TITLE PAGE

Title: Effects of weather variability and air pollutants on emergency admissions for cardiovascular and cerebrovascular diseases

Corresponding Author:

Aya Hori

Department of Preventive Medicine and Public Health, Shinshu University School of Medicine, 3-1-1, Asahi, Matsumoto, Nagano 390-0804, Japan

E-mail: aya_iizawa@yahoo.co.jp

Tel +81-263-37-2622 Fax +81-263-37-3499

Authors:

Masahiro Hashizume

Institute of Tropical Medicine, Nagasaki University, 1-12-4, Sakamoto, Nagasaki 852-8523, Japan.

Yoko Tsuda

Department of Preventive Medicine and Public Health, Shinshu University School of Medicine, 3-1-1, Asahi, Matsumoto, Nagano 390-0804, Japan.

Teruomi Tsukahara

Department of Preventive Medicine and Public Health, Shinshu University School of Medicine, 3-1-1, Asahi, Matsumoto, Nagano 390-0804, Japan.

Tetsuo Nomiyama

Department of Preventive Medicine and Public Health, Shinshu University School of Medicine, 3-1-1, Asahi, Matsumoto, Nagano 390-0804, Japan.

ABSTRACT

We examined the effect of ambient temperature, air pressure and air pollutants on daily emergency admissions by identifying the cause of admission for each type of stroke and cardiovascular disease using generalized linear Poisson regression models allowing for overdispersion, and controlling for seasonal and inter annual variations, days of the week and public holidays, levels of influenza and respiratory syncytial viruses. Every 1 °C decrease in mean temperature was associated with an increase in the daily number of emergency admissions by 7.83% (95%CI 2.06-13.25) for acute coronary syndrome (ACS) and heart failure, by 35.57% (95%CI 15.59-59.02) for intracerebral haemorrhage (ICH) and by 11.71% (95%CI 4.1-19.89) for cerebral infarction. An increase of emergency admissions due to ICH (3.25% (95%CI 0.94-5.51)), heart failure (3.56% (95%CI 1.09-5.96)) was observed at every 1hPa decrease in air pressure from the previous days. We found stronger detrimental effect of cold on stroke than cardiovascular disease.

Introduction

Meteorological effects on mortality have been widely studied[1,2]. More recently, the relationship between weather and morbidity has been studied. The effect of ambient temperature on AMI was investigated, and both hot and cold weather were shown to have a detrimental effect on the short-term risk of myocardial infarction[3]. Some studies indicated that the risk of stroke increased at lower temperatures[4], but the results remain controversial[5]. Several studies have analyzed different types of strokes separately[6], but, the results were unclear and further investigations are needed.

Stroke is a great burden on health care resources because patients often require lifetime care due to the resulting physical disability. In Japan, stroke is a leading cause of nursing care introduction[7]. The prevention of stroke is, therefore, of major importance as well as the prevention of the cardiovascular disease.

Furthermore, although air pressure is one of the main factors determining what weather is like, it has seldom been analyzed as a main cause of diseases[8].

In addition, air pollutants have also recently been reported to have a detrimental effect on health, and the effect on each disease is currently being investigated. Both particle matter and gaseous products have been proven to raise the risk of cardiovascular disease and stroke, but the association with each pollutant and disease is not consistent[9,10].

In this study, we examined the effects of ambient temperature, air pressure, and air pollutants on emergency admissions in the Ina area of Japan after Emergency Department (ED) transport by identifying the cause of admission for each type of stroke and cardiovascular disease.

Methods

Study design and subjects

3

The primary outcome for this study was the number of daily emergency admissions to Ina Central Hospital after ED transport. The Ina area, located in the center of Japan, is in a basin 632 meters above sea level surrounded by 3,000 meter high mountains. There are four seasons, the ambient temperature ranges from -15 °C to 35 °C throughout the year, and the yearly mean humidity is about 70%. This area is 1000 square kilometers and has a population of about 130,000.

Most ambulances transport patients needing emergency treatment to Ina Central Hospital's ED the only ED in the area with specialists who can provide advanced emergency services. For sampling, we used the emergency admission data (the day of admission, diagnosis at admission, age and sex) of patients admitted during a 4-year period (April 2006 to March 2010) from the database of the ED. To minimize the effect of the day of the week and holidays, we only sampled the data of patients transported by ambulance. To study the meteorological influences in this area, we excluded any non-residential patients. We categorized diseases of the circulatory system as ACS, cardiac arrest, heart failure, subarachnoid hemorrhage (SAH), intracerebral haemorrhage (ICH), cerebral infarction and aortic dissection and ruptured aortic aneurysm. We excluded any trauma cause disease from ICH and SAH.

The diagnosis was made after the consultation with a specialist or specialists who conducted standard diagnostic tests. ACS and heart failure was diagnosed after echocardiography by a specialist, and by electrocardiographs and blood examination. The diagnosis of SAH and ICH was made after a head computerized tomography (CT) scan. Cerebral infarction was diagnosed after head magnetic resonance imaging. The diagnosis of aortic dissection and a ruptured aortic aneurysm was made by a contrast-enhanced CT scan. The patients were grouped into three age categories (<65, 65-74, 74<).

Meteorological and air pollution measurements

Meteorological data (daily mean, maximum and minimum ambient temperature)

for the 4-year period in this area were provided by the Automated Meteorological Data Acquisition System (AMeDAS) and data on air pollutants (daily mean concentration of suspended particle matter (SPM), sulfur dioxide (SO_2), photochemical oxidant (O_X), and nitrogen dioxide (NO_2)) were from the Atmospheric Environmental Regional Observation System ; their observing stations in Ina city (the biggest city in the area) are situated within 3km from Ina central hospital. Missing pollutant data were inputed by multiple linear regression models using the data for other pollutants, weather variables, days of the week, month, year and holidays. Air pressure data for Ina city from April 2009 to March 2010 was provided by the Ina Fire Bureau. Before April 2009, we used the mean air pressure data from two nearby AMeDAS observing stations, located 28 and 37 km away from Ina city, because no data from the area was available. The air pressure measured in Ina city and the average air pressure from the two nearby stations during April 2009 to March 2010 were highly correlated ($r^2=0.998$).

As a measure of the level of circulating viral infections, we obtained a weekly report of influenza and respiratory syncytial (RS) virus infections in the Ina area from the infectious disease surveillance data collected at a public health center in Nagano prefecture.

Statistical analyses

We examined the relationship between daily emergency admissions after ED transport and the daily mean ambient temperature, mean air pressure or air pollutants using generalized linear Poisson regression models allowing for overdispersion. To investigate the effect of fluctuations in temperature and pressure, we also examined the effect of day to day changes in mean temperature (temperature change) and mean pressure (pressure change).

Because the patterns of admission and behavior influencing exposure to ambient temperature, pressure or pollutants may vary depending on the day, indicator

variables for the years of the study were incorporated in the model. To account for seasonality of admission not directly due to temperature, pressure or pollutants, Fourier terms up to the sixth harmonic per year were introduced into the model. Fourier terms can capture repeated periodic patterns comprising a combination of pairs of sine and cosine terms (harmonics) of varying wavelengths. This number of harmonics was chosen as a compromise between providing adequate control for unmeasured confounders and leaving sufficient information from which to estimate temperature effects[11]. We adjusted the model for the day of the week and public holidays as well as the level of influenza and RS viruses. When not selected as the main exposure, we controlled for daily mean pressure at lag 0-1 days (mean temperature at lag 0-4 days, mean SPM, SO_2, O_X and NO_2 levels at lag 0-3 days) for the temperature (air pressure, pollutant) models.

