-46.
- 373 6 Han J, Liu S, Zhang J, *et al.* The impact of temperature extremes on mortality: a time-
374 series study in Jinan, China. *BMJ open* 2017;**7**:e014741.
- 375 7 Rabe KF, Watz H. Chronic obstructive pulmonary disease. *The Lancet* 2017;**389**:1931-
376 40.
- 377 8 Lopez-Campos JL, Tan W, Soriano JB. Global burden of COPD. *Respirology*
378 2016;**21**:14-23.
- 379 9 Donaldson GC, Goldring JJ, Wedzicha JA. Influence of season on exacerbation
380 characteristics in patients with COPD. *Chest* 2012;**141**:94-100.
- 381 10 McCormack MC, Paulin LM, Gummerson CE, *et al.* Colder temperature is associated
382 with increased COPD morbidity. *Eur Respir J* 2017;**49**.
- 383 11 Chaturvedi S, Tseng C-M, Chen Y-T, *et al.* The Effect of Cold Temperature on Increased
384 Exacerbation of Chronic Obstructive Pulmonary Disease: A Nationwide Study. *PloS one*
385 2013;**8**.
- 386 12 Monteiro A, Carvalho V, Gois J, *et al.* Use of "Cold Spell" indices to quantify excess
387 chronic obstructive pulmonary disease (COPD) morbidity during winter (November to March
388 2000-2007): case study in Porto. *International journal of biometeorology* 2013;**57**:857-70.
- 389 13 Wang C, Xu J, Yang L, *et al.* Prevalence and risk factors of chronic obstructive
390 pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-
391 sectional study. *The Lancet* 2018;**391**:1706-17.
- 392 14 Xie H, Yao Z, Zhang Y, *et al.* Short-term effects of the 2008 cold spell on mortality in
393 three subtropical cities in Guangdong Province, China. *Environmental health perspectives*
394 2013;**121**:210-6.
- 395 15 Zhou B, Gu L, Ding Y, *et al.* The Great 2008 Chinese Ice Storm: Its Socioeconomic-
396 Ecological Impact and Sustainability Lessons Learned. *Bulletin of the American*
397 *Meteorological Society* 2011;**92**:47-60.
- 398 16 Ban J, Huang L, Chen C, *et al.* Integrating new indicators of predictors that shape the

- 1
2
3 399 public's perception of local extreme temperature in China. *The Science of the total*
4 400 *environment* 2017;**579**:529-36.
- 5
6 401 17 Wang L, Liu T, Hu M, *et al.* The impact of cold spells on mortality and effect modification
7 402 by cold spell characteristics. *Scientific reports* 2016;**6**:38380.
- 8
9 403 18 Gao J, Yu F, Xu Z, *et al.* The association between cold spells and admissions of
10 404 ischemic stroke in Hefei, China: Modified by gender and age. *The Science of the total*
11 405 *environment* 2019;**669**:140-7.
- 12
13 406 19 Wedzicha JA, Seemungal TAR. COPD exacerbations: defining their cause and
14 407 prevention. *The Lancet* 2007;**370**:786-96.
- 15
16 408 20 Cowling BJ, Wong IO, Ho LM, *et al.* Methods for monitoring influenza surveillance data.
17 409 *Int J Epidemiol* 2006;**35**:1314-21.
- 18
19 410 21 Song X, Wang S, Li T, *et al.* The impact of heat waves and cold spells on respiratory
20 411 emergency department visits in Beijing, China. *The Science of the total environment*
21 412 2018;**615**:1499-505.
- 22
23 413 22 Guo Y, Jiang F, Peng L, *et al.* The association between cold spells and pediatric
24 414 outpatient visits for asthma in Shanghai, China. *PloS one* 2012;**7**:e42232.
- 25
26 415 23 Gasparrini A. Modeling exposure-lag-response associations with distributed lag non-
27 416 linear models. *Stat Med* 2014;**33**:881-99.
- 28
29 417 24 Cheng Q, Wang X, Wei Q, *et al.* The short-term effects of cold spells on pediatric
30 418 outpatient admission for allergic rhinitis in Hefei, China. *The Science of the total environment*
31 419 2019;**664**:374-80.
- 32
33 420 25 Liang Z, Wang P, Zhao Q, *et al.* Effect of the 2008 cold spell on preterm births in two
34 421 subtropical cities of Guangdong Province, Southern China. *The Science of the total*
35 422 *environment* 2018;**642**:307-13.
- 36
37 423 26 de'Donato FK, Leone M, Noce D, *et al.* The impact of the February 2012 cold spell on
38 424 health in Italy using surveillance data. *PloS one* 2013;**8**:e61720.
- 39
40 425 27 Lin Z, Gu Y, Liu C, *et al.* Effects of ambient temperature on lung function in patients with
41 426 chronic obstructive pulmonary disease: A time-series panel study. *The Science of the total*
42 427 *environment* 2018;**619-620**:360-5.
- 43
44 428 28 Donaldson GC, Seemungal T, Jeffries DJ, *et al.* Effect of temperature on lung function
45 429 and symptoms in chronic obstructive pulmonary disease. *Eur Respir J* 1999;**13**:844-9.
- 46
47 430 29 Koskela HO, Koskela AK, Tukiainen HO. Bronchoconstriction due to cold weather in
48 431 COPD. The roles of direct airway effects and cutaneous reflex mechanisms. *Chest*
49 432 1996;**110**:632-6.
- 50
51 433 30 Shephard RJ, Shek PN. Cold exposure and immune function. *Can J Physiol Pharmacol*
52 434 1998;**76**:828-36.
- 53
54 435 31 Lowen AC, Mubareka S, Steel J, *et al.* Influenza virus transmission is dependent on
55 436 relative humidity and temperature. *PLoS pathogens* 2007;**3**:1470-6.
- 56
57 437 32 Li M, Li Q, Yang G, *et al.* Cold temperature induces mucin hypersecretion from normal
58
59
60

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2
3 438 human bronchial epithelial cells in vitro through a transient receptor potential melastatin 8
4 439 (TRPM8)-mediated mechanism. *J Allergy Clin Immunol* 2011;**128**:626-34.e1-5.
5
6 440 33 Juan Y, Haiqiao W, Xie W, *et al.* Cold-inducible RNA-binding protein mediates airway
7 441 inflammation and mucus hypersecretion through a post-transcriptional regulatory mechanism
8 442 under cold stress. *Int J Biochem Cell Biol* 2016;**78**:335-48.
9
10 443 34 Chung Y, Noh H, Honda Y, *et al.* Temporal Changes in Mortality Related to Extreme
11 444 Temperatures for 15 Cities in Northeast Asia: Adaptation to Heat and Maladaptation to Cold.
12 445 *American journal of epidemiology* 2017;**185**:907-13.
13
14 446 35 Ma W, Yang C, Chu C, *et al.* The impact of the 2008 cold spell on mortality in Shanghai,
15 447 China. *International journal of biometeorology* 2013;**57**:179-84.
16
17 448 36 Tseng CM, Chen YT, Ou SM, *et al.* The effect of cold temperature on increased
18 449 exacerbation of chronic obstructive pulmonary disease: a nationwide study. *PloS one*
19 450 2013;**8**:e57066.
20
21 451 37 Goodwin JS. Decreased immunity and increased morbidity in the elderly. *Nutr Rev*
22 452 1995;**53**:S41-4; discussion S4-6.
23
24 453 38 Donaldson GC, Ermakov SP, Komarov YM, *et al.* Cold related mortalities and protection
25 454 against cold in Yakutsk, eastern Siberia: observation and interview study. *BMJ* 1998;**317**:978-
26 455 82.
27
28 456 39 Qiu H, Tan K, Long F, *et al.* The Burden of COPD Morbidity Attributable to the Interaction
29 457 between Ambient Air Pollution and Temperature in Chengdu, China. *International journal of*
30 458 *environmental research and public health* 2018;**15**.
31
32 459 40 Huynen MM, Martens P, Schram D, *et al.* The impact of heat waves and cold spells on
33 460 mortality rates in the Dutch population. *Environmental health perspectives* 2001;**109**:463-70.
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Table 1 Statistic summary of daily hospitalizations for COPD, meteorological variables and air quality index in cold seasons (November-March) in Beijing, China, 2012–2016.

	Total	Mean (SD)	Min	P25	Media n	P75	Max
COPD cases	8457	111.7(41.0)	22.0	78.0	113.0	141.0	226.0
Gender	1)					
Male	5382	71.1(25.8)	12.0	49.0	75.0	89.0	158.0
Female	3074	40.6(17.7)	7.0	27.0	39.0	53.0	110.0
Age	2						
0-64 years old	1360	18.0(8.3)	2.0	12.0	18.0	23.0	43.0
≥65 years old	7097	93.8(34.3)	19.0	67.0	95.0	118.0	189.0
Mean temperature (°C)	/	0.9(5.4)	-16.0	-3.0	0.0	4.0	18.0
Relative humidity (%)	/	46.6(20.4)	8.0	30.0	43.0	61.0	98.0
Air pressure (hPa)	/	1025.3(6.5)	1005.0	1021.0	1026.0	1030.0	1044.0
Air quality index	/	126.3(89.2)	17.0	61.0	97.0	170.0	485.0

COPD, chronic obstructive pulmonary disease; P25, the 25th percentile; P75, the 75th percentile; SD, standard deviation.

Table 2 Overview information of cold spells under different definitions

Model	Temperature threshold	Duration	Cold spell episodes	Cold spell days	Non-cold spell days	Q-AIC value
1	$\leq 10\%$ (-6°C)	$\geq 2\text{d}$	17	77	680	7819.6
2	$\leq 10\%$ (-6°C)	$\geq 3\text{d}$	11	65	692	7799.7
3	$\leq 10\%$ (-6°C)	$\geq 4\text{d}$	6	50	707	7769.8
4	$\leq 5\%$ (-7°C)	$\geq 2\text{d}$	8	37	720	7794.3
5	$\leq 5\%$ (-7°C)	$\geq 3\text{d}$	5	31	726	7786.6
6	$\leq 5\%$ (-7°C)	$\geq 4\text{d}$	3	25	732	7782.5
7	$\leq 3\%$ (-8°C)	$\geq 2\text{d}$	7	23	734	7786.5
8	$\leq 3\%$ (-8°C)	$\geq 3\text{d}$	5	19	738	7789.8
9	$\leq 3\%$ (-8°C)	$\geq 4\text{d}$	2	10	747	7804.4

Q-AIC, quasi-Poisson Akaike Information Criterion.

Table 3 Cumulative relative risk of cold spells under different definitions on COPD hospitalizations of the total population in Beijing, 2012-2016.

Definition	CRR (95% CI)			
	Lag0	Lag0-7	Lag0-14	Lag0-21
≤10% & ≥2d	1.030 (1.002-1.058)*	1.200 (1.087-1.326)*	1.278 (1.134-1.439)*	1.236 (1.055-1.438)*
≤10% & ≥3d	1.027 (1.000-1.054)*	1.188 (1.084-1.303)*	1.299 (1.166-1.448)*	1.353 (1.161-1.577)*
≤10% & ≥4d	1.042 (1.013-1.072)*	1.249 (1.136-1.374)*	1.343 (1.206-1.496)*	1.394 (1.193-1.630)*
≤5% & ≥2d	1.012 (0.980-1.045)	1.173 (1.055-1.304)*	1.344 (1.134-1.439)*	1.354 (1.141-1.608)*
≤5% & ≥3d	1.031 (1.000-1.063)*	1.235 (1.114-1.369)*	1.381 (1.220-1.563)*	1.428 (1.206-1.692)*
≤5% & ≥4d	1.042 (1.006-1.079)*	1.268 (1.132-1.421)*	1.404 (1.234-1.598)*	1.511 (1.262-1.809)*
≤3% & ≥2d	0.982 (0.944-1.021)	1.113 (0.960-1.290)	1.412 (1.171-1.703)*	1.444 (1.113-1.873)*
≤3% & ≥3d	1.009 (0.970-1.049)	1.217 (1.051-1.411)*	1.525 (1.264-1.841)*	1.659 (1.278-2.154)*
≤3% & ≥4d	0.992 (0.951-1.035)	1.201 (0.999-1.443)	1.644 (1.261-2.145)*	1.889 (1.315-2.712)*

CI, confidence interval; CRR, cumulative relative risk.

