Vulnerability to heat-related mortality: a multicity, population-based, case-crossover analysis.

Vulnerability to Heat-Related Mortality

A Multicity, Population-Based, Case-Crossover Analysis

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Background: Although studies have documented increased mortality during heat waves, little information is available on the subgroups most susceptible to these effects. We evaluated the effects of summertime high temperature on daily mortality among population subgroups defined by demographic characteristics, socioeconomic status, and episodes of hospitalization for various conditions during the preceding 2 years.

Methods: We studied a total of 205,019 residents of 4 Italian cities (Bologna, Milan, Rome, and Turin) age 35 or older who died during 1997–2003. The case-crossover design was applied to evaluate the association between mean apparent temperature (same and previous day) and all-cause mortality. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of dying at 30°C (apparent temperature) relative to 20°C were estimated accounting for time, population changes, and air pollution.

Results: We found an overall OR of 1.34 (CI = 1.27–1.42) at 30°C relative to 20°C. The odds ratio increased with age and was higher among women (OR = 1.45; 1.37–1.52) and among widows and widowers (1.50; 1.33–1.69). Low area-based income modestly increased the effect. Among the preexisting medical conditions investigated, effect modification was detected for previous psychiatric disorders (1.69; 1.39–2.07), depression (1.72; 1.24–2.39), heart conduction disorders (1.77; 1.38–2.27), and circulatory disorders of the brain (1.47; 1.34–1.62). Temperature-related mortality was higher among people residing in nursing homes, and a large effect was also detected for hospitalized subjects.

Conclusions: Subsets of the population that are particularly vulnerable to high summer temperatures include the elderly, women, widows and widowers, those with selected medical conditions, and those staying in nursing homes and healthcare facilities.

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Several studies have investigated the relationship between high temperature and mortality,[1] both during specific heat waves[2–4] and over a long time period, using modern time-series analysis[5–8] or the case-crossover approach.[9] A J-shaped relationship between daily temperature and all-cause mortality has been found, with an immediate time lag (same day or previous day at the most) of the heat effect.[1,5,6,10] However, little information is available on the subgroups most vulnerable to the effects of hot temperatures, ie, those fractions of the population with a larger than average response either resulting from intrinsic susceptibility factors (such as clinical conditions) or higher exposure.[11] Small-scale investigations[2,3,12] suggest the following vulnerability factors: living alone among the elderly, having a low socioeconomic status, and being ill. However, comprehensive evaluation at the population level is lacking. In the United States, O'Neill and coworkers[10] found that place of death (out of hospital), black race, and low educational level intensified the temperature–mortality relationship. Schwartz[13] identified having been hospitalized for diabetes as an effect modifier for heat-related mortality. In Europe, the heat wave episode in summer 2003[12,14,15] has focused public health attention on heat-related mortality and the possible preventive actions to be introduced, especially among targeted population subgroups.

Our study was aimed at identifying specific conditions that render the individual particularly vulnerable to hot weather. We considered individual demographic characteristics, socioeconomic status, place of death, and chronic diseases of deceased subjects in 4 Italian cities. Extensive record linkage procedures were used to characterize subjects with respect to previous morbidity. We then applied the case-crossover approach, a method proposed to study triggers of acute events such as myocardial infarction[16] and largely used in air pollution epidemiology[17] to evaluate effect modification of the high temperature–mortality association.

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METHODS

Subjects and Individual Information

We considered subjects age 35 or older residing and dying in 4 Italian cities from all noninjury causes (International Classification of Diseases, 9th Revision [ICD-9]: 1–799) in the following periods: 2000–2003 in Bologna, 1999–2003 in Milan, 1998–2001 in Rome, and 1997–2003 in Turin. Death status was retrieved from Regional Registers of Causes of Death, which also include data on sex and age. Record linkage with city-specific population registers provided information on marital status (Milan and Turin only) and census block of residence (approximately 500 inhabitants per block). Median population income (family income in 1998) for each census block of residence, provided by the Ministry of Finance, was considered as an area-based indicator of socioeconomic status and divided into categories based on percentiles.