To allow for autocorrelations, an autoregressive term at order 1 was incorporated into the models[12]. To identify the optimum lag period, we first assumed a linear relationship between the temperature and number of admissions. We performed sequential regressions of temperature on emergency admissions adjusted for trend, seasonality, day of the week and public holidays, adding one lag at a time (0, 0-1, 0-2,0-3, ・・・,0-26) to determine the linear contribution of each additional lag for lags ranging from 0 to 26. We selected the lag period for which the relative risk from the nearest five lag periods was highest. A smaller lag period was preferred. In the exploratory analysis, we found only cold effects; no heat effects were observed. Therefore, lags for cold effects were selected for each disease category. The same method was applied to select lags for air pressure, temperature change and pressure change. For each pollutant, we conducted an analysis using the lags of days 0, 1, 2 and 3.

To obtain an initial visual estimate of the temperature effect, we fitted natural cubic splines (3 df)[13] to the average mean temperature to create graphs of the

temperature-admission relationship, where admissions were plotted as a smoothed function of temperature. Wald tests were used to assess the statistical significance of the temperature effect.

When the significance was lower than 0.05 with the spline model, we simplified the temperature effects with more directly interpretable numerical coefficients as linear or threshold models. In the threshold models, a linear temperature effect only operates below or above a certain "threshold" temperature. To find the threshold we repeatedly fitted the model with every possible threshold between the observed daily mean temperature range in 1 °C steps[11]. We compared these models and chose the model with the lowest deviance. When a difference in the values of deviance between the linear and best-fitted threshold models was less than 3.84 (chi-square value for one degree of freedom at the $p = 0.05$ level), the linear model was chosen. The same method was applied to pressure, temperature change and pressure change. For pollutant models, we used linear models.

Finally, we did an exploratory analysis to assess the effect modification by age (<65, 65-74, 74 <) and sex. As sensitivity analyses, the temperature-admission relationships were also estimated using different degrees of seasonal control. We also fitted natural cubic splines of 4 df and 5 df to the mean temperature on the temperature-admission relationships. Lastly, we used alternative temperature indices (maximum and minimum).

We used Stata11 (Stata Corporation, College Station, Texas) for analysis.

Results

A total of 4355 emergency admissions for all causes were observed from April 2006 to Mar 2010 (Table 1).

Air pressure has seasonal variation and tends to be high in winter and low in summer (Figure 1). Each pollutant also has a seasonal trend.

There was an increase in all cause and cause-specific admissions due to ICH, cerebral infarction and the combination of ACS and heart failure with lower temperature (Figure 2). Admissions due to ACS and heart failure separately tended to increase at lower temperatures, but these increases were not significant (p=0.31, p=0.11, respectively). Their lag times were 0-3 with ICH and 0-4 with the others. The relationship is leveled-off below a certain cut-off of temperature for cerebrovascular disease.

With lower pressure, there is an increase in all cause and cause-specific admissions due to ICH (lag 0-3) and heart failure and aortic dissection and a ruptured aortic aneurysm (lag 0-1).

Admissions due to SAH changed significantly with the daily mean temperature change (lag 0-3 days), but the shape of the relationship was difficult to interpret. Admissions due to all causes and ICH, heart failure, the combination of ACS and heart failure, aortic dissection and a ruptured aortic aneurysm increased with a decrease in pressure from previous days (pressure change)(Figure 3).

For the linear model, all cause admissions increased by 3.24% (95% CI 1.25-5.18) for every 1 °C decrease in temperature (Table2). The best-fit threshold model with a cut-off point where RR peaked out was selected for ICH and cerebral infarction. Admissions due to ICH were the most strongly affected by temperature with an increase of 35.57% (95% CI 15.59-59.02) for every 1 °C decrease in temperature up to the cut-off of 15 °C.

All cause admissions increased by 1.04% (95% CI 0.44-1.63) for every 1hPa decrease in pressure. The linear model was selected for all pressure analyses. The effect of pressure was strongest for admissions due to aortic dissection and a ruptured aortic aneurysm, showing an increase of 6.82% (95% CI 2.38-11.05). ICH did not show a significant relationship with the linear model (p=0.29).

All cause admissions increased by 0.95% (95% CI 0.37-1.52) for every 1hPa decrease of the daily mean pressure from previous days. A linear model without threshold was

selected for all pressure change analyses. The effect of pressure change was strongest for admissions due to aortic dissection and a ruptured aortic aneurysm, giving an increase of 6.1% (95% CI 2.29-9.76). Admissions due to heart failure increased 3.56% (95%CI 1.09-5.96) by decreasing pressure from previous days, and an increase of the combination of ACS and heart failure was marginally significant in the linear model (p=0.052).

All cause admissions and admissions due to SAH increased with an increase of NO_2, all cause admissions and cerebral infarction decreased, and admissions due to aortic dissection and a ruptured aneurysm increased with an increase of Ox. Admissions due to ACS significantly increased as SO_2 increased. In the linear model, the risk of SAH increased by 6.59% (95%CI 0.79-12.73) for every 1ppb increase of NO_2 (p=0.025), and the risk of ACS by 18.9% (95%CI4.98-34.66) increased for every 1ppb increase of SO_2 (p=0.006). The risk of aortic dissection and a ruptured aneurysm increased by 4.48% (95%CI 1.39-7.66) for every 1ppb increase of Ox (p=0.004). The other effect was relatively small. (Table3)

In the age subgroups, temperature and pressure changes strongly affected those over 74 years old, giving an increase of 3.96% (95%CI 1.44-6.42) for every 1 °C decrease in temperature and 1.33% (95%CI 0.61-2.05) for every 1hPa decrease in pressure change in the all cause admissions (see Table S1). On the other hand, Ox protectively affected this age group more strongly than the other age groups, giving a decrease of 0.68% (95%CI 0.17-1.19) for every 1ppb increase of Ox (see Table S2). In addition, NO_2 affected the 65 - 74 years old age group more stronger than the other age groups, giving an increase of 1.99% (95%CI 0.08-3.94) for every 1ppb increase of NO_2. Men were more sensitive than women to temperature and pressure changes with an increase in all cause admissions of 4.87% (95%CI 2.13-7.53) for every 1 °C decrease in temperature and 1.13%(95%CI 0.33-1.91) for every 1hPa decrease in pressure change. Ox and NO_2 did not show clear differences between the sexes. We did not analyse by age and sex for

each disease due to the low number of patients in the sub-groups.

Estimates from the linear model also showed the effects of the level of RS and influenza virus infection and the day of the week. The level of influenza viral infection slightly increased the risk of heart failure. The level of RS viral infection decreased the risk of ICH. On Tuesdays, the risk of cerebral infarction increased and aortic dissection and a ruptured aortic aneurysm increased on Thursdays, while ICH decreased on Fridays. All cause admissions decreased on Fridays and Saturdays.

The sensitivity analysis showed that varying the level of seasonal control by modifying the Fourier term had very little effect on the RR of the linear model; models for the temperature effect on all cause admissions with three harmonics models showed a 3.08% (95%CI 1.12- 5) increase, and with 12 harmonics, showed a 3.08 % (95%CI 1.06-5.05) increase (see Table S3). Controlling the natural cubic splines (4 df and 5 df) to the mean temperature on the temperature-admission relationships(spline model) also had little effect.