* $p < 0.05$.

Table 4 Cumulative relative risk of cold spells on COPD hospitalizations stratified by gender and age in Beijing, 2012-2016.

Subgroup	CRR (95% CI)			
	Lag0	Lag0-7	Lag0-14	Lag0-21
Male	1.042 (1.011-1.074)*	1.243 (1.123-1.375)*	1.316 (1.173-1.477)*	1.342 (1.136-1.586)*
Female	1.041 (1.005-1.077)*	1.257 (1.119-1.411)*	1.383 (1.215-1.574)*	1.476 (1.211-1.783)*
Age<65	1.017 (0.972-1.064)	1.120 (0.963-1.303)	1.159 (0.977-1.376)	1.107 (0.862-1.422)
Age≥65	1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.382 (1.240-1.540)*	1.456 (1.244-1.705)*

CI, confidence interval; CRR, cumulative relative risk.

* $p < 0.05$.

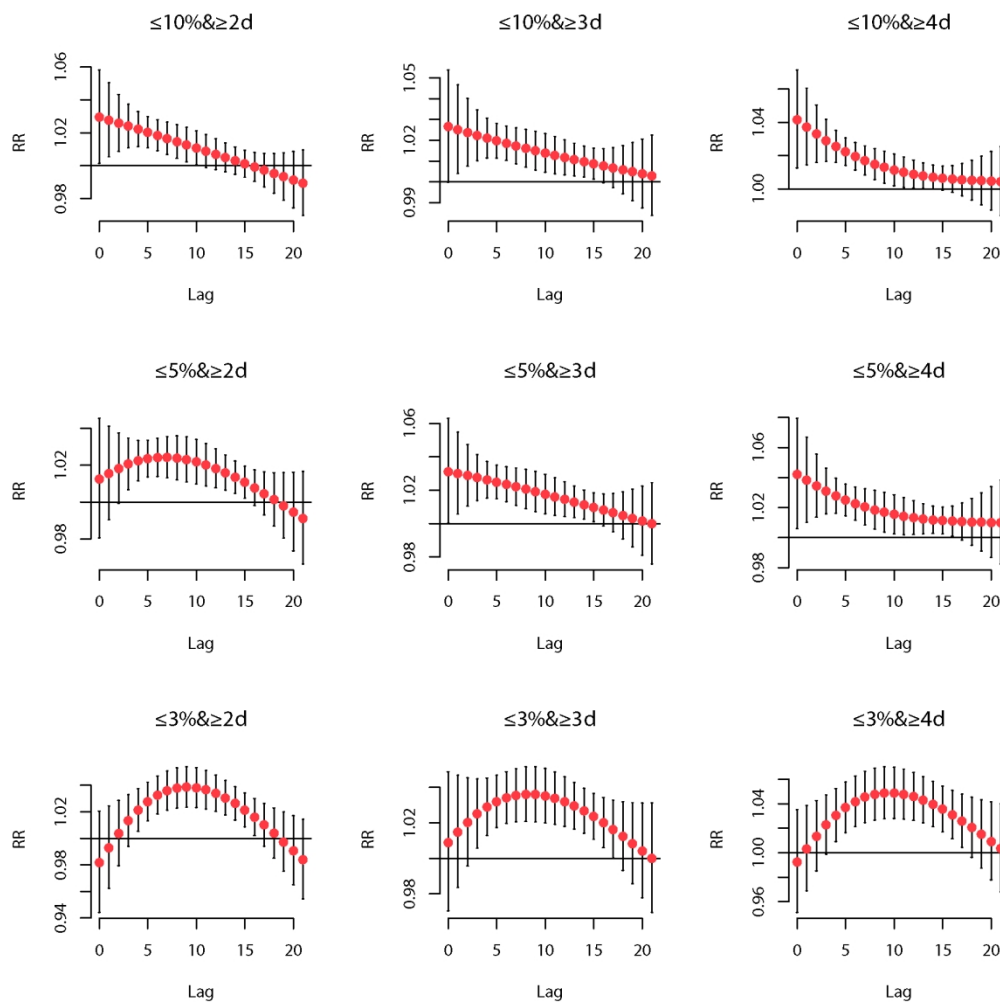


Figure 1 Lag-response relationships between cold spells under different definitions and AECOPD hospitalizations of the total population in Beijing, 2012-2016.

161x159mm (300 x 300 DPI)

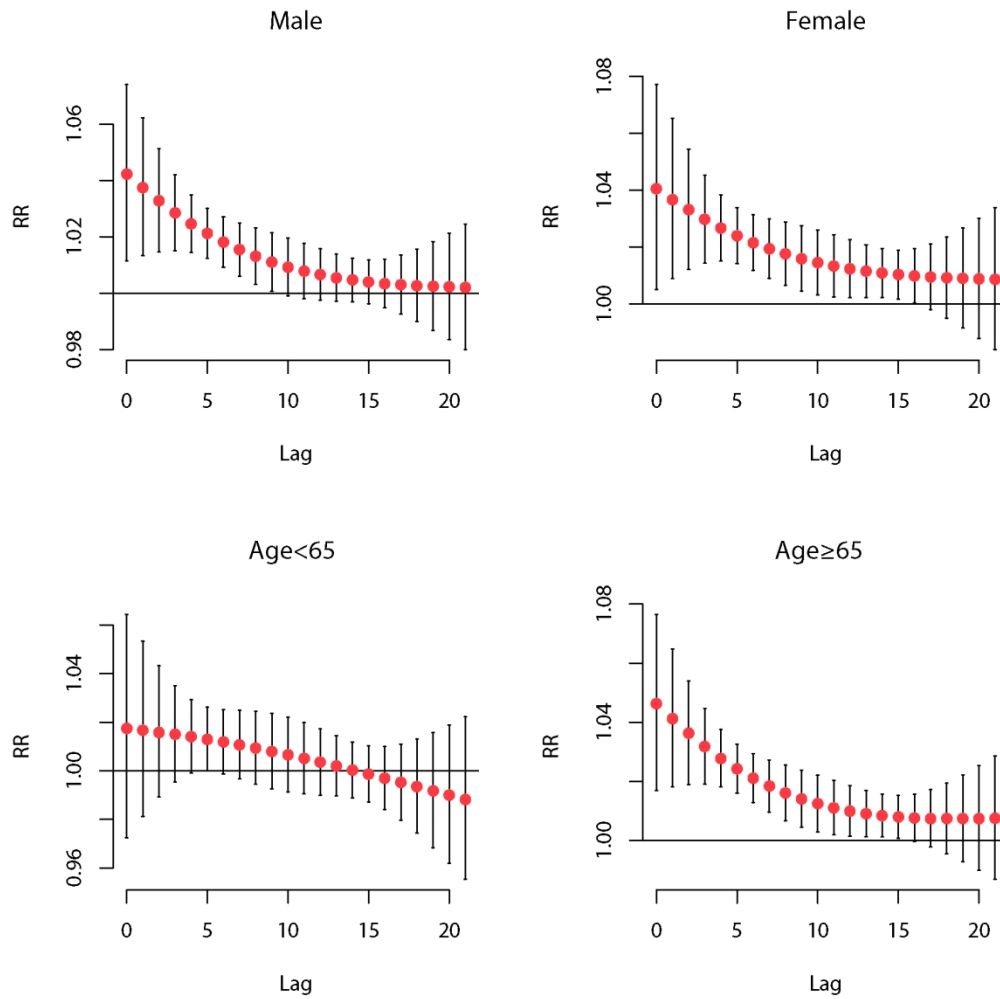


Figure 2 Lag-response relationships between cold spells and AECOPD hospitalizations stratified by gender and age in Beijing, 2012-2016.

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Supplementary Materials

Supplementary Tables

Table S1 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for lag dimension in the DLM model

Table S2 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for time per year in the DLM model

Table S3 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for relative humidity in the DLM model

Table S4 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for air pressure in the DLM model

Table S5 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for air quality index in the DLM model

Table S1 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for lag dimension in the DLM model

df for lag dimension	Group	CRR (95% CI)			
		Lag0	Lag0-7	Lag0-14	Lag0-21
3 ^a	Total	1.042 (1.013-1.072)*	1.249 (1.136-1.374)*	1.343 (1.206-1.496)*	1.394 (1.193-1.630)*
	Male	1.042 (1.011-1.074)*	1.243 (1.123-1.375)*	1.316 (1.173-1.477)*	1.342 (1.136-1.586)*
	Female	1.041 (1.005-1.077)*	1.257 (1.119-1.411)*	1.383 (1.215-1.574)*	1.476 (1.211-1.783)*
	Age<65	1.017 (0.972-1.064)	1.120 (0.963-1.303)	1.159 (0.977-1.376)	1.107 (0.862-1.422)
	Age≥65	1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.382 (1.240-1.540)*	1.456 (1.244-1.705)*
	Total	0.989 (0.926-1.057)	1.265 (1.149-1.392)*	1.311 (1.173-1.465)*	1.382 (1.182-1.615)*
	Male	0.992 (0.925-1.064)	1.257 (1.135-1.393)*	1.285 (1.141-1.448)*	1.331 (1.126-1.573)*
4	Female	0.983 (0.906-1.067)	1.274 (1.133-1.432)*	1.347 (1.178-1.540)*	1.462 (1.210-1.766)*
	Age<65	0.919 (0.827-1.022)	1.151 (0.988-1.340)	1.106 (0.926-1.320)	1.091 (0.850-1.401)
	Age≥65	1.003 (0.938-1.073)	1.288 (1.169-1.419)*	1.355 (1.211-1.515)*	1.446 (1.235-1.692)*
	Total	1.001 (0.888-1.128)	1.271 (1.150-1.404)*	1.313 (1.174-1.468)*	1.389 (1.185-1.628)*
5	Male	0.999 (0.880-1.136)	1.261 (1.134-1.403)*	1.287 (1.141-1.451)*	1.336 (1.127-1.583)*
	Female	1.004 (0.868-1.161)	1.285 (1.137-1.451)*	1.350 (1.180-1.545)*	1.474 (1.216-1.787)*
	Age<65	0.892 (0.737-1.080)	1.143 (0.975-1.341)	1.102 (0.922-1.317)	1.084 (0.840-1.398)
	Age≥65	1.023 (0.907-1.155)	1.297 (1.172-1.434)*	1.358 (1.213-1.520)*	1.456 (1.240-1.710)*

CI, confidence interval; df, degree of freedom; RR, relative risk.

* $P < 0.05$.^aUsed in the study.

Table S2 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for time per year in the DLM model

df for time per year	Group	CRR (95% CI)			
		Lag0	Lag0-7	Lag0-14	Lag0-21
3 ^a	Total	1.042 (1.013-1.072)*	1.249 (1.136-1.374)*	1.343 (1.206-1.496)*	1.394 (1.193-1.630)*
	Male	1.042 (1.011-1.074)*	1.243 (1.123-1.375)*	1.316 (1.173-1.477)*	1.342 (1.136-1.586)*
	Female	1.041 (1.005-1.077)*	1.257 (1.119-1.411)*	1.383 (1.215-1.574)*	1.476 (1.211-1.783)*
	Age<65	1.017 (0.972-1.064)	1.120 (0.963-1.303)	1.159 (0.977-1.376)	1.107 (0.862-1.422)
	Age≥65	1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.382 (1.240-1.540)*	1.456 (1.244-1.705)*
	4	Total	1.023 (0.992-1.055)	1.150 (1.033-1.280)*	1.218 (1.078-1.376)*
Male		1.029 (0.997-1.063)	1.173 (1.045-1.316)*	1.226 (1.074-1.399)*	1.225 (1.015-1.480)*
Female		1.011 (0.974-1.050)	1.107 (0.971-1.262)	1.196 (1.034-1.385)*	1.232 (0.998-1.520)
Age<65		1.010 (0.961-1.061)	1.077 (0.906-1.280)	1.105 (0.907-1.345)	1.056 (0.795-1.401)
Age≥65		1.026 (0.995-1.058)	1.166 (1.046-1.300)*	1.244 (1.100-1.406)*	1.272 (1.067-1.517)*
5		Total	1.022 (0.990-1.056)	1.144 (1.008-1.298)*	1.208 (1.031-1.415)*
	Male	1.030 (0.994-1.066)	1.171 (1.021-1.343)*	1.222 (1.027-1.452)*	1.223 (0.960-1.559)
	Female	1.009 (0.970-1.050)	1.093 (0.938-1.275)	1.174 (0.972-1.418)	1.203 (0.923-1.569)
	Age<65	1.011 (0.959-1.066)	1.082 (0.883-1.327)	1.127 (0.874-1.453)	1.127 (0.788-1.612)
	Age≥65	1.025 (0.992-1.059)	1.158 (1.019-1.316)*	1.227 (1.045-1.440)*	1.245 (0.994-1.559)

CI, confidence interval; df, degree of freedom; RR, relative risk.