The city-specific mortality datasets were then linked (using individuals' fiscal codes) with the regional hospital discharge files (which include hospitalizations in public and private hospitals nationwide of all resident citizens). All hospital admissions during the 2 years preceding death (excluding the last 28 days) were selected. We obtained information on both primary causes of admission and secondary contributing diagnoses, and classified each subject according to having been hospitalized for a list of 28 groups of diagnoses chosen a priori by adapting the Elixauser list of comorbidities.[18] The 28-day exclusion was applied to distinguish between chronic conditions and a sudden deterioration of health in the few days before death. Information on hospitalization within 28 days of death was used only as part of the identification of the place of death. This variable was categorized as out-of-hospital (neither admission nor discharge in the last 4-week period), discharged 2–28 days before death, in-hospital, or in a nursing home (for Milan and Turin only).

Environmental Variables

Daily environmental data were obtained from the Italian Air Force Meteorological Service, which provided temperature, relative humidity/dew point temperature, and barometric pressure measured at the nearest city airport. We used daily mean apparent temperature as the exposure variable.[19] This combination of air temperature and dew point temperature represents physical stress deriving from extreme summer conditions better than does air temperature alone. The average exposure on the day of death and on the day before (lag 0–1) was used, because many studies found a short latency of the effect of high temperatures on mortality.[1,5,6,10] We also collected daily data on particulate matter with aerodynamic diameter lower than 10 μm (PM_{10}; lag 0–1) and ozone (daily maximum 8-hour running mean during May–September) from the Regional Environmental Protection Agencies, because air pollution has been associated with short-term increase in mortality.[20–22] Urban background city monitors provided these latter variables.

Data Analysis

Statistical analysis was performed in 3 stages. First, the concentration–response curve of the relationship between apparent temperature and noninjury mortality was explored for each city using the case-crossover design.[16] Control periods were selected using the "time-stratified" approach,[23] in which the study period was divided into monthly strata, and control days for each case were selected as the same days of the week in the stratum. A conditional logistic regression analysis was performed for each city, modeling the exposure variable as a cubic penalized spline. The numbers of knots, and the smoothness of the curves, were chosen to minimize the Akaike information criterion (AIC) index. The final smoothness was tuned to avoid overfitting. For each location, the regression model controlled for the confounding effects of temporary population decrease in the summer period, holidays, influenza epidemics, linear terms for PM_{10} (lag 0–1), and barometric pressure (lag 0). Long-term and seasonal time trends, as well as day of the week, were controlled for by design. The role of summer ozone as a potential confounder was evaluated in a sensitivity analysis. All analyses were performed with R software version 2.1.0 (R Foundation for Statistical Computing, http://www.R-project.org).

We inspected the 4 plots of the temperature–mortality association to identify 2 city-specific cut points of the J curve: the level of apparent temperature when mortality starts to increase in a nonlinear way and the point at which the temperature–mortality relationship assumes a steep linear trend. The objective was to approximate the smoothed curve into 3 linear splines to simplify the overall relationship. Alternative models were inspected with a higher number of degrees of freedom and different location of the knots, but the model with 3 linear splines turned out to be the best in terms of AIC index.

In the second stage, the analysis of effect modification was performed in each location, approximating the apparent temperature–mortality relationship with 3 linear splines with 2 inner knots according to the city-specific cut points. The effect of apparent temperature at 30°C versus 20°C was then estimated.

Third, city-specific results were combined in a meta-analysis and potential heterogeneity was explored using random-effects models. The maximum likelihood method was used.[24] All results are expressed as pooled odds ratios (ORs), with 95% confidence intervals (CIs), of dying on a day with 30°C apparent temperature relative to 20°C. Effect modification was tested and results are reported as the relative effect modification (REM) index calculated as the ratio between the specific odds ratio and the odds ratio from the reference category.