Finally, when the minimum and maximum daily temperatures were used in place of the mean temperature, except for cerebral infarction, there was little change of deviance in the temperature-admission relationship (see Table S4, Figures S1 and S2)(deviance of maximum temperature: 1150.804 mean temperature: 1157.366).

Discussion

Extreme temperature has been shown to have a detrimental effect on cardiovascular and cerebrovascular diseases[3,5,14]. A raise in the risk of the occurrence of AMI by either heat or cold has shown[15,16]. A winter peak in morbidity due to heart failure has also been observed, and exposure to cold is the cause of the winter peak in morbidity[14]. With regards to the stroke type, ICH was reported as sensitive to cold[17]. In Japan, a negative correlation between temperature and the onset of ICH and cerebral infarction, and no correlation with SAH was shown in a population-based

study[18], which was consistent with our result.

In previous studies examining the effect of weather on cardiovascular and cerebrovascular diseases in the same geographical area, stroke occurrence was found to be more sensitive to the effect of temperature than cardiovascular diseases. In young women from 17 different countries, the risk of stroke occurrence was higher than AMI (incidence rate ratio for a 5 °C change in temperature; 0.93 vs 0.88)[4]. In California, it was reported that a temperature change of more than 3 °C increased hospitalizations by 6-11% for AMI and congestive heart failure and by 10-18% for stroke[19]. In London, for a 1°C decrease in temperature above a certain threshold, there was a 0.88% increase in cerebrovascular disease admission and a small or no effect on cardiovascular admissions[20]. Thus, cerebrovascular diseases seem to be more sensitive to temperature than cardiovascular diseases, consistent with our results. The magnitude of the effect is great and protective behavior and housing against cold ambient temperature would reduce the number of stroke patients. Especially, elderly and male should me more protective to cold considering from our results.

On the other hand, the shape of the temperature-admission relationship was different between these diseases, and was less linear in cerebrovascular diseases. In ICH and cerebral infarction, the RR sharply increased as temperature decreased until it reached a threshold, and then leveled-off below the threshold. Although the mechanism is not clear, this difference may also result in different outcomes for the assessment of the effect on emergency admissions.

Although there are fewer studies on the effect of pressure than on temperature, one report found that a decrease in pressure increased the AMI occurrence the day after a pressure decrease[21]. Although we both analyzed by the pressure change from previous days and by pressure itself, no effect on ACS was found. Dawson et al. reported that decreasing pressure causes an increase in ICH (6.6% increase per 10hPa decrease), which is consistent with our result, though our RR is much higher[6]. In our analysis,

pressure change and ICH admissions showed more linear relationships than pressures. Jimenez-Conde et al. reported that a pressure change from the previous day seemed to affect stroke occurrence much more strongly than pressure itself[22]. Therefore, a pressure change may correlate more directly with the occurrence of ICH.

Air pollutants and the effect of these pollutants on cardiovascular disease and stroke are well reported[9,10,23,24]. Although our results showed their detrimental effect on SAH, ACS and aortic dissection and a ruptured aneurysm, we could not find the predominant pollutant. More investigation of this is needed to find it. A protective effect of Ox on myocardial infarction has been reported[15], and we also found a protective effect on all cause admissions and cerebral infarction. However, the effect is relatively small compared to other effect of pollutants.

Some physiological mechanisms are shown concerning the relationship between temperature and the incidence of cardiovascular and cerebrovascular diseases[25-28]. Cold weather induces an increase in blood pressure, a reduction of coronary vascular flow, which can trigger cardiac ischemia[25][26]. Elevated blood pressure can raise the after load of the left ventricle and lead to heart failure and increased risk of ICH. Cold also raises plasma noradrenaline, leading to sympathetic nervous activity, and enhance platelet function[28]. Thus, cold may trigger ischemia of the organs, which may cause AMI, heart failure and stroke. On the other hand, the physiological mechanisms that might be associated with the relationship between pressure and the incidence of cardiovascular diseases and cerebrovascular diseases have not been studied. Interestingly, the fact that lowering barometric pressure raises blood pressure in rats was found by the researchers who search the mechanisms of chronic pain which increase when the weather changes.[29][30] They say activation of sympathetic nervous system in response to lowering barometric pressure exposure has been demonstrated by increased blood pressure and heart rate in the rats. It may trigger the occurrence of those diseases. But in human, air pressure does not affect blood pressure[31]. Although

it remains a hypothesis, Houck speculated that barometric pressure changes cause mechanical stress in blood vessels and this may lead to vascular disease[21]. However, without experimental data, this hypothesis cannot be confirmed.

Air pollutants and their physiological mechanisms are well reported. Pollutants cause thrombosis, vascular dysfunction, atherosclerosis, disturbance in cardiac autonomic control and cardiac hypertrophy[32], which lead to an increased risk of ACS and major aortic disease by pollutants.

Our study benefitted from a small measurement error of exposure because the Ina area covers only about 1000 km² and because we used the meteorological data from this area. Moreover, because mountains limit access to other areas, we were able to include almost all of the patients in the area. Although our data are not population-based, our ED records effectively detected the occurrence of these diseases because we chose diseases which usually require ambulance transfer and emergency hospitalization. We adjusted all potential confounders including season, trend, air pollutants, infectious levels and days of the week by investigating the lag effect. Furthermore, all diagnoses were validated by specialists who conducted examinations of the patients.

There are several limitations to this study. There is a potential for exposure misclassification because we used stationary monitoring data. Exposure level measured at the monitoring station may only partially reflect the true individual exposure because patient might have lived indoors with air condition or travelled to different locations throughout the day. But we excluded any non-residential patients and included only patients transported from Ina area by ambulance to minimize the bias of exposure.

In addition, there might be a reduction of power and bias because of low daily number of admission and low concentration of air pollutants. Although there were about 5% days of no all cause admission through the period we surveyed, there are 73 to 95%

days of no admission due to each disease. Vascular diseases are known to happen in a cluster, so lots of zero days would be partly due to the fact. But they would be also because of the small population of the area we made research. We may need to research in larger area to reduce bias. On the other hand, it is interesting that we got some significant results analyzing these relatively small numbers of cases.

Conclusion

We investigated the effect of weather variability and air pollutants on emergency admissions. A detrimental effect of low temperature and air pressure decrease from previous days on admissions due to both cardiovascular and cerebrovascular diseases was observed. We found stronger detrimental effect of cold on stroke than cardiovascular disease. Some pollutants were found to have a detrimental effect on cardiovascular disease and stroke.

ACKNOWLEDGEMENTS, COMPETING INTERESTS, FUNDING

REFERENCES

1. The Eurowinter Group. 1997. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. The Eurowinter Group.Lancet. 349:1341-1346

2. Hajat S, Kovats RS, Lachowycz K. 2007. Heat-related and cold-related deaths in England and Wales: who is at risk?Occup Environ Med. 64:93-100

3. Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. 2009. Effects of ambient temperature on the incidence of myocardial infarction.Heart. 95:1760-1769

4. Chang CL, Shipley M, Marmot M, Poulter N. 2004. Lower ambient temperature was associated with an increased risk of hospitalization for stroke and acute myocardial infarction in young women.J Clin Epidemiol. 57:749-757

5. McArthur K, Dawson J, Walters M. 2010. What is it with the weather and stroke?Expert Rev Neurother. 10:243-249

6. Dawson J, Weir C, Wright F, Bryden C, Aslanyan S, Lees K, Bird W, Walters M. 2008. Associations between meteorological variables and acute stroke hospital admissions in the west of Scotland.Acta Neurol Scand. 117:85-89