* $P < 0.05$.

^aUsed in the study.

Table S3 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for relative humidity in the DLM model

df for relative humidity	Group	CRR (95% CI)			
		Lag0	Lag0-7	Lag0-14	Lag0-21
3 ^a	Total	1.042 (1.013-1.072)*	1.249 (1.136-1.374)*	1.343 (1.206-1.496)*	1.394 (1.193-1.630)*
	Male	1.042 (1.011-1.074)*	1.243 (1.123-1.375)*	1.316 (1.173-1.477)*	1.342 (1.136-1.586)*
	Female	1.041 (1.005-1.077)*	1.257 (1.119-1.411)*	1.383 (1.215-1.574)*	1.476 (1.211-1.783)*
	Age<65	1.017 (0.972-1.064)	1.120 (0.963-1.303)	1.159 (0.977-1.376)	1.107 (0.862-1.422)
	Age≥65	1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.382 (1.240-1.540)*	1.456 (1.244-1.705)*
	4	Total	1.041 (1.012-1.071)*	1.248 (1.135-1.373)*	1.343 (1.205-1.495)*
Male		1.042 (1.011-1.073)*	1.240 (1.120-1.372)*	1.314 (1.170-1.475)*	1.336 (1.130-1.580)*
Female		1.041 (1.006-1.078)*	1.259 (1.120-1.414)*	1.385 (1.217-1.578)*	1.482 (1.225-1.792)*
Age<65		1.017 (0.972-1.064)	1.119 (0.961-1.302)	1.158 (0.975-1.375)	1.105 (0.859-1.420)
Age≥65		1.046 (1.017-1.076)*	1.274 (1.157-1.403)*	1.381 (1.239-1.540)*	1.455 (1.242-1.704)*
5		Total	1.041 (1.012-1.071)*	1.244 (1.131-1.369)*	1.337 (1.200-1.490)*
	Male	1.041 (1.010-1.073)*	1.236 (1.116-1.368)*	1.307 (1.164-1.468)*	1.327 (1.121-1.569)*
	Female	1.040 (1.005-1.077)*	1.256 (1.117-1.411)*	1.381 (1.212-1.574)*	1.474 (1.218-1.785)*
	Age<65	1.015 (0.970-1.062)	1.111 (0.955-1.293)	1.148 (0.967-1.363)	1.089 (0.847-1.400)
	Age≥65	1.046 (1.016-1.076)*	1.271 (1.154-1.400)*	1.377 (1.234-1.536)*	1.448 (1.235-1.697)*

CI, confidence interval; df, degree of freedom; RR, relative risk.

* $P < 0.05$.

^aUsed in the study.

Table S4 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for air pressure in the DLM model

df for air pressure	Group	CRR (95% CI)			
		Lag0	Lag0-7	Lag0-14	Lag0-21
3 ^a	Total	1.042 (1.013-1.072)*	1.249 (1.136-1.374)*	1.343 (1.206-1.496)*	1.394 (1.193-1.630)*
	Male	1.042 (1.011-1.074)*	1.243 (1.123-1.375)*	1.316 (1.173-1.477)*	1.342 (1.136-1.586)*
	Female	1.041 (1.005-1.077)*	1.257 (1.119-1.411)*	1.383 (1.215-1.574)*	1.476 (1.211-1.783)*
	Age<65	1.017 (0.972-1.064)	1.120 (0.963-1.303)	1.159 (0.977-1.376)	1.107 (0.862-1.422)
	Age≥65	1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.382 (1.240-1.540)*	1.456 (1.244-1.705)*
	4	Total	1.042 (1.012-1.071)*	1.248 (1.134-1.373)*	1.342 (1.205-1.495)*
Male		1.042 (1.011-1.074)*	1.240 (1.120-1.373)*	1.313 (1.170-1.475)*	1.340 (1.134-1.584)*
Female		1.041 (1.005-1.078)*	1.259 (1.120-1.414)*	1.385 (1.216-1.578)*	1.478 (1.223-1.786)*
Age<65		1.018 (0.973-1.065)	1.123 (0.965-1.306)	1.162 (0.978-1.380)	1.109 (0.863-1.425)
Age≥65		1.046 (1.016-1.076)*	1.273 (1.156-1.402)*	1.380 (1.238-1.539)*	1.455 (1.242-1.704)*
5		Total	1.041 (1.012-1.071)*	1.247 (1.133-1.373)*	1.342 (1.204-1.495)*
	Male	1.042 (1.011-1.074)*	1.240 (1.120-1.374)*	1.314 (1.170-1.476)*	1.341 (1.134-1.585)*
	Female	1.041 (1.005-1.077)*	1.257 (1.118-1.413)*	1.383 (1.214-1.576)*	1.475 (1.220-1.784)*
	Age<65	1.019 (0.974-1.067)	1.129 (0.970-1.314)	1.168 (0.984-1.388)	1.115 (0.868-1.433)
	Age≥65	1.046 (1.016-1.076)*	1.271 (1.154-1.401)*	1.378 (1.235-1.537)*	1.452 (1.240-1.701)*

CI, confidence interval; df, degree of freedom; RR, relative risk.

* $P < 0.05$.

^aUsed in the study.

Table S5 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for air quality index in the DLM model

df for AQI	Group	CRR (95% CI)			
		Lag0	Lag0-7	Lag0-14	Lag0-21
3 ^a	Total	1.042 (1.013-1.072)*	1.249 (1.136-1.374)*	1.343 (1.206-1.496)*	1.394 (1.193-1.630)*
	Male	1.042 (1.011-1.074)*	1.243 (1.123-1.375)*	1.316 (1.173-1.477)*	1.342 (1.136-1.586)*
	Female	1.041 (1.005-1.077)*	1.257 (1.119-1.411)*	1.383 (1.215-1.574)*	1.476 (1.211-1.783)*
	Age<65	1.017 (0.972-1.064)	1.120 (0.963-1.303)	1.159 (0.977-1.376)	1.107 (0.862-1.422)
	Age≥65	1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.382 (1.240-1.540)*	1.456 (1.244-1.705)*
	4	Total	1.042 (1.013-1.072)*	1.249 (1.135-1.374)*	1.342 (1.205-1.495)*
Male		1.042 (1.012-1.074)*	1.242 (1.123-1.375)*	1.315 (1.171-1.476)*	1.342 (1.135-1.586)*
Female		1.041 (1.005-1.077)*	1.257 (1.119-1.412)*	1.382 (1.214-1.573)*	1.475 (1.221-1.783)*
Age<65		1.018 (0.973-1.065)	1.120 (0.963-1.303)	1.157 (0.974-1.373)	1.106 (0.861-1.421)
Age≥65		1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.381 (1.239-1.539)*	1.456 (1.243-1.704)*
5		Total	1.042 (1.013-1.071)*	1.249 (1.136-1.373)*	1.347 (1.210-1.500)*
	Male	1.042 (1.011-1.074)*	1.242 (1.123-1.373)*	1.320 (1.177-1.480)*	1.355 (1.148-1.601)*
	Female	1.041 (1.005-1.077)*	1.257 (1.119-1.412)*	1.385 (1.216-1.577)*	1.482 (1.226-1.792)*
	Age<65	1.018 (0.973-1.065)	1.120 (0.963-1.303)	1.161 (0.978-1.378)	1.116 (0.869-1.433)
	Age≥65	1.046 (1.017-1.076)*	1.275 (1.159-1.403)*	1.386 (1.243-1.545)*	1.468 (1.254-1.718)*

AQI, air quality index; CI, confidence interval; df, degree of freedom; RR, relative risk.

* $P < 0.05$.

^aUsed in the study.

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The short-term effects of cold spells on hospitalizations for acute exacerbation of chronic obstructive pulmonary disease: a time-series study in Beijing, China

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4 1 **The short-term effects of cold spells on hospitalizations for acute exacerbation**
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6 2 **of chronic obstructive pulmonary disease: a time-series study in Beijing, China**
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50 21 **Keywords:** cold spells, acute exacerbation of chronic obstructive pulmonary disease,
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52 22 hospitalizations, intensity and duration
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4 23 **ABSTRACT**

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6 24 **Objectives:** Our work aimed at exploring the relationship between cold spells and acute
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8 25 exacerbation of chronic obstructive pulmonary disease (AECOPD) hospitalizations in
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10 26 Beijing, China, and assessing the moderating effects of the intensities and the durations
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13 27 of cold spells, as well as identifying the vulnerable.

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15 28 **Design:** A time-series study.

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18 29 **Setting:** We obtained time-series data of AECOPD hospitalizations, meteorological
19
20 30 variables and air quality index in Beijing, China during 2012–2016.

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22 31 **Participants:** All AECOPD hospitalizations among permanent residents in Beijing,
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24 32 China in cold seasons (November to March) during 2012-2016 were included.
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26 33 (n=84,571).

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29 34 **Primary and secondary outcome measures:** A quasi-Poisson regression with a
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31 35 distributed lag model was fitted to investigate the short-term effects of cold spells on
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33 36 AECOPD hospitalizations by comparing the counts of AECOPD admissions during
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35 37 cold spell days with those during non-cold spell days.

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38 38 **Results:** Cold spells under different definitions were associated with increased risks of
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40 39 AECOPD hospitalizations, with the maximum cumulative relative risk (CRR) over three
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42 40 weeks (lag0-21). The cumulative effects at lag0-21 increased with the intensities and the
43
44 41 durations of cold spells. Under the optimal definition, the most significant single-day
45
46 42 relative risk (RR) was found on the days of cold spells (lag0) with RR=1.042 (95%CI:
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48 43 1.013, 1.072), and the CRR at lag0-21 was 1.394 (95%CI: 1.193, 1.630). The elderly
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50 44 (aged \geq 65) were more vulnerable to the effects of cold spells on AECOPD
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52 45 hospitalizations.
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57 46 **Conclusion:** Cold spells are associated with increased AECOPD hospitalizations in
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3 47 Beijing, with the cumulative effects increased with their intensities and durations. The
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6 48 elderly are at particular risk of AECOPD hospitalizations triggered by cold spells.
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11 **Strengths and limitations of this study:**

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13 51 · This study was the first to examine the association between cold spells and
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15 52 AECOPD hospitalizations in China.
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17 53 · The study assessed the effects of cold spells under different definitions on AECOPD
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19 54 hospitalizations to find out the optimal cold spell definition on the issue.
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22 55 · The ecological design cannot imply causality definitely, while limited information on
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24 56 individual-level factors and inevitable exposure measurement errors may lead to
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26 57 bias.
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29 58 · The data from one specific city limited the extrapolation of the findings.
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33 **INTRODUCTION**

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36 61 The Intergovernmental Panel on Climate Change (IPCC) has predicted that human
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38 62 activities and global climate change cause variations in frequency, intensity and duration
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40 63 of many extreme weather events, including heatwaves and cold spells.[1] Although the
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42 64 amount of cold spells may decrease over most land areas due to global warming, a few
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45 65 recent studies found that the persistent shift of the Arctic polar vortex and Arctic
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47 66 amplification associated with global warming could lead to increased extremely cold
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49 67 events in mid-latitudes.[2, 3]. Over the last few years, the impacts of cold spells on
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52 68 human health have gained growing attention from the public. Many studies have reported
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54 69 positive relationships between cold spells and mortality[4-6] while the impacts of cold
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56 70 spells on hospital visits or admissions are under-examined.