7. Comprehensive Survey of Living Conditions of the People on Health and Welfare.[Internet]. 2007.Tokyo: Ministry of Health, Labor and Welfare;[cited 2011 June].Available from http://www.mhlw.go.jp/toukei/list/20-19-1.html

8. Danet S, Richard F, Montaye M, Beauchant S, Lemaire B, Graux C, Cottel D, Marecaux N, Amouyel P. 1999. Unhealthy effects of atmospheric temperature and pressure on the occurrence of myocardial infarction and coronary deaths. A 10-year survey: the Lille-World Health Organization MONICA project (Monitoring trends and determinants in cardiovascular disease).Circulation. 100:E1-E7

9. Mateen FJ, Brook RD. 2011. Air pollution as an emerging global risk factor for stroke.JAMA. 305:1240-1241

10. Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. 2009. Effects of air pollution on the incidence of myocardial infarction.Heart. 95:1746-1759

11. Armstrong B. 2006. Models for the relationship between ambient temperature and daily mortality.Epidemiology. 17:624-631

12. Brumback B, Burge HA, Neas LM, Ryan LM, Schwartz JD, Stark PC. 2000. Transitional regression models, with application to environmental time series.J Am Stat Assoc. 95:16-27

13. Durrleman S, Simon R. 1989. Flexible regression models with cubic splines.Stat Med. 8:551-561

14. Stewart S, McIntyre K, Capewell S, McMurray JJ. 2002. Heart failure in a cold climate. Seasonal variation in heart failure-related morbidity and mortality.J Am Coll Cardiol. 39:760-766

15. Koken PJ, Piver WT, Ye F, Elixhauser A, Olsen LM, Portier CJ. 2003. Temperature, air pollution, and hospitalization for cardiovascular diseases among elderly people in

Denver.Environ Health Perspect. 111:1312-1317

16. Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. 2010. Short term effects of temperature on risk of myocardial infarction in England and Wales: time series regression analysis of the Myocardial Ischaemia National Audit Project (MINAP) registry.BMJ. 341:c3823

17. Ohwaki K, Yano E, Murakami H, Nagashima H, Nakagomi T. 2004. Meteorological factors and the onset of hypertensive intracerebral hemorrhage.Int J Biometeorol. 49:86-90

18. Shinkawa A, Ueda K, Hasuo Y, Kiyohara Y, Fujishima M. 1990. Seasonal variation in stroke incidence in Hisayama, Japan.Stroke. 21:1262-1267

19. Ebi KL, Exuzides KA, Lau E, Kelsh M, Barnston A. 2004. Weather changes associated with hospitalizations for cardiovascular diseases and stroke in California, 1983-1998.Int J Biometeorol. 49:48-58

20. Kovats RS, Hajat S, Wilkinson P. 2004. Contrasting patterns of mortality and hospital admissions during hot weather and   heat waves in Greater London, UK.Occup Environ Med. 61:893-898

21. Houck PD, Lethen JE, Riggs MW, Gantt DS, Dehmer GJ. 2005. Relation of atmospheric pressure changes and the occurrences of acute myocardial   infarction and stroke.Am J Cardiol. 96:45-51

22. Jimenez-Conde J, Ois A, Gomis M, Rodriguez-Campello A, Cuadrado-Godia E, Subirana I, Roquer J. 2008. Weather as a trigger of stroke. Daily meteorological factors and incidence of stroke subtypes.Cerebrovasc Dis. 26:348-354

23. Yorifuji T, Kawachi I, Sakamoto T, Doi H. 2011. Associations of outdoor air pollution with hemorrhagic stroke mortality.J Occup Environ Med. 53:124-126

24. Linares C, Diaz J. 2010. Short-term effect of PM(2.5) on daily hospital admissions in Madrid (2003-2005).Int J Environ Health Res. 20:129-140

25. Kimura T, Senda S, Masugata H, Yamagami A, Okuyama H, Kohno T, Hirao T, Fukunaga M, Okada H, Goda F. 2010. Seasonal blood pressure variation and its relationship to environmental temperature in healthy elderly Japanese studied by home measurements.Clin Exp Hypertens. 32:8-12

26. Mudge GH Jr, Grossman W, Mills RM Jr, Lesch M, Braunwald E. 1976. Reflex increase in coronary vascular resistance in patients with ischemic heart disease.N Engl J Med. 295:1333-1337

27. Neild PJ, Syndercombe-Court D, Keatinge WR, Donaldson GC, Mattock M, Caunce M. 1994. Cold-induced increases in erythrocyte count, plasma cholesterol and plasma fibrinogen of elderly people without a comparable rise in protein C or factor X.Clin Sci (Lond). 86:43-48

28. Kawahara J, Sano H, Fukuzaki H, Saito K, Hirouchi H. 1989. Acute effects of exposure to cold on blood pressure, platelet function and sympathetic nervous activity in humans.Am J Hypertens. 2:724-726

29. Sato J, Takanari K, Omura S, Mizumura K. 2001. Effects of lowering barometric pressure on guarding behavior, heart rate and blood pressure in a rat model of neuropathic pain.Neurosci

Lett. 299:17-20

30. Messlinger K, Funakubo M, Sato J, Mizumura K. 2010. Increases in neuronal activity in rat spinal trigeminal nucleus following changes in barometric pressure--relevance for weather-associated headaches?Headache. 50:1449-1463

31. Jehn M, Appel LJ, Sacks FM, Miller ER 3rd. 2002. The effect of ambient temperature and barometric pressure on ambulatory blood pressure variability.Am J Hypertens. 15:941-945

32. Kohli Shrey, Ahuja Suchit, Dogra Deepika, Krishnan Shruti, Rani Vibha. 2011. Air pollutants: The key stages in the pathway towards the development of cardiovascular disorders.Environmental Toxicology and Pharmacology. 31:1-9

Figure Legends

Main text

Figure 1 Time scale distribution of the daily number of admissions and daily mean temperature,

pressure and pollutants, April.2006-March.2010

Figure 2 Estimated relative risk of emergency admissions by temperature

Figure 3 Estimated relative risk of emergency admissions by pressure change

Supplement

Figure S1 Estimated relative risk of emergency admissions by maximum temperature

Figure S2 Estimated relative risk of emergency admissions by minimum temperature
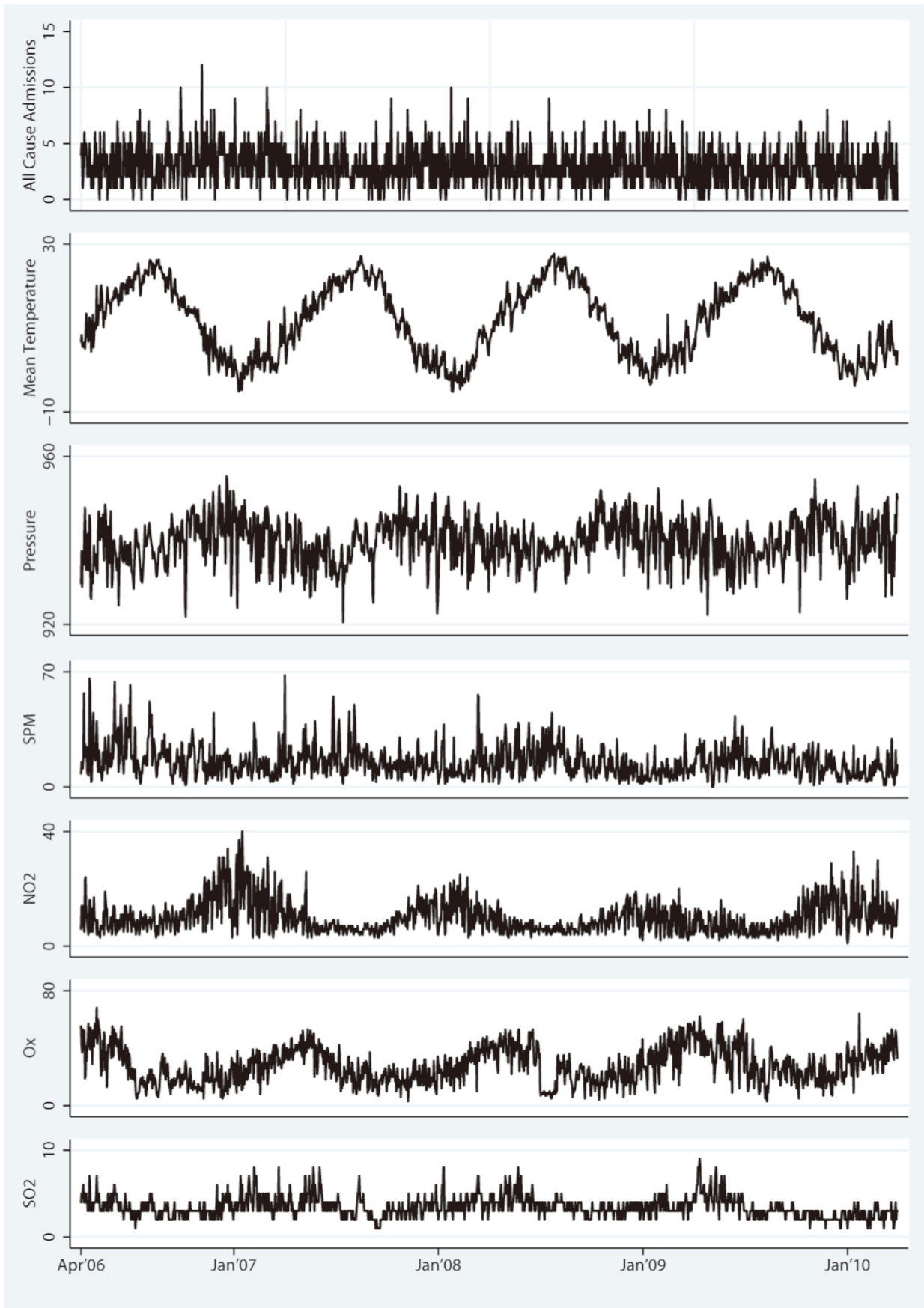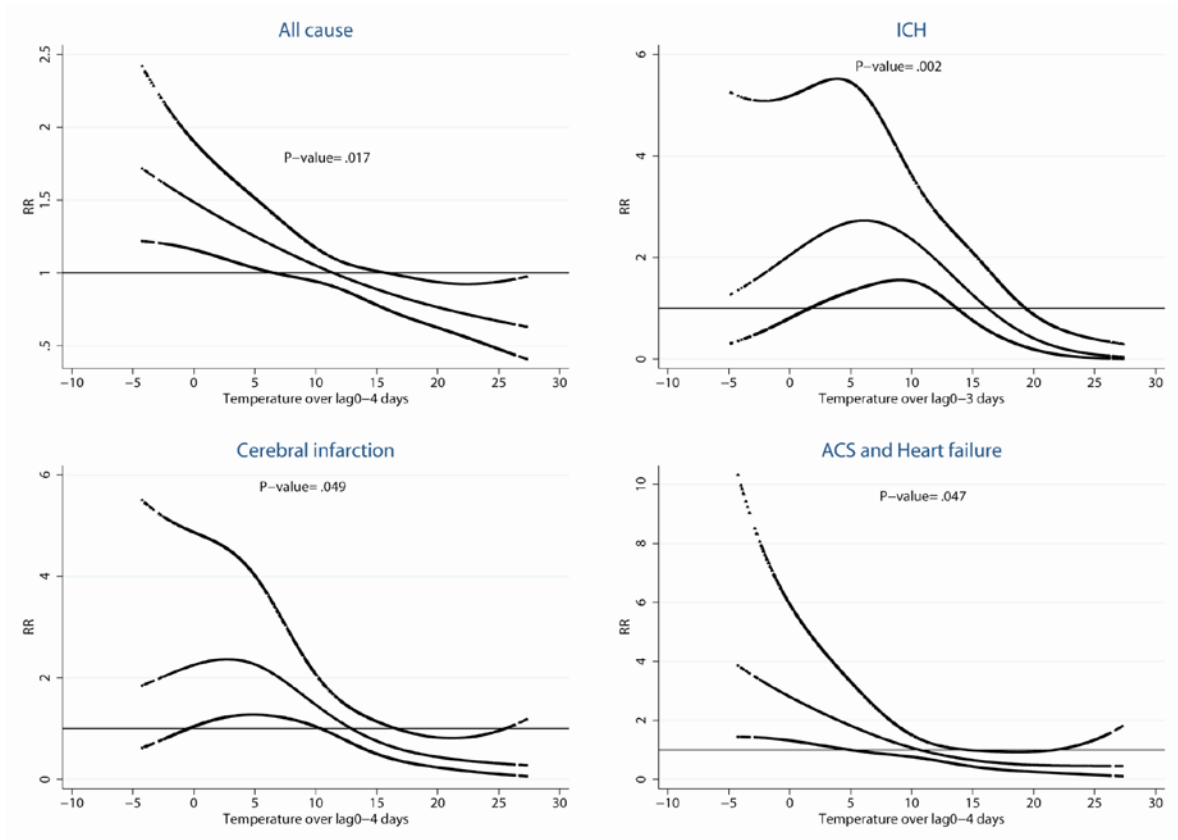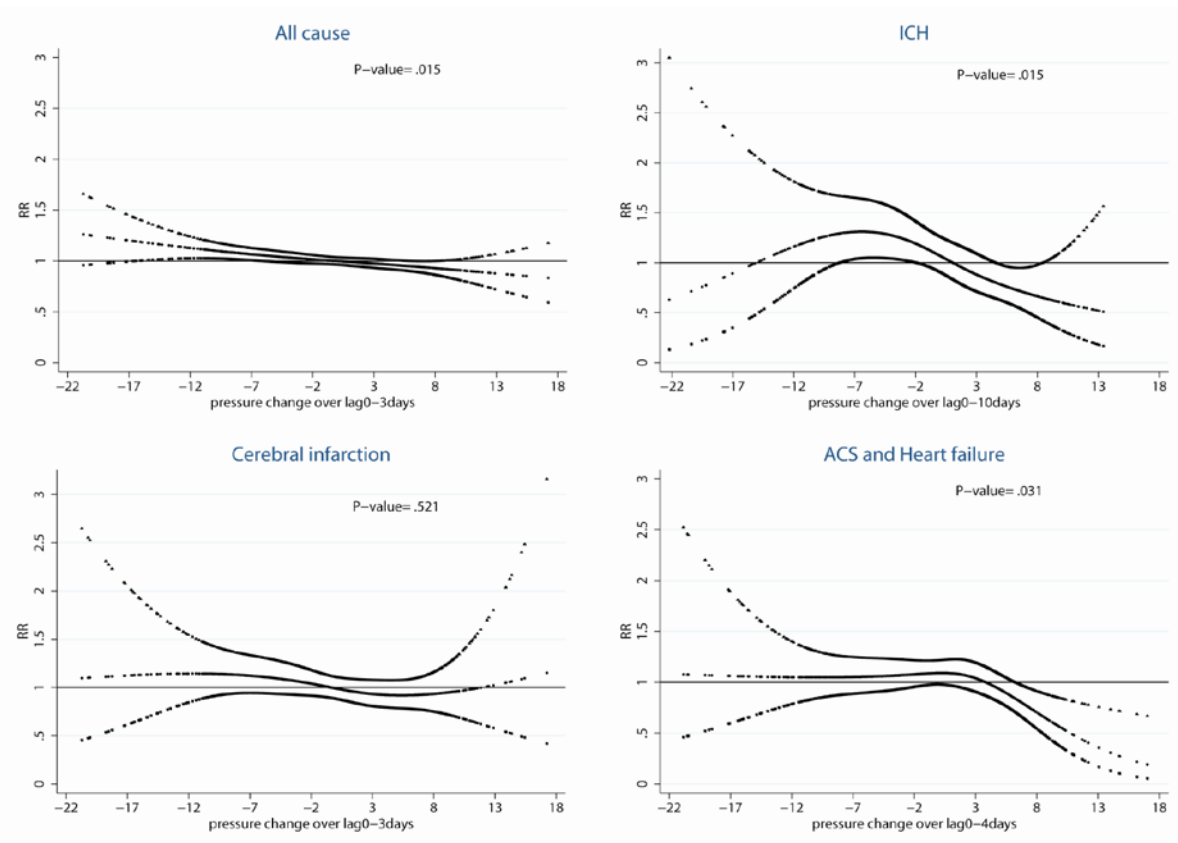
Figures