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59 71 Chronic obstructive pulmonary disease (COPD) is one of the common respiratory
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3 72 diseases characterized by poorly reversible limitation of airflow.[7] Owing to its high
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5 73 prevalence, morbidity, mortality and economic burden globally, COPD has been an
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8 74 important public health concern and will remain a huge challenge for healthcare
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10 75 practitioners in the foreseeable future.[8] Thus, it is crucial to identify the risk factors of
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12 76 COPD to improve strategies on prevention and intervention. Given the projected climate
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14 77 change, extreme temperature events potentially pose threats to COPD patients. Many
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16 78 epidemiological studies have indicated that COPD has higher rates of exacerbation and
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18 79 hospitalization with lower temperatures.[9-13] We hypothesized that cold spells, defined
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20 80 as prolonged periods of extremely cold weather, may be more detrimental to COPD
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22 81 patients, and could cause more hospitalizations for acute exacerbations (AECOPD).[14]
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24 82 However, few studies have been carried out on the association between cold spells and
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26 83 AECOPD hospitalizations.[15]
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31 84 As the world's largest country by population, China shoulders the enormous burden of
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33 85 COPD. A national cross-sectional study from 2012 to 2015 showed that the prevalence of
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35 86 COPD among Chinese adults aged 20 years and older was 8.6% (an estimated of 99.9
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37 87 million COPD patients).[16] On the other hand, with most areas located in mid-latitudes,
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39 88 China has experienced several severe cold spells in recent years. The cold spells in
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41 89 2008 resulted in a significantly higher all-cause mortality in subtropical China and
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43 90 estimated losses exceeding \$22.3 billion.[17, 18] Moreover, the public now has a better
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45 91 perception of the potential risks of extreme temperatures in China, especially those with
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47 92 chronic conditions.[19] Since no relevant studies have been reported in China, it is of
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49 93 great value to assess the association between cold spells and AECOPD hospitalizations
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51 94 to build prevention and adaption strategies suitable to local conditions (e.g., climate type,
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53 95 socio-demographic status of residents), which may be different from other regions.
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58 96 Cold spells have been defined differently due to the heterogeneity of climate and
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3 97 people's adaptive capacities in different regions. Previous studies suggested that the
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5 98 effects of cold spells varied by different cold spell characteristics and individual-specific
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8 99 factors.[20, 21] we have three main objectives in this work: (1) to illuminate the short-term
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10 100 effects of cold spells on the risk of hospitalizations for AECOPD with time-series
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12 101 methods; (2) to investigate the effect modification of cold spell intensities and durations
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14 102 by fitting different definitions and to explore the optimal cold spell definition in this region;
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17 103 (3) to identify potentially vulnerable populations through stratified analyses. The results
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19 104 could help better understand the relationship between extremely cold events and
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21 105 AECOPD hospitalizations, and provide scientific evidence in policymaking for local
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23 106 prevention and intervention of AECOPD.
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29 108 **MATERIALS AND METHODS**

30 109 **Data collection**

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32 110 Beijing, the capital of China, is located in the northern part of China (39°56'N,
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34 111 116°20'E). The area covers 16410.54 km², with more than 21 million population in 2016.
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37 112 Beijing has a typical semi-humid continental monsoon climate with four distinctive
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39 113 seasons.
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43 114 Daily hospitalizations for AECOPD from January 1, 2012, to December 31, 2016, were
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45 115 collected from the Beijing Public Health Information Center (<http://www.phic.org.cn/>). All
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47 116 government and private hospitals at the secondary or tertiary level in Beijing are required
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49 117 to submit their discharge records to the database.[22, 23] Each record consists of the
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51 118 following information: admission date, discharge date, age, gender, address, diagnosis
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53 119 and International Classification of Diseases 10th revision (ICD-10) diagnostic code. We
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55 120 excluded the records with missing or wrong information on residential addresses. Only
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57 121 those among Beijing residents admitted to hospitals with AECOPD as the primary
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4 122 discharge diagnosis (ICD-10: J44) were included in the study.[23] The study was
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6 123 approved by the ethical committee of Peking Union Medical College Hospital. All the data
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8 124 for the analysis were anonymous at collection.
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10 125 We collected the daily 2012–2016 meteorological data in Beijing from the China
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12 126 Meteorological Data Sharing Service System, including daily mean temperature (°C),
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14 127 daily mean relative humidity (%) and daily mean air pressure (hPa). For the same period,
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16 128 the daily air quality index (AQI) was obtained from the China National Environmental
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18 129 Monitoring Centre. The AQI value denotes the maximum value of individual air quality
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20 130 indexes (IAQI) of six monitored air pollutants (particulate matter with aerodynamic
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22 131 diameter < 2.5 μm (PM_{2.5}), particulate matter with aerodynamic diameter < 10 μm (PM₁₀),
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24 132 nitrogen dioxide, sulfur dioxide, carbon monoxide, and ozone). Considering the impact of
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26 133 influenza viral infectious on AECOPD,[13, 24] we also accessed the data of virological
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28 134 surveillance from the Chinese National Influenza Center (CNIC)
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30 135 (<http://www.chinaivdc.cn/cnic/>). The CNIC monitors the activity of seasonal influenza
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32 136 viruses in China and reports weekly positive rates of influenza isolations in the northern
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34 137 and southern parts separately. In this study, the onset of influenza epidemics (a binary
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36 138 variable representing days with relatively high influenza episodes)[25, 26] was defined as
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38 139 when the proportion of isolates positive for influenza in any given week exceeded 30% of
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40 140 the maximum weekly positive isolation rate in the whole surveillance season (Influenza
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42 141 surveillance season was defined from the 27th week of the previous year to the 26th week
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44 142 of the following year) in northern China.[27]
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52 144 **Cold spell definitions**

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54 145 The definition of cold spells varied across the research field due to distinct climatic
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56 146 features and temperature variations in different regions. As to the prior studies, cold
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4 147 spells were usually defined based on their temperature thresholds and durations.[4, 15,
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6 148 28] Instead of specific temperatures as thresholds, percentiles of temperature were
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8 149 shown to have a better model fit according to quasi-Poisson Akaike Information Criterion
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10 150 (Q-AIC).[6] Moreover, some researchers suggested that daily mean temperature is
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12 151 superior to the minimum or maximum temperature as an indicator to define cold spells
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14 152 because it reflects the exposure throughout the day rather than a short period.[20, 29]
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16 153 Therefore, we defined cold spell episodes as days when daily mean temperature at or
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18 154 below the 10th, 5th or 3rd percentile for at least 2, 3 or 4 consecutive days of the study
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20 155 period.[21] To avoid the possible biases caused by a few extreme summer events, we
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22 156 restricted the study period to the five coldest adjacent months (from November of the
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24 157 previous year to March of the following year) for each year.[6, 15, 20] The cold spell was
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26 158 treated as a dichotomous variable, with a value of 1 during the cold spell period. The
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28 159 statistical analyses were performed separately for each definition of cold spells.
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35 161 **Statistical methods**

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37 162 In the analyses, the dependent variable was the number of daily AECOPD
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39 163 hospitalizations following a quasi-Poisson distribution. Hence, we adopted a distributed
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41 164 lag model (DLM) [30] with a quasi-Poisson generalized linear regression model. To
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43 165 investigate the effects of cold spells on AECOPD hospitalizations, we compared the
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45 166 counts of AECOPD admissions during cold spell days with those during non-cold spell
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47 167 days, after adjusting for relative humidity, atmospheric pressure, AQI, seasonality, long-
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49 168 term trends, statutory holiday, influenza epidemics, and day of the week (DOW). The Q-
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51 169 AIC was employed to choose the optimal cold spell definition and degrees of freedom
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53 170 (df). The model was established as follows:

$$54 171 Y_t \sim \text{quasiPoisson}(\mu_t)$$

$$\begin{aligned} \text{Log}(\mu_t) = & \alpha + \text{cb}(\text{CS}_t, \text{lag}, \text{df} = 3) + \text{ns}(\text{RH}_t, \text{df} = 3) + \text{ns}(\text{AP}_t, \text{df} = 3) + \text{ns}(\text{AQI}_t, \text{df} = 3) \\ & + \text{ns}(\text{Time}_t, \text{df} = 3/\text{per year}) + \gamma \text{DOW}_t + \delta \text{Holiday}_t + \nu \text{Influenza}_t, \end{aligned}$$

where t is the day of observation; Y_t is the expected number of hospitalizations for AECOPD on day t ; α is the intercept; CS_t denotes the cold spells on day t (0=non-cold spell days, and 1=cold spell days); cb represents the cross-basis function, including a linear function and a natural cubic spline function with 3 df to assess the linear and lagged effects of the cold spells separately. We fitted a lag structure up to 21 days in the models to completely capture the flexible lagged effects of cold spells exposure. ns refers to the natural cubic spline function. ns with 3 df was applied for the mean relative humidity (RH_t), mean atmospheric pressure (AP_t) and air quality index (AQI_t), respectively. ns with 3 df per year was used to control the seasonality and long-term trends. DOW_t is a categorical variable indicating the day of the week on day t , and γ is the coefficient. Holiday_t is a binary variable (0=non-statutory holiday, and 1=statutory holiday) and δ is the coefficient. Influenza_t is a dichotomous variable with the value of "1" for the influenza epidemic on day t , and ν is the coefficient. The statistical methods, maximum lag days and confounding factors included in the model were commonly utilized and described in previous publications.[4, 17, 20, 21, 31, 32]

To observe the variation trend of lagged effects, we calculated the single-day lagged effects (from lag0 to lag21) and cumulative effects (lag0, lag0–7, lag0–14 and lag0–21) of cold spells on AECOPD hospitalizations, respectively. To identify the susceptible subpopulations for more targeted public health interventions, we further conducted subgroup analyses to investigate the potential modification effects by gender (male and female) and age (0-64 years old and ≥ 65 years old) under the optimal definition of cold spells. The statistical differences of the risk estimates between the subgroups were examined by the Z-test with the following equation:

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$$Z = (E_1 - E_2) / \sqrt{(SE_1^2 + SE_2^2)}$$

5
6 198 where Z represents the Z-test value; E_1 and E_2 denote the effect estimates of two
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8 199 categories; SE_1 and SE_2 are corresponding standard errors of E_1 and E_2 .

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12 201 **Sensitivity analysis**

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15 202 We performed the sensitivity analyses by altering the df with 3–5 df per year of the
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17 203 long-term trend, 3–5 df of the relative humidity, 3–5 df of the air pressure, 3–5 df of the
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19 204 AQI and 3–5 df of the lag dimension in the DLM under the optimal definition of cold
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21 205 spells. We used R software version 3.6.1 with the “dlnm” and “splines” packages to run
22
23 206 the analyses. All statistical tests were two-sided and values of $p < 0.05$ were considered
24
25 207 statistically significant.

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29 209 **Patient and public involvement**

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31 210 Patients were not involved in the development of the research question and outcome
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33 211 measures, study design or conduct of this study.

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37 213 **RESULTS**

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39 214 **Data description**

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41 215 Table 1 shows the descriptive statistics of the study population, meteorological
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43 216 variables and AQI during the cold seasons (November to March) from 2012 to 2016 in
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45 217 Beijing. There was a total of 84,571 AECOPD hospitalizations throughout the study
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47 218 period. Among these cases, 63.6% were males and 36.4% were females. 83.9% of all
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49 219 patients were aged 65 years and above. The average of daily mean temperature, relative
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51 220 humidity, air pressure, and AQI were 0.9°C (range, -16.0-18.0°C), 46.6% (range, 8.0-
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53 221 98.0%), 1025.3hPa (range, 1005.0-1044.0hPa) and 126.3 (range, 17.0-485.0),
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4 222 respectively.