Figure 1

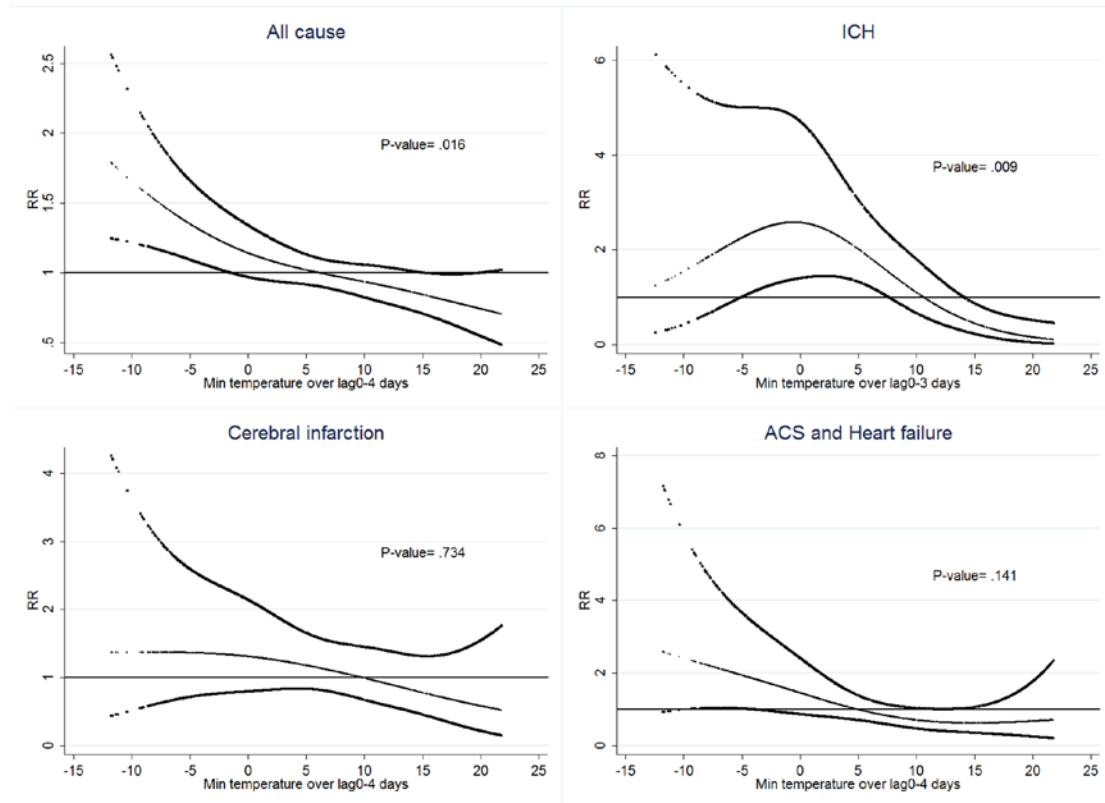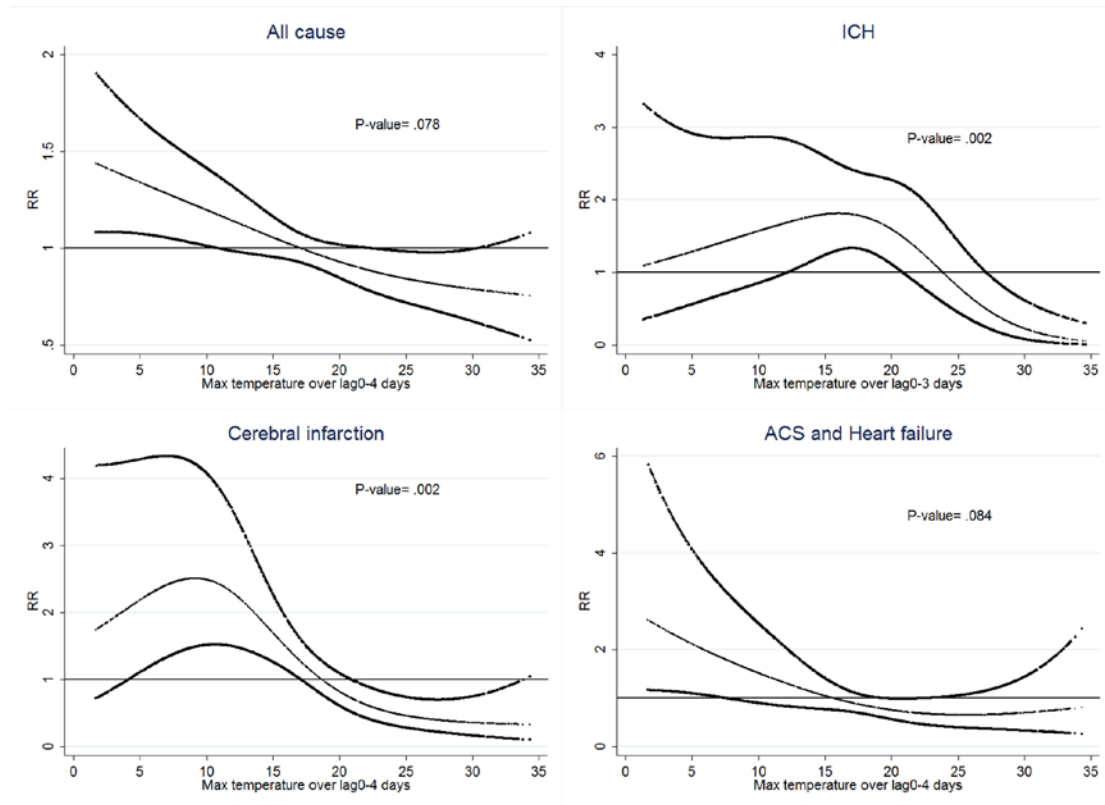Figure 2

Figure 3

Supplement figure

Figure S1

Figure S2

Tables

Table1 Summary statistics for numbers of admissions, levels of air pollutants and meteorological factors