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6 223 Table 2 shows the overview information of cold spells under different definitions. More
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8 224 days were defined as cold spell days with higher temperature thresholds and shorter
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10 225 duration. We observed the most cold spell episodes and days in four years with the
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12 226 definition of periods for at least 2 days and daily mean temperature below or at the 10th
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14 227 percentile (-6°C). In contrast, there were only 2 cold spell episodes (10 cold spell days) if
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17 228 we defined cold spells as periods for 4 or more consecutive days when daily mean
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19 229 temperature was below or at the 3rd percentile (-8°C).

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23 231 **Effects of cold spells under different definitions**

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26 232 Figure 1 depicts the lag structures of associations between cold spells under 9 different
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28 233 definitions and AECOPD hospitalizations of the total population. All cold spells had
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30 234 impacts on the risks of hospitalizations for AECOPD and most trends of their lagged
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32 235 effects were non-linear with two patterns. One was that the relative risk (RR) of
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34 236 hospitalizations for AECOPD reached a maximum on the days (lag0) of cold spells, then
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36 237 decreased and remained significant for 10-16 days (lag10-lag16). The other one was that
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38 238 the RR became significant on the 3rd or 4th day (lag3 or lag4) after exposure to cold
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40 239 spells, then gradually reached the maximum at about the 8th day (lag8) and lasted till the
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42 240 15th-17th days (lag15-lag17).

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46 241 Table 3 shows the cumulative effects of cold spells on AECOPD hospitalizations under
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48 242 different definitions. For each definition, the cumulative relative risk (CRR) increased with
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50 243 longer cumulative lags, with the highest CRR at lag0-21. Among 9 different definitions,
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52 244 the CRRs of cold spells at lag0-21 increased as the definition had a longer duration or
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54 245 lower temperature threshold. The maximum CRR over lag0-21 when the temperature
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56 246 threshold was set at the 10th percentile appeared at the duration \geq 4 consecutive days. In
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4 247 comparison, the CRR values of the duration ≥ 3 consecutive days and ≥ 2 consecutive
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6 248 days were lower. Likewise, when the duration was set for at least 4 consecutive days, the
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8 249 maximum CRR over lag0-21 appeared at the temperature range defined as $\leq 3^{\text{rd}}$
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10 250 percentile, while the CRRs of temperature threshold at the 5th and 10th percentile were
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12 251 lower. The lowest Q-AIC value (7769.8) indicating the best model fit was observed in
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14
15 252 Model 3 (Table 2). Hence, the optimal cold spell definition was daily mean temperature
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17 253 $\leq 10^{\text{th}}$ percentile (-6°C) with at least 4 consecutive days during the study period. The
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19 254 optimal model was able to find the most significant single-day lagged effect earliest (lag0)
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22 255 and remained significant until the 14th day (lag14) (Figure 1).

23
24 256 Table 4 and Figure 2 reveal the results for the subgroup analyses of gender and age
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26 257 based on the optimal cold spell definition. The effects of cold spells were similar between
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28 258 males and females, with the most significant single-day lagged effect both occurred at
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30 259 lag0 ($Z=0.041$, $P=0.48$). The cumulative effects at lag0-21 of the two genders also
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32
33 260 differed slightly ($Z=-0.730$, $P=0.23$). Additionally, in the subgroups stratified by the age,
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35 261 the most significant single-day lagged effect and cumulative effect for people aged ≥ 65
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37 262 years were at lag0 and lag0-21, respectively. However, no significant effect of cold spells
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39 263 was observed in those aged 0-64 years. The results of sensitivity analyses indicated that
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41
42 264 the effect estimates of cold spells under the optimal definition on AECOPD
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44 265 hospitalizations were still robust. (See Supplementary Materials, Tables S1–S5).

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48 49 267 **DISCUSSION**

50
51 268 In this study, we showed that cold spells were associated with increase hospitalizations
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53 269 for AECOPD. The adverse impacts of cold spells varied with their durations and
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55 270 intensities. Based on the statistical model fit, the optimal definition of cold spells was daily
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58 271 mean temperature less than or equal to the 10th percentile lasting for at least 4
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4 272 consecutive days during the study period. The elderly seemed more sensitive to cold
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6 273 spells than the younger, while the susceptibility difference between genders was not
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8 274 noticeable.

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10 275 Our finding is in accordance with previous studies reporting an excess of AECOPD
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12 276 hospitalizations,[15] emergency visits[33] and mortality[4, 6, 33] associated with cold
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14 277 spells. For instance, Monteiro et al. reported significant effects of cold spells identified by
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16 278 various indices on COPD hospitalizations with a lagged effect of at least two weeks.[15]
17
18 279 Several underlying mechanisms may explain for elevated COPD morbidity and mortality
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20 280 attributable to extremely cold events. Firstly, cold exposure has been found to be related
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22 281 to a decline in lung function (FEV₁, FVC and PEF) among COPD patients.[34, 35]
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24 282 Secondly, Koskela et al. reported that cold air could directly induce bronchoconstriction,
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26 283 leading to excessive dyspnea in patients with COPD.[36] Thirdly, cold exposure may
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28 284 suppress the immune response and increase susceptibility to viral infections in
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30 285 humans.[37] Meanwhile, the transmission efficiency of the influenza virus is inversely
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32 286 correlated with ambient temperature.[38] Fourthly, the cold temperature may provoke
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34 287 airway inflammation and mucin hypersecretion in airway epithelium, which results in
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36 288 COPD morbidity and mortality by blocking airways and causing recurrent infections.[39,
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38 289 40]

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40 290 We found that the CRR values of AECOPD hospitalizations increased with longer
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42 291 duration and higher intensity of cold spells. Some prior studies had similar findings,[20,
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44 292 21] indicating that both the duration and the intensity affect the health risks of cold spells.
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46 293 According to the minimum Q-AIC value criterion, the optimal definition of cold spells was
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48 294 the daily average temperature at or below the 10th percentile with 4 or more consecutive
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50 295 days. Compared with other definitions, this one had a lower intensity and longer duration,
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52 296 and the most significant single-day lagged effect of cold spells on AECOPD
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3 297 hospitalizations appeared earliest (lag0). Our results agree with a study in Porto showing
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5 298 that the moderately low temperature with long periods contributed greater to COPD
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8 299 exacerbation than extremely low temperature with shorter-lasting days.[15] However,
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10 300 studies on some other diseases defined the optimal cold spell definitions with a threshold
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12 301 at the 5th percentile or at least 2 days duration,[21, 31] indicating different definitions may
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14 302 apply to different outcomes. In addition, some studies reported the temporal changes in
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16 303 people's adaption capacities to cold spells during recent decades under climate
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18 304 change.[5, 41] Overall, more effective cold spell definitions and warning systems adapted
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20 305 to regional climate, specific diseases, and dynamic changes of the population's sensitivity
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22 306 should be further studied and implemented in the future.

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26 307 In the subgroup analyses based on the optimal cold spell definition, we found that the
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28 308 effects of cold spells on AECOPD hospitalizations were more significant in the elderly
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30 309 (aged ≥ 65 years) than people aged 0–64 years. This finding is consistent with previous
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32 310 studies.[4, 12, 42] The reasons may point to reduced thermoregulatory ability, higher
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34 311 prevalence of chronic diseases[20, 33] and impaired immunity[43] in the elderly. Note
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36 312 that since aging is one of the risk factors of COPD, most patients in our study were over
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38 313 64, giving more power to achieve statistical significance. However, some studies showed
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40 314 the opposite results.[6] It was speculated that the younger tend to spend more time
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42 315 outdoors, which increase opportunities for exposure to extremely cold temperature. In
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44 316 terms of gender, we found similar impacts of cold spells among males and females,
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46 317 which corresponds with previous studies.[4, 12, 42]

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49 318 Our study has significant public health implications for local prevention of AECOPD,
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51 319 development of early warning systems and rational allocation of medical and health
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53 320 resources to mitigate the COPD burden caused by cold spells. We showed substantial
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55 321 effects of cold spells on the risk of AECOPD hospitalizations with a lagged effect of about
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3 322 3 weeks, urging for effective and practical guidelines for preventions, particularly for
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5 323 COPD patients during cold spells in China. Both the government and individuals should
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7 324 take practical actions. The meteorological departments should improve early warning
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9 325 systems with timely forecast and publication of extremely cold events. Moreover, the
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11 326 government should exert great efforts to raise public awareness of the health hazards of
12
13 327 cold spells and ensure adequate public and medical services coping with cold spells.[4]
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15 328 As for individuals, it has been reported that staying indoor and wearing warm clothing
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17 329 could reduce mortality in extremely cold weather.[44] Tseng et al. suggested that COPD
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19 330 patients who received inhaled medicine were less affected by cold temperature-related
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21 331 COPD exacerbation.[12] Therefore, keeping warm, minimizing the outdoor activities and
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23 332 taking medications regularly are vital measures to fight against cold spells for individuals
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25 333 with COPD, especially for the elderly.
26
27 334 The main strengths of our study are as follows: Firstly, to the best of our knowledge,
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29 335 this is the first study to investigate the relationship between cold spells and AECOPD
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31 336 hospitalizations in China. Secondly, we controlled air quality and influenza epidemics as
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33 337 confounding factors, which were not included by some previous studies. Lee et al. have
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35 338 reported that a higher influenza virus detection rate was correlated with AECOPD.[14] A
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37 339 previous study from Beijing has found significant associations between short-term
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39 340 exposures to air pollution and hospitalizations for AECOPD.[23] Existing literatures have
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41 341 also shown that both air pollution and influenza epidemics could contribute to cold-related
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43 342 health effects.[45, 46] Moreover, air pollutants may interact with viral infections to
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45 343 precipitate AECOPD rather than acting alone. Feng and colleagues reported that ambient
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47 344 PM_{2.5} was associated with influenza-like illness risk in Beijing in the flu season.[47]
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49 345 Further research on the interactions among cold spells, air pollution and influenza on
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51 346 AECOPD is therefore needed. Thirdly, we identified the elderly more vulnerable to cold
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4 347 spells by stratified analyses, which guide more targeted prevention strategies.

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6 348 Meanwhile, the study also has several limitations: Firstly, as an ecological study, the

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8 349 association between cold spells and AECOPD hospitalizations does not imply causality.

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10 350 Secondly, different socio-economic status or other factors on an individual level might be

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12 351 confounding factors and were not considered in the association. Thirdly, the

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14 352 meteorological variables and AQI were all from monitoring stations, not reflecting the

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16 353 individual level of exposures. Moreover, people are more likely to stay indoors with

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18 354 heating systems during extremely cold days in northern China, so inevitable exposure

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20 355 measurement errors may lead to bias. Fourthly, due to the limited availability of local

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22 356 data, the positive rates of influenza isolations were from the northern part of China but

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24 357 not only Beijing. Further studies with local influenza data included as a continuous

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26 358 variable in the model are warranted. Lastly, the data from only one city weakens the

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28 359 extrapolation validity of the study.

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34 35 361 **CONCLUSION**

36
37 362 Our study demonstrates that short-term exposure to cold spells is associated with an

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39 363 increased risk of AECOPD hospitalizations. The cumulative effects increased with the

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41 364 intensities and the durations of cold spells. The elderly are more vulnerable to AECOPD

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43 365 hospitalizations during cold spell periods. These findings provide scientific foundations for

44
45 366 comprehensive public health strategies to reduce cold spell-related AECOPD

46
47 367 hospitalizations in Beijing, China.

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53 369 **Contributors:** ZF obtained the original data and funding. ZF, XJ, YL and YC designed the

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55 370 study. DK, XL, JF, YZ and ZC preprocessed the data. YL, YC, and YZ analyzed the data.

56
57 371 YL and YC drafted the manuscript. XZ, KX, CJ and ZF reviewed and edited the

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3 372 manuscript. All authors have read and approved the final manuscript. ZF is the study
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5 373 guarantor.

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7
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11
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16
17 378 **Competing interests:** None declared.

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19 379 **Ethical approval:** This study was approved by the ethical review committee of Peking
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21 380 Union Medical College Hospital.

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24 381 **Data sharing statement:** No additional data are available.
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382 **REFERENCES**

- 383 1 IPCC, 2014. *Climate Change 2014: Synthesis Report. Contribution of Working Groups I,*
384 *II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change*
385 [Core Writing Team, R.K. Pachauri and L.A. Meyer (eds.)]. IPCC, Geneva, Switzerland, 151
386 pp.
- 387 2 Cohen J, Screen JA, Furtado JC, *et al.* Recent Arctic amplification and extreme mid-
388 latitude weather. *Nature Geoscience* 2014;**7**:627-37.
- 389 3 Zhang J, Tian W, Chipperfield MP, *et al.* Persistent shift of the Arctic polar vortex towards
390 the Eurasian continent in recent decades. *Nature Climate Change* 2016;**6**:1094-9.
- 391 4 Chen J, Yang J, Zhou M, *et al.* Cold spell and mortality in 31 Chinese capital cities:
392 Definitions, vulnerability and implications. *Environment international* 2019;**128**:271-8.
- 393 5 Lee W, Choi HM, Lee JY, *et al.* Temporal changes in mortality impacts of heat wave and
394 cold spell in Korea and Japan. *Environment international* 2018;**116**:136-46.
- 395 6 Han J, Liu S, Zhang J, *et al.* The impact of temperature extremes on mortality: a time-
396 series study in Jinan, China. *BMJ open* 2017;**7**:e014741.
- 397 7 Rabe KF, Watz H. Chronic obstructive pulmonary disease. *The Lancet* 2017;**389**:1931-
398 40.
- 399 8 Lopez-Campos JL, Tan W, Soriano JB. Global burden of COPD. *Respirology*
400 2016;**21**:14-23.
- 401 9 Donaldson GC, Goldring JJ, Wedzicha JA. Influence of season on exacerbation
402 characteristics in patients with COPD. *Chest* 2012;**141**:94-100.
- 403 10 McCormack MC, Paulin LM, Gummerson CE, *et al.* Colder temperature is associated
404 with increased COPD morbidity. *Eur Respir J* 2017;**49**:1601501.
- 405 11 Chaturvedi S, Tseng C-M, Chen Y-T, *et al.* The Effect of Cold Temperature on Increased
406 Exacerbation of Chronic Obstructive Pulmonary Disease: A Nationwide Study. *PloS one*
407 2013;**8**: e57066.
- 408 12 Tseng CM, Chen YT, Ou SM, *et al.* The effect of cold temperature on increased
409 exacerbation of chronic obstructive pulmonary disease: a nationwide study. *PloS one*
410 2013;**8**:e57066.
- 411 13 Lee J, Jung HM, Kim SK, *et al.* Factors associated with chronic obstructive pulmonary
412 disease exacerbation, based on big data analysis. *Scientific reports* 2019;**9**:6679.
- 413 14 Hajat S, Armstrong B, Baccini M, *et al.* Impact of high temperatures on mortality: is there
414 an added heat wave effect? *Epidemiology (Cambridge, Mass)* 2006;**17**:632-8.
- 415 15 Monteiro A, Carvalho V, Gois J, *et al.* Use of "Cold Spell" indices to quantify excess
416 chronic obstructive pulmonary disease (COPD) morbidity during winter (November to March
417 2000-2007): case study in Porto. *International journal of biometeorology* 2013;**57**:857-70.
- 418 16 Wang C, Xu J, Yang L, *et al.* Prevalence and risk factors of chronic obstructive
419 pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-
420 sectional study. *The Lancet* 2018;**391**:1706-17.

- 1
2
3 421 17 Xie H, Yao Z, Zhang Y, *et al.* Short-term effects of the 2008 cold spell on mortality in
4 422 three subtropical cities in Guangdong Province, China. *Environmental health perspectives*
5 423 2013;**121**:210-6.
6
7 424 18 Zhou B, Gu L, Ding Y, *et al.* The Great 2008 Chinese Ice Storm: Its Socioeconomic–
8 425 Ecological Impact and Sustainability Lessons Learned. *Bulletin of the American*
9 426 *Meteorological Society* 2011;**92**:47-60.
10
11 427 19 Ban J, Huang L, Chen C, *et al.* Integrating new indicators of predictors that shape the
12 428 public's perception of local extreme temperature in China. *The Science of the total*
13 429 *environment* 2017;**579**:529-36.
14
15 430 20 Wang L, Liu T, Hu M, *et al.* The impact of cold spells on mortality and effect modification
16 431 by cold spell characteristics. *Scientific reports* 2016;**6**:38380.
17
18 432 21 Gao J, Yu F, Xu Z, *et al.* The association between cold spells and admissions of
19 433 ischemic stroke in Hefei, China: Modified by gender and age. *The Science of the total*
20 434 *environment* 2019;**669**:140-7.
21
22 435 22 Liu X, Kong D, Fu J, *et al.* Association between extreme temperature and acute
23 436 myocardial infarction hospital admissions in Beijing, China: 2013-2016. *PloS one*
24 437 2018;**13**:e0204706.
25
26 438 23 Liang L, Cai Y, Barratt B, *et al.* Associations between daily air quality and hospitalisations
27 439 for acute exacerbation of chronic obstructive pulmonary disease in Beijing, 2013–17: an
28 440 ecological analysis. *The Lancet Planetary Health* 2019;**3**:e270-e9.
29
30 441 24 Wedzicha JA, Seemungal TAR. COPD exacerbations: defining their cause and
31 442 prevention. *The Lancet* 2007;**370**:786-96.25 Solimini AG, Renzi M. Association between Air
32 443 Pollution and Emergency Room Visits for Atrial Fibrillation. *International journal of*
33 444 *environmental research and public health* 2017;**14**:661.
34
35 445 26 Stafoggia M, Samoli E, Alessandrini E, *et al.* Short-term associations between fine and
36 446 coarse particulate matter and hospitalizations in Southern Europe: results from the MED-
37 447 PARTICLES project. *Environmental health perspectives* 2013;**121**:1026-33.
38
39 448 27 Cowling BJ, Wong IO, Ho LM, *et al.* Methods for monitoring influenza surveillance data.
40 449 *Int J Epidemiol* 2006;**35**:1314-21.
41
42 450 28 Song X, Wang S, Li T, *et al.* The impact of heat waves and cold spells on respiratory
43 451 emergency department visits in Beijing, China. *The Science of the total environment*
44 452 2018;**615**:1499-505.
45
46 453 29 Guo Y, Jiang F, Peng L, *et al.* The association between cold spells and pediatric
47 454 outpatient visits for asthma in Shanghai, China. *PloS one* 2012;**7**:e42232.
48
49 455 30 Gasparrini A. Modeling exposure-lag-response associations with distributed lag non-
50 456 linear models. *Stat Med* 2014;**33**:881-99.
51
52 457 31 Cheng Q, Wang X, Wei Q, *et al.* The short-term effects of cold spells on pediatric
53 458 outpatient admission for allergic rhinitis in Hefei, China. *The Science of the total environment*
54 459 2019;**664**:374-80.
55
56
57
58
59
60

- 1
2
3
4 460 32 Liang Z, Wang P, Zhao Q, *et al.* Effect of the 2008 cold spell on preterm births in two
5 461 subtropical cities of Guangdong Province, Southern China. *The Science of the total*
6 462 *environment* 2018;**642**:307-13.
- 7
8 463 33 de'Donato FK, Leone M, Noce D, *et al.* The impact of the February 2012 cold spell on
9 464 health in Italy using surveillance data. *PLoS one* 2013;**8**:e61720.
- 10
11 465 34 Lin Z, Gu Y, Liu C, *et al.* Effects of ambient temperature on lung function in patients with
12 466 chronic obstructive pulmonary disease: A time-series panel study. *The Science of the total*
13 467 *environment* 2018;**619-620**:360-5.
- 14
15 468 35 Donaldson GC, Seemungal T, Jeffries DJ, *et al.* Effect of temperature on lung function
16 469 and symptoms in chronic obstructive pulmonary disease. *Eur Respir J* 1999;**13**:844-9.
- 17
18 470 36 Koskela HO, Koskela AK, Tukiaineu HO. Bronchoconstriction due to cold weather in
19 471 COPD. The roles of direct airway effects and cutaneous reflex mechanisms. *Chest*
20 472 1996;**110**:632-6.
- 21
22 473 37 Shephard RJ, Shek PN. Cold exposure and immune function. *Can J Physiol Pharmacol*
23 474 1998;**76**:828-36.
- 24
25 475 38 Lowen AC, Mubareka S, Steel J, *et al.* Influenza virus transmission is dependent on
26 476 relative humidity and temperature. *PLoS pathogens* 2007;**3**:1470-6.
- 27
28 477 39 Li M, Li Q, Yang G, *et al.* Cold temperature induces mucin hypersecretion from normal
29 478 human bronchial epithelial cells in vitro through a transient receptor potential melastatin 8
30 479 (TRPM8)-mediated mechanism. *J Allergy Clin Immunol* 2011;**128**:626-34.e1-5.
- 31
32 480 40 Juan Y, Haiqiao W, Xie W, *et al.* Cold-inducible RNA-binding protein mediates airway
33 481 inflammation and mucus hypersecretion through a post-transcriptional regulatory mechanism
34 482 under cold stress. *Int J Biochem Cell Biol* 2016;**78**:335-48.
- 35
36 483 41 Chung Y, Noh H, Honda Y, *et al.* Temporal Changes in Mortality Related to Extreme
37 484 Temperatures for 15 Cities in Northeast Asia: Adaptation to Heat and Maladaptation to Cold.
38 485 *American journal of epidemiology* 2017;**185**:907-13.
- 39
40 486 42 Ma W, Yang C, Chu C, *et al.* The impact of the 2008 cold spell on mortality in Shanghai,
41 487 China. *International journal of biometeorology* 2013;**57**:179-84.
- 42
43 488 43 Goodwin JS. Decreased immunity and increased morbidity in the elderly. *Nutr Rev*
44 489 1995;**53**:S41-4; discussion S4-6.
- 45
46 490 44 Donaldson GC, Ermakov SP, Komarov YM, *et al.* Cold related mortalities and protection
47 491 against cold in Yakutsk, eastern Siberia: observation and interview study. *BMJ* 1998;**317**:978-
48 492 82.
- 49
50 493 45 Qiu H, Tan K, Long F, *et al.* The Burden of COPD Morbidity Attributable to the Interaction
51 494 between Ambient Air Pollution and Temperature in Chengdu, China. *International journal of*
52 495 *environmental research and public health* 2018;**15**:492.
- 53
54 496 46 Huynen MM, Martens P, Schram D, *et al.* The impact of heat waves and cold spells on
55 497 mortality rates in the Dutch population. *Environmental health perspectives* 2001;**109**:463-70.
- 56
57 498 47 Feng C, Li J, Sun W, *et al.* Impact of ambient fine particulate matter (PM_{2.5}) exposure on
58
59
60

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2
3 499 the risk of influenza-like-illness: a time-series analysis in Beijing, China. *Environmental*
4 500 *health : a global access science source* 2016;**15**:17.

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502 **Figure legend/caption:**

503 **Figure 1** Lag-response relationships between cold spells under different definitions and
504 AECOPD hospitalizations of the total population in Beijing, 2012-2016.

505

506 **Figure 2** Lag-response relationships between cold spells and AECOPD hospitalizations
507 stratified by gender and age in Beijing, 2012-2016.

Table 1 Statistic summary of daily hospitalizations for AECOPD (counts per day), meteorological variables and air quality index in cold seasons (November-March) in Beijing, China, 2012–2016.

	Total	Mean (SD)	Min	P25	Media n	P75	Max
AECOPD hospitalizations	8457 1	111.7(41.0))	22.0	78.0	113.0	141.0	226.0
Gender							
Male	5382 9	71.1(25.8)	12.0	49.0	75.0	89.0	158.0
Female	3074 2	40.6(17.7)	7.0	27.0	39.0	53.0	110.0
Age							
0-64 years old	1360 0	18.0(8.3)	2.0	12.0	18.0	23.0	43.0
≥65 years old	7097 1	93.8(34.3)	19.0	67.0	95.0	118.0	189.0
Environmental variables							
Mean temperature (°C)	/	0.9(5.4)	-16.0	-3.0	0.0	4.0	18.0
Relative humidity (%)	/	46.6(20.4)	8.0	30.0	43.0	61.0	98.0
Air pressure (hPa)	/	1025.3(6.5))	1005. 0	1021. 0	1026.0	1030. 0	1044. 0
Air quality index	/	126.3(89.2))	17.0	61.0	97.0	170.0	485.0

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; P25, the 25th percentile; P75, the 75th percentile; SD, standard deviation.