Cause of hospital admissions	Total No of admissions	Male(%)	Mean (interquartile range) age
All cause	4355	2333/4355(53.6)	71(64-85)
ACS*	304	187/304(61.5)	73(65-82)
Cardiac arrest	306	195/306(63.7)	75(69-86)
Heart failure	204	102/204(50.0)	82(78-89)
SAH*	67	19/67(28.4)	68(58-81)
ICH*	265	152/265(57.4)	72(65-82)
Cerebral infarction	446	230/446(51.6)	79(73-86)
Aortic dissection and a ruptured aortic aneurysm	89	56/89(62.9)	77(71-94)

Levels of air pollutants and meteorological factors	Mean (range)
mean temperature (℃)	12 (-5.2-27.7)
pressure （hPa）	940(920.55-955.25)
no$_2$ (ppb)	10(1-40)
ox (ppb)	28(3-68)
so$_2$ (ppb)	3(1-9)
spm (μg/m^3)	32(0-68)

*ACS=acute coronary syndrome SAH=subarachinoid hemorrhage ICH=intracerebral hemorrhage

Table2 Estimated effects of temperature and pressure change

	mean temperature				pressure change			
	lag	% change (95%CI)	P value	threshold (℃)	lag	% change (95%CI)	P value	threshold (hPa)
All cause	0-4	3.24 (1.25 to 5.18)	0.001	*	0-3	0.95(0.37 to 1.52)	0.001	*
ICH	0-3	35.57(15.59 to 59.02)	0	15	0-10	3.25(0.94 to 5.51)	0.006	*
Cerebral infarction	0-4	11.71(4.1 to 19.89)	0.002	2		-		
ACS and Heart failure	0-4	7.83(2.06 to 13.25)	0.008	*	0-4	1.65(-0.015 to 3.28)	0.052	*
Aortic dissection and a ruptured aortic aneurysm		-			0-9	6.1(2.29 to 9.76)	0.002	*

Percent increase in number of admissions associated with 1℃decrease in temperature or 1hPa decrease in pressure change

* No threshold was identified

Table3 Estimated effects of pollutants

	lag	NO2 % change (95%CI)	Ox % change (95%CI)	SO2 % change (95%CI)	SPM % change (95%CI)
All cause	0	-0.42(-1.22 to 0.38)	-0.07(-0.47 to 0.33)	2.06(-1.28 to 5.51)	-3.47(-7.33 to 0.41)
	1	0.83(0.07 to 1.59)	-0.59(-0.99 to -0.19)	1.45(-2.04 to 5.06)	-2.03(-5.95 to 1.9)
	2	0.11(-0.65 to 0.88)	-0.15(-0.56 to 0.25)	3.29(-0.29 to 6.99)	0.05(-3.84 to 3.96)
	3	-0.32(-1.06 to 0.43)	0.11(-0.28 to 0.5)	2.28(-1.21 to 5.89)	0.56(-3.16 to 4.3)
ACS	0	-0.82(-3.76 to 2.22)	-0.19(-1.71 to 1.35)	18.9(4.98 to 34.66)	-6.54(-21.92 to 9.09)
	1	0.69(-2.1 to 3.56)	-0.93(-2.46 to 0.62)	12.97(-1.04 to 28.95)	2.55(-12.64 to 17.96)
	2	-0.89(-3.69 to 2)	-0.77(-2.31 to 0.79)	4.69(-8.79 to 20.17)	2.94(-18.55 to 12.94)
	3	-1.01(-3.75 to 1.79)	-0.19(-1.69 to 1.34)	0.46(-12.45 to 15.28)	0.13(-14.73 to 15.22)
Cardiac arrest	0	-1.75(-4.76 to 1.36)	1.51(-0.07 to 3.11)	7.61(-5.19 to 22.15)	-7.57(-22.77 to 7.87)
	1	-0.29(-3.17 to 2.68)	-0.24(-1.79 to 1.32)	12.17(-1.76 to 28.08)	10.48(-26.15 to 5.66)
	2	-0.39(-3.29 to 2.59)	0.73(-0.86 to 2.35)	3.2(-10.12 to 18.49)	11.5(-27.25 to 4.77)
	3	1.21(-1.57 to 4.07)	0(-1.53 to 1.55)	9.44(-4.22 to 25.05)	3.09(-17.74 to 11.79)
Heart failure	0	-1.92(-5.34 to 1.63)	0.97(-0.96 to 2.94)	3.7(-17.86 to 13.2)	-5.9(-24.64 to 13.19)
	1	1.69(-1.54 to 5.02)	-0.51(-2.42 to 1.43)	4.11(-11.46 to 22.41)	9.64(-7.85 to 27.44)
	2	1.58(-1.67 to 4.94)	-1.16(-3.06 to 0.78)	12.1(-4.67 to 31.81)	2.43(-15.77 to 20.97)
	3	0.45(-2.65 to 3.65)	-0.08(-1.96 to 1.84)	6.11(-9.57 to 24.52)	10.14(-28.7 to 8.97)
SAH	0	-1.71(-8.23 to 5.26)	0.99(-2.2 to 4.29)	15.04(-12.87 to 51.9)	-8.73(-42.03 to 25.72)
	1	0.03(-6.05 to 6.51)	2.2(-1.13 to 5.63)	19.73(-39.31 to 14.95)	34.82(-70.19 to 4.33)
	2	2.17(-3.76 to 8.46)	-0.14(-3.33 to 3.17)	20.46(-40.17 to 15.19)	-14.63(-48.93 to 20.92)
	3	6.59(0.79 to 12.73)	-1.2(-4.29 to 1.98)	12.07(-35.25 to 22.96)	3.55(-26.93 to 34.99)
ICH	0	-1.67(-5.14 to 1.93)	1.03(-0.63 to 2.72)	2.87(-10.28 to 17.95)	1.96(-13.85 to 18.02)
	1	2.85(-0.43 to 6.24)	-1.6(-3.19 to 0.01)	7.03(-7.25 to 23.52)	1.01(-15.36 to 17.65)
	2	-0.36(-3.66 to 3.05)	0.69(-0.97 to 2.38)	2.88(-11.08 to 19.04)	6.6(-23.7 to 10.9)
	3	-2.88(-6.03 to 0.38)	0.83(-0.81 to 2.49)	2.65(-15.7 to 12.58)	5.57(-21.9 to 11.12)
Cerebral infarction	0	-2.49(-4.92 to 0.01)	-0.55(-1.75 to 0.66)	0.77(-9.09 to 11.7)	-0.35(-12.23 to 11.68)
	1	0.5(-1.87 to 2.91)	-1.44(-2.64 to -0.22)	3.38(-7.29 to 15.27)	5.76(-18.34 to 7.03)
	2	-0.8(-3.18 to 1.64)	-0.72(-1.95 to 0.52)	8.9(-2.35 to 21.45)	6.52(-5.43 to 18.61)
	3	-1.02(-3.3 to 1.32)	-0.28(-1.48 to 0.94)	7.97(-2.98 to 20.15)	4.73(-6.71 to 16.3)
Aortic dissection and a ruptured aortic aneurysm	0	-2.85(-8.29 to 2.92)	4.48(1.39 to 7.66)	3.86(-18.51 to 32.38)	-3.41(-32.52 to 26.58)
	1	3.01(-2.14 to 8.43)	1.31(-1.59 to 4.3)	-1.6(-23.63 to 26.78)	16.93(-10.11 to 44.71)
	2	4.24(-0.92 to 9.67)	1.52(-1.49 to 4.61)	1.92(-23.7 to 26.18)	12.56(-14.78 to 40.65)
	3	3(-2.11 to 8.39)	-0.02(-2.87 to 2.92)	1.83(-20.04 to 29.67)	5.92(-33.66 to 22.68)