Table 2 Overview information of cold spells under different definitions

Model	Temperature threshold	Duration	Cold spell episodes	Cold spell days	Non-cold spell days	Q-AIC value
1	$\leq 10\%$ (-6°C)	$\geq 2\text{d}$	17	77	680	7819.6
2	$\leq 10\%$ (-6°C)	$\geq 3\text{d}$	11	65	692	7799.7
3	$\leq 10\%$ (-6°C)	$\geq 4\text{d}$	6	50	707	7769.8
4	$\leq 5\%$ (-7°C)	$\geq 2\text{d}$	8	37	720	7794.3
5	$\leq 5\%$ (-7°C)	$\geq 3\text{d}$	5	31	726	7786.6
6	$\leq 5\%$ (-7°C)	$\geq 4\text{d}$	3	25	732	7782.5
7	$\leq 3\%$ (-8°C)	$\geq 2\text{d}$	7	23	734	7786.5
8	$\leq 3\%$ (-8°C)	$\geq 3\text{d}$	5	19	738	7789.8
9	$\leq 3\%$ (-8°C)	$\geq 4\text{d}$	2	10	747	7804.4

Q-AIC, quasi-Poisson Akaike Information Criterion.

Table 3 Cumulative relative risk of cold spells under different definitions
on AECOPD hospitalizations of the total population in Beijing, 2012-2016.

Definition	CRR (95% CI)			
	Lag0	Lag0-7	Lag0-14	Lag0-21
≤10% & ≥2d	1.030 (1.002-1.058)*	1.200 (1.087-1.326)*	1.278 (1.134-1.439)*	1.236 (1.055-1.448)*
≤10% & ≥3d	1.027 (1.000-1.054)*	1.188 (1.084-1.303)*	1.299 (1.166-1.448)*	1.353 (1.161-1.577)*
≤10% & ≥4d	1.042 (1.013-1.072)*	1.249 (1.136-1.374)*	1.343 (1.206-1.496)*	1.394 (1.193-1.630)*
≤5% & ≥2d	1.012 (0.980-1.045)	1.173 (1.055-1.304)*	1.344 (1.188-1.519)*	1.354 (1.141-1.608)*
≤5% & ≥3d	1.031 (1.000-1.063)*	1.235 (1.114-1.369)*	1.381 (1.220-1.563)*	1.428 (1.206-1.692)*
≤5% & ≥4d	1.042 (1.006-1.079)*	1.268 (1.132-1.421)*	1.404 (1.234-1.598)*	1.511 (1.262-1.809)*
≤3% & ≥2d	0.982 (0.944-1.021)	1.113 (0.960-1.290)	1.412 (1.171-1.703)*	1.444 (1.113-1.873)*
≤3% & ≥3d	1.009 (0.970-1.049)	1.217 (1.051-1.411)*	1.525 (1.264-1.841)*	1.659 (1.278-2.154)*
≤3% & ≥4d	0.992 (0.951-1.035)	1.201 (0.999-1.443)	1.644 (1.261-2.145)*	1.889 (1.315-2.712)*

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CI, confidence interval; CRR, cumulative relative risk.

* $p < 0.05$.

Table 4 Cumulative relative risk of cold spells# on AECOPD hospitalizations stratified by gender and age in Beijing, 2012-2016.

Subgroup	CRR (95% CI)			
	Lag0	Lag0-7	Lag0-14	Lag0-21
Male	1.042 (1.011-1.074)*	1.243 (1.123-1.375)*	1.316 (1.173-1.477)*	1.342 (1.136-1.586)*
Female	1.041 (1.005-1.077)*	1.257 (1.119-1.411)*	1.383 (1.215-1.574)*	1.476 (1.211-1.783)*
Age<65	1.017 (0.972-1.064)	1.120 (0.963-1.303)	1.159 (0.977-1.376)	1.107 (0.862-1.422)
Age≥65	1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.382 (1.240-1.540)*	1.456 (1.244-1.705)*

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CI, confidence interval; CRR, cumulative relative risk.

#The optimal cold spell definition was daily mean temperature ≤10th percentile (-6°C) with at least 4 consecutive days during the study period.

* $p < 0.05$.

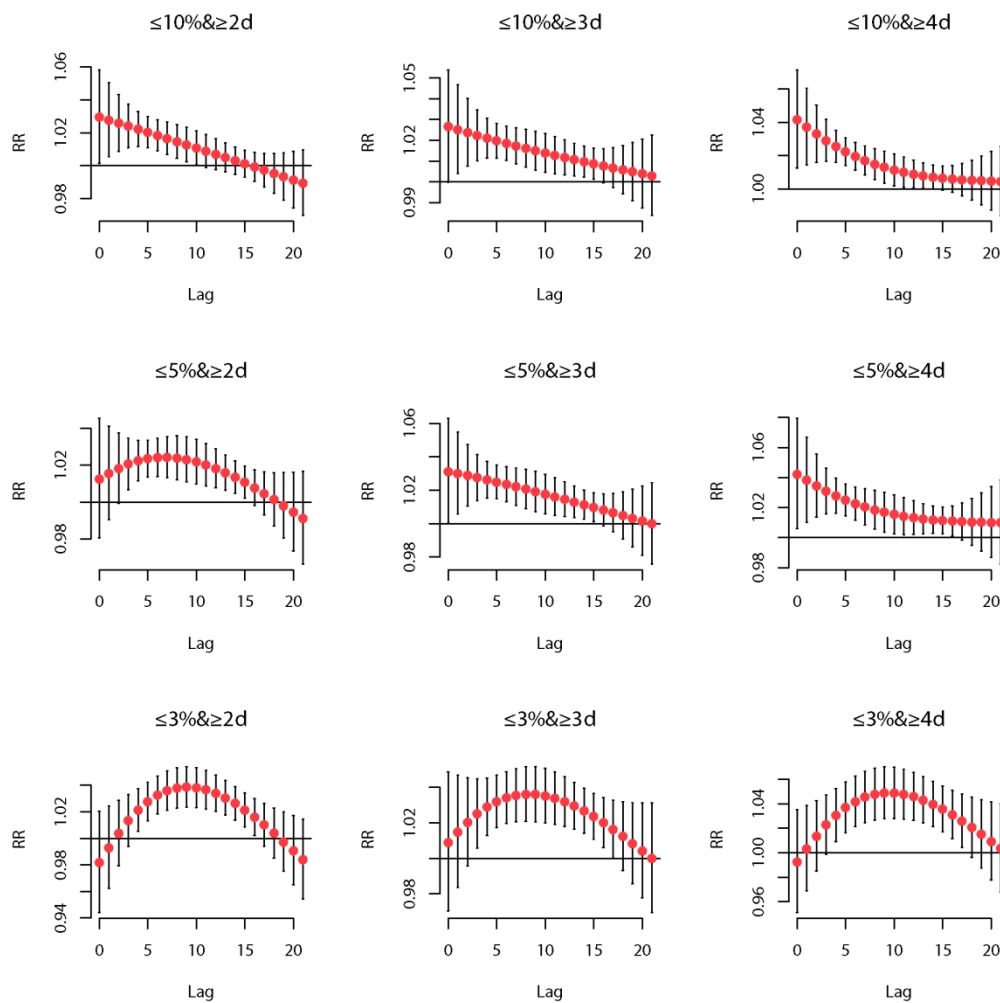


Figure 1 Lag-response relationships between cold spells under different definitions and AECOPD hospitalizations of the total population in Beijing, 2012-2016.

161x159mm (300 x 300 DPI)

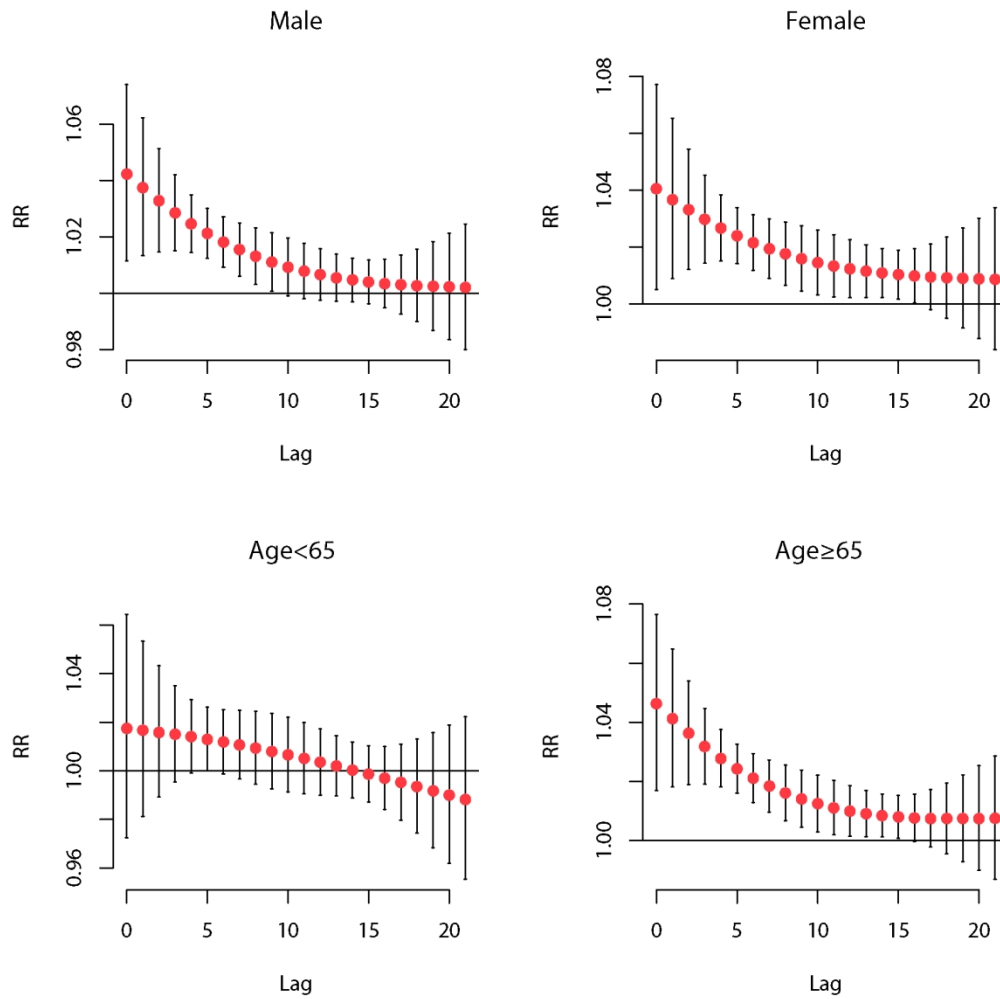


Figure 2 Lag-response relationships between cold spells and AECOPD hospitalizations stratified by gender and age in Beijing, 2012-2016.