Percent increase in number of admissions associated with a 1ppb increase in NO2,Ox or SO2, or a 10μg/m³ increase in SPM

Supplement table

TableS1 Estimated effects of temperature and pressure change in subgroups on all cause admission

	mean temperature		pressure change	
	% change (95%CI)	P value	% change (95%CI)	P value
<65	-		-	
65-74	-		-	
74<	3.96 (1.44-6.42)	0.002	1.33(0.61-2.05)	0
Male	4.87 (2.13-7.53)	0.001	1.13(0.33-1.91)	0.005
Female	-		-	

Percent increase in number of admissions associated with 1℃decrease in temperature or 1hPa decrease in pressure change

TableS2 Estimated effects of pollutants in subgroups on all cause admission

lag	subgroup	No2 % change (95%CI)	Ox % change (95%CI)	SO2 % change (95%CI)	SPM % change (95%CI)
0	<65	1.13(-0.59 to 2.89)	-0.34(-1.17 to 0.5)	-3.71(-10.47 to 3.55)	-5.45(-13.71 to 2.87)
	65-74	0.17(-1.83 to 2.22)	-0.07(-1.06 to 0.94)	5.75(-2.73 to 14.98)	-13.31(-23.41 to -3.11)
	74<	-1.17(-2.18 to -0.15)	0.03(-0.48 to 0.54)	3.41(-0.88 to 7.89)	-0.09(-5 to 4.84)
1	<65	1.03(-0.62 to 2.71)	-0.43(-1.27 to 0.42)	-1.17(-8.37 to 6.59)	-2.05(-10.34 to 6.31)
	65-74	1.99(0.08 to 3.94)	-0.48(-1.48 to 0.53)	3.33(-5.46 to 12.93)	-2.27(-12.18 to 7.73)
	74<	0.41(-0.55 to 1.39)	-0.68(-1.19 to -0.17)	2.02(-2.44 to 6.67)	-1.95(-6.99 to 3.1)
2	<65	0.36(-1.29 to 2.04)	0.15(-0.7 to 1.01)	-1.27(-8.58 to 6.63)	-3.74(-12.11 to 4.69)
	65-74	1.19(-0.74 to 3.15)	0.09(-0.92 to 1.11)	11.77(2.37 to 22.04)	-2.61(-12.47 to 7.35)
	74<	-0.28(-1.25 to 0.7)	-0.34(-0.86 to 0.17)	2.84(-1.69 to 7.58)	2.12(-2.84 to 7.11)
3	<65	0.4(-1.21 to 2.02)	0.74(-0.09 to 1.58)	3.59(-3.85 to 11.61)	4.1(-3.66 to 11.93)
	65-74	-0.67(-2.56 to 1.25)	0.42(-0.57 to 1.42)	2.36(-6.27 to 11.78)	-10.86(-20.66 to -0.95)
	74<	-0.49(-1.43 to 0.45)	-0.23(-0.73 to 0.27)	1.77(-2.65 to 6.39)	2.16(-2.6 to 6.94)
0	Male	-0.5(-1.6 to 0.61)	-0.05(-0.61 to 0.5)	-0.55(-5.07 to 4.2)	-1.77(-7.11 to 3.6)
	Female	-0.34(-1.48 to 0.82)	-0.1(-0.66 to 0.47)	5.01(0.16 to 10.09)	-5.48(-11.06 to 0.13)
1	Male	0.93(-0.12 to 1.99)	-0.72(-1.28 to -0.17)	2.94(-1.92 to 8.04)	0.97(-4.41 to 6.37)
	Female	0.73(-0.36 to 1.83)	-0.45(-1.02 to 0.12)	0(-4.92 to 5.17)	-5.68(-11.37 to 0.04)
2	Male	0.07(-0.98 to 1.13)	-0.22(-0.78 to 0.34)	2.41(-2.51 to 7.58)	2.61(-2.72 to 7.98)
	Female	0.14(-0.96 to 1.25)	-0.07(-0.64 to 0.51)	4.22(-0.88 to 9.6)	-3.15(-8.8 to 2.53)
3	Male	-0.8(-1.82 to 0.23)	0.51(-0.04 to 1.06)	1.79(-3.02 to 6.84)	1.04(-4.13 to 6.24)
	Female	0.25(-0.81 to 1.32)	-0.34(-0.89 to 0.22)	2.91(-2.06 to 8.12)	-0.13(-5.46 to 5.23)

Percent increase in number of admissions associated with a 1ppb increase in NO2,Ox or SO2, or a 10μg/m³ increase in SPM

TableS4 Estimated effects of maximum and minimum temperature

		maximum temperature			minimum temperature		
	lag	% change (95%CI)	P value	threshold (℃)	% change (95%CI)	P value	threshold (℃)
All cause	0-4	-			2.65(0.96 to 4.31)	0.002	*
ICH	0-3	27.61(12.64 to 44.56)	0	22	25.25(10.23 to 42.30)	0.001	8
Cerebral infarction	0-4	12.13(5.52 to 19.16)	0	10	-		
ACS and Heart failure		-			-		
Aortic dissection and rupture of aortic aneurysm		-			-		

Percent increase in number of admissions associated with 1℃decrease in temperature

* No threshold was identified

TableS3 Coefficients of Fourier terms

	all cause	ICH	Cerebral infarction	ACS and Heart failure
Harmonics		% change(95%CI)		
1	2.78(0.99 to 4.54)	14.59(6.03 to 23.84)	9.29(2.6 to 16.41)	7.92(2.75 to 12.81)
2	3.38(1.48 to 5.25)	30(15.03 to46.91)	8.28(1.29 to 15.76)	8.17(2.67 to 13.37)
3	3.08(1.12 to 5.00)	33.6(14.69 to 55.64)	3.19(1.91 to 16.98)	7.66(1.99 to 12.99)
4	3.24(1.28 to 5.17)	38.18(17.99 to 61.83)	10.3(2.85 to 18.29)	7.86(2.17 to 13.22)
5	3.25(1.28 to 5.19)	35.73(15.67 to 59.26)	10.62(3.16 to 18.63)	7.73(2.02 to 13.12)
6	3.24(1.25 to 5.18)	35.57(15.59 to 59.02)	11.71(4.1 to 19.89)	7.83(2.06 to 13.25)
7	3.21(1.22 to 5.16)	36.95(16.48 to 61)	11.25(3.61 to 19.45)	8.01(2.25 to 13.43)
8	3.23(1.23 to 5.19)	36.1(15.62 to 60.21)	10.9(3.25 to 19.11)	8.52(2.81 to 13.9)
9	3.01(1 to 4.98)	38.73(17.52 to 63.77)	10.22(2.53 to 18.49)	8.07(2.33 to 13.46)
10	3.07(1.06 to 5.04)	38.23(17.1 to 63.17)	10.14(2.4 to 18.46)	7.98(2.22 to 13.4)
11	3.03(1.01 to 5)	37.3(16.31 to 62.07)	9.92(2.18 to 18.24)	8.03(2.26 to 13.46)
12	3.08(1.06 to 5.05)	37.49(16.41 to 62 38)	10.21(2.4 to 18.62)	8(2.23 to 13.44)

Percent increase in number of admissions associated with 1℃decrease in temperature