159x157mm (300 x 300 DPI)

Supplementary Materials

Supplementary Tables

Table S1 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for lag dimension in the DLM model

Table S2 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for time per year in the DLM model

Table S3 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for relative humidity in the DLM model

Table S4 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for air pressure in the DLM model

Table S5 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for air quality index in the DLM model

Table S1 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for lag dimension in the DLM model

df for lag dimension	Group	CRR (95% CI)			
		Lag0	Lag0-7	Lag0-14	Lag0-21
3 ^a	Total	1.042 (1.013-1.072)*	1.249 (1.136-1.374)*	1.343 (1.206-1.496)*	1.394 (1.193-1.630)*
	Male	1.042 (1.011-1.074)*	1.243 (1.123-1.375)*	1.316 (1.173-1.477)*	1.342 (1.136-1.586)*
	Female	1.041 (1.005-1.077)*	1.257 (1.119-1.411)*	1.383 (1.215-1.574)*	1.476 (1.211-1.783)*
	Age<65	1.017 (0.972-1.064)	1.120 (0.963-1.303)	1.159 (0.977-1.376)	1.107 (0.862-1.422)
	Age≥65	1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.382 (1.240-1.540)*	1.456 (1.244-1.705)*
	Total	0.989 (0.926-1.057)	1.265 (1.149-1.392)*	1.311 (1.173-1.465)*	1.382 (1.182-1.615)*
	Male	0.992 (0.925-1.064)	1.257 (1.135-1.393)*	1.285 (1.141-1.448)*	1.331 (1.126-1.573)*
4	Female	0.983 (0.906-1.067)	1.274 (1.133-1.432)*	1.347 (1.178-1.540)*	1.462 (1.210-1.766)*
	Age<65	0.919 (0.827-1.022)	1.151 (0.988-1.340)	1.106 (0.926-1.320)	1.091 (0.850-1.401)
	Age≥65	1.003 (0.938-1.073)	1.288 (1.169-1.419)*	1.355 (1.211-1.515)*	1.446 (1.235-1.692)*
	Total	1.001 (0.888-1.128)	1.271 (1.150-1.404)*	1.313 (1.174-1.468)*	1.389 (1.185-1.628)*
5	Male	0.999 (0.880-1.136)	1.261 (1.134-1.403)*	1.287 (1.141-1.451)*	1.336 (1.127-1.583)*
	Female	1.004 (0.868-1.161)	1.285 (1.137-1.451)*	1.350 (1.180-1.545)*	1.474 (1.216-1.787)*
	Age<65	0.892 (0.737-1.080)	1.143 (0.975-1.341)	1.102 (0.922-1.317)	1.084 (0.840-1.398)
	Age≥65	1.023 (0.907-1.155)	1.297 (1.172-1.434)*	1.358 (1.213-1.520)*	1.456 (1.240-1.710)*

CI, confidence interval; df, degree of freedom; RR, relative risk.

* $P < 0.05$.^aUsed in the study.

Table S2 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for time per year in the DLM model

df for time per year	Group	CRR (95% CI)			
		Lag0	Lag0-7	Lag0-14	Lag0-21
3 ^a	Total	1.042 (1.013-1.072)*	1.249 (1.136-1.374)*	1.343 (1.206-1.496)*	1.394 (1.193-1.630)*
	Male	1.042 (1.011-1.074)*	1.243 (1.123-1.375)*	1.316 (1.173-1.477)*	1.342 (1.136-1.586)*
	Female	1.041 (1.005-1.077)*	1.257 (1.119-1.411)*	1.383 (1.215-1.574)*	1.476 (1.211-1.783)*
	Age<65	1.017 (0.972-1.064)	1.120 (0.963-1.303)	1.159 (0.977-1.376)	1.107 (0.862-1.422)
	Age≥65	1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.382 (1.240-1.540)*	1.456 (1.244-1.705)*
	Total	1.023 (0.992-1.055)	1.150 (1.033-1.280)*	1.218 (1.078-1.376)*	1.233 (1.036-1.467)*
4	Male	1.029 (0.997-1.063)	1.173 (1.045-1.316)*	1.226 (1.074-1.399)*	1.225 (1.015-1.480)*
	Female	1.011 (0.974-1.050)	1.107 (0.971-1.262)	1.196 (1.034-1.385)*	1.232 (0.998-1.520)
	Age<65	1.010 (0.961-1.061)	1.077 (0.906-1.280)	1.105 (0.907-1.345)	1.056 (0.795-1.401)
	Age≥65	1.026 (0.995-1.058)	1.166 (1.046-1.300)*	1.244 (1.100-1.406)*	1.272 (1.067-1.517)*
	Total	1.022 (0.990-1.056)	1.144 (1.008-1.298)*	1.208 (1.031-1.415)*	1.222 (0.978-1.526)
	Male	1.030 (0.994-1.066)	1.171 (1.021-1.343)*	1.222 (1.027-1.452)*	1.223 (0.960-1.559)
5	Female	1.009 (0.970-1.050)	1.093 (0.938-1.275)	1.174 (0.972-1.418)	1.203 (0.923-1.569)
	Age<65	1.011 (0.959-1.066)	1.082 (0.883-1.327)	1.127 (0.874-1.453)	1.127 (0.788-1.612)
	Age≥65	1.025 (0.992-1.059)	1.158 (1.019-1.316)*	1.227 (1.045-1.440)*	1.245 (0.994-1.559)

CI, confidence interval; df, degree of freedom; RR, relative risk.

* $P < 0.05$.

^aUsed in the study.

Table S3 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for relative humidity in the DLM model

df for relative humidity	Group	CRR (95% CI)			
		Lag0	Lag0-7	Lag0-14	Lag0-21
3 ^a	Total	1.042 (1.013-1.072)*	1.249 (1.136-1.374)*	1.343 (1.206-1.496)*	1.394 (1.193-1.630)*
	Male	1.042 (1.011-1.074)*	1.243 (1.123-1.375)*	1.316 (1.173-1.477)*	1.342 (1.136-1.586)*
	Female	1.041 (1.005-1.077)*	1.257 (1.119-1.411)*	1.383 (1.215-1.574)*	1.476 (1.211-1.783)*
	Age<65	1.017 (0.972-1.064)	1.120 (0.963-1.303)	1.159 (0.977-1.376)	1.107 (0.862-1.422)
	Age≥65	1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.382 (1.240-1.540)*	1.456 (1.244-1.705)*
	4	Total	1.041 (1.012-1.071)*	1.248 (1.135-1.373)*	1.343 (1.205-1.495)*
Male		1.042 (1.011-1.073)*	1.240 (1.120-1.372)*	1.314 (1.170-1.475)*	1.336 (1.130-1.580)*
Female		1.041 (1.006-1.078)*	1.259 (1.120-1.414)*	1.385 (1.217-1.578)*	1.482 (1.225-1.792)*
Age<65		1.017 (0.972-1.064)	1.119 (0.961-1.302)	1.158 (0.975-1.375)	1.105 (0.859-1.420)
Age≥65		1.046 (1.017-1.076)*	1.274 (1.157-1.403)*	1.381 (1.239-1.540)*	1.455 (1.242-1.704)*
5		Total	1.041 (1.012-1.071)*	1.244 (1.131-1.369)*	1.337 (1.200-1.490)*
	Male	1.041 (1.010-1.073)*	1.236 (1.116-1.368)*	1.307 (1.164-1.468)*	1.327 (1.121-1.569)*
	Female	1.040 (1.005-1.077)*	1.256 (1.117-1.411)*	1.381 (1.212-1.574)*	1.474 (1.218-1.785)*
	Age<65	1.015 (0.970-1.062)	1.111 (0.955-1.293)	1.148 (0.967-1.363)	1.089 (0.847-1.400)
	Age≥65	1.046 (1.016-1.076)*	1.271 (1.154-1.400)*	1.377 (1.234-1.536)*	1.448 (1.235-1.697)*

CI, confidence interval; df, degree of freedom; RR, relative risk.

* $P < 0.05$.

^aUsed in the study.

Table S4 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for air pressure in the DLM model

df for air pressure	Group	CRR (95% CI)			
		Lag0	Lag0-7	Lag0-14	Lag0-21
3 ^a	Total	1.042 (1.013-1.072)*	1.249 (1.136-1.374)*	1.343 (1.206-1.496)*	1.394 (1.193-1.630)*
	Male	1.042 (1.011-1.074)*	1.243 (1.123-1.375)*	1.316 (1.173-1.477)*	1.342 (1.136-1.586)*
	Female	1.041 (1.005-1.077)*	1.257 (1.119-1.411)*	1.383 (1.215-1.574)*	1.476 (1.211-1.783)*
	Age<65	1.017 (0.972-1.064)	1.120 (0.963-1.303)	1.159 (0.977-1.376)	1.107 (0.862-1.422)
	Age≥65	1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.382 (1.240-1.540)*	1.456 (1.244-1.705)*
	4	Total	1.042 (1.012-1.071)*	1.248 (1.134-1.373)*	1.342 (1.205-1.495)*
Male		1.042 (1.011-1.074)*	1.240 (1.120-1.373)*	1.313 (1.170-1.475)*	1.340 (1.134-1.584)*
Female		1.041 (1.005-1.078)*	1.259 (1.120-1.414)*	1.385 (1.216-1.578)*	1.478 (1.223-1.786)*
Age<65		1.018 (0.973-1.065)	1.123 (0.965-1.306)	1.162 (0.978-1.380)	1.109 (0.863-1.425)
Age≥65		1.046 (1.016-1.076)*	1.273 (1.156-1.402)*	1.380 (1.238-1.539)*	1.455 (1.242-1.704)*
5		Total	1.041 (1.012-1.071)*	1.247 (1.133-1.373)*	1.342 (1.204-1.495)*
	Male	1.042 (1.011-1.074)*	1.240 (1.120-1.374)*	1.314 (1.170-1.476)*	1.341 (1.134-1.585)*
	Female	1.041 (1.005-1.077)*	1.257 (1.118-1.413)*	1.383 (1.214-1.576)*	1.475 (1.220-1.784)*
	Age<65	1.019 (0.974-1.067)	1.129 (0.970-1.314)	1.168 (0.984-1.388)	1.115 (0.868-1.433)
	Age≥65	1.046 (1.016-1.076)*	1.271 (1.154-1.401)*	1.378 (1.235-1.537)*	1.452 (1.240-1.701)*

CI, confidence interval; df, degree of freedom; RR, relative risk.

* $P < 0.05$.

^aUsed in the study.

Table S5 The cumulative effects of cold spells under the optimal definition using different degrees of freedom for air quality index in the DLM model

df for AQI	Group	CRR (95% CI)			
		Lag0	Lag0-7	Lag0-14	Lag0-21
3 ^a	Total	1.042 (1.013-1.072)*	1.249 (1.136-1.374)*	1.343 (1.206-1.496)*	1.394 (1.193-1.630)*
	Male	1.042 (1.011-1.074)*	1.243 (1.123-1.375)*	1.316 (1.173-1.477)*	1.342 (1.136-1.586)*
	Female	1.041 (1.005-1.077)*	1.257 (1.119-1.411)*	1.383 (1.215-1.574)*	1.476 (1.211-1.783)*
	Age<65	1.017 (0.972-1.064)	1.120 (0.963-1.303)	1.159 (0.977-1.376)	1.107 (0.862-1.422)
	Age≥65	1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.382 (1.240-1.540)*	1.456 (1.244-1.705)*
	4	Total	1.042 (1.013-1.072)*	1.249 (1.135-1.374)*	1.342 (1.205-1.495)*
Male		1.042 (1.012-1.074)*	1.242 (1.123-1.375)*	1.315 (1.171-1.476)*	1.342 (1.135-1.586)*
Female		1.041 (1.005-1.077)*	1.257 (1.119-1.412)*	1.382 (1.214-1.573)*	1.475 (1.221-1.783)*
Age<65		1.018 (0.973-1.065)	1.120 (0.963-1.303)	1.157 (0.974-1.373)	1.106 (0.861-1.421)
Age≥65		1.046 (1.017-1.077)*	1.275 (1.158-1.404)*	1.381 (1.239-1.539)*	1.456 (1.243-1.704)*
5		Total	1.042 (1.013-1.071)*	1.249 (1.136-1.373)*	1.347 (1.210-1.500)*
	Male	1.042 (1.011-1.074)*	1.242 (1.123-1.373)*	1.320 (1.177-1.480)*	1.355 (1.148-1.601)*
	Female	1.041 (1.005-1.077)*	1.257 (1.119-1.412)*	1.385 (1.216-1.577)*	1.482 (1.226-1.792)*
	Age<65	1.018 (0.973-1.065)	1.120 (0.963-1.303)	1.161 (0.978-1.378)	1.116 (0.869-1.433)
	Age≥65	1.046 (1.017-1.076)*	1.275 (1.159-1.403)*	1.386 (1.243-1.545)*	1.468 (1.254-1.718)*

AQI, air quality index; CI, confidence interval; df, degree of freedom; RR, relative risk.

* $P < 0.05$.

^aUsed in the study.

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No.
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	4
		(d) If applicable, describe analytical methods taking account of sampling strategy	NA
		€ Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9

		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

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