RESULTS

Table 1 displays a summary of the environmental variables considered and the number of deaths included in the analysis for each city. Overall, mean apparent temperature was highest in Rome and lowest in Turin. Milan had the greatest variability and the most extreme values in apparent temperature, whereas Rome's distribution was less dispersed. Table 1 also reports the distribution of the difference between

TABLE 1. Environmental Variables and Number of Deaths in the 4 Italian Cities

Environmental Variables	Bologna (2000–2003)	Milan (1999–2003)	Rome (1998–2001)	Turin (1997–2003)
Apparent temperature (°C)				
Mean ± SD	13.8 ± 10.0	14.3 ± 10.4	15.5 ± 8.4	11.9 ± 9.4
Minimum	−5.8	−6.1	−1.5	−6.0
Maximum	33.9	37.5	32.2	33.2
Percentiles				
25th	5.0	5.4	8.1	3.7
50th	13.3	13.6	15.4	11.2
75th	22.1	23.1	22.7	19.8
Difference of apparent temperature between "cases" and "controls" (°C)				
Mean ± SD	0.1 ± 3.7	0.1 ± 3.7	0.1 ± 3.3	0.1 ± 3.7
Minimum	−10.2	−10.4	−10.5	−13.7
Maximum	12.5	12.9	12.3	12.0
Percentiles				
25th	−2.2	−2.3	−2.2	−2.3
50th	0.2	0.1	0.1	0.1
75th	2.5	2.5	2.2	2.5
Barometric pressure (hPa)				
Mean ± SD	1016 ± 7.4	1016 ± 7.4	1016 ± 6.6	1017 ± 7.6
PM_{10} ($\mu g/m^3$)				
Mean ± SD	50.4 ± 31.7	56.7 ± 37.4	51.0 ± 21.0	65.5 ± 34.8
Ozone ($\mu g/m^3$) (May–September)				
Mean ± SD	106.4 ± 35.7	123.9 ± 42.1	119.1 ± 32.5	105.7 ± 39.7
Population under study				
No. of deaths, age 35+ years	16,612	52,908	83,253	52,246

SD indicates standard deviation.

apparent temperature in cases and controls in that the case-crossover design is focused on the within-subject variation and so the relevant exposure variable relates to the variability among case periods and control periods rather than the exposure of the cases alone.[25] The 4 cities seem to be quite similar, with Rome showing the smallest variability. A total of 205,019 deaths were included in the study with the largest contribution from Rome.

Figure 1 shows the concentration–response curves between daily mean apparent temperature (lag 0–1) and noninjury mortality for the 4 locations. All 4 curves are J-shaped, with slightly different turning points (20°C and 26°C for Bologna, 22°C and 29°C for Milan, 20°C and 26°C for Rome, and 23°C and 27°C for Turin) and different slopes in the right arm (steeper in Milan and Turin than in Bologna and Rome). The effect of apparent temperature was approximately zero in the left arm of the concentration–response curves, but apparent temperature was modeled at immediate lag, whereas the cold effect has usually a much higher latency, up to several weeks.

The city-specific results, expressed as odds ratio of dying on days with 30°C in mean apparent temperature (lag 0–1) versus days with 20°C were: Bologna 1.37 (95% CI = 1.22–1.54), Milan 1.27 (1.19–1.53), Rome 1.30 (1.22–1.39), and Turin 1.45 (1.37–1.54). When the city-specific results were combined, we found an overall OR of 1.34 (1.27–1.42). In Table 2, combined effect estimates by age and sex are presented from either fixed or random-effects models. The odds ratios for women were higher than for men in each age category. In addition, there was a clear increasing trend of harmful effect of high temperature on mortality with age for both men and women.

Table 3 shows the combined results for the overall population and by sex, age, marital status, area-based income, previous hospital admissions, and place of death. Relative effect modification indexes and exact *P* values are also reported. A greater OR was found among widowed, unmarried, and divorced subjects (OR = 1.50; 95% CI = 1.33–1.69) than among married subjects (1.21; 1.13–1.28). No effect modification for area-based income was detected, although the OR was slightly lower among those in the highest quintile of the distribution. Subjects who had been hospitalized in the 2 preceding years had a smaller effect than those who had not. Place of death was an important effect modifier, because those discharged from a hospital 2–28 days before death had a reduced heat-related mortality, whereas people who were in a nursing home were more susceptible. In-hospital and out-of-hospital deaths had a similar association with mean apparent temperature, and there was an increase in mortality for both long-term care patients (more than 59 days) and those whose hospital stay lasted less than 60 days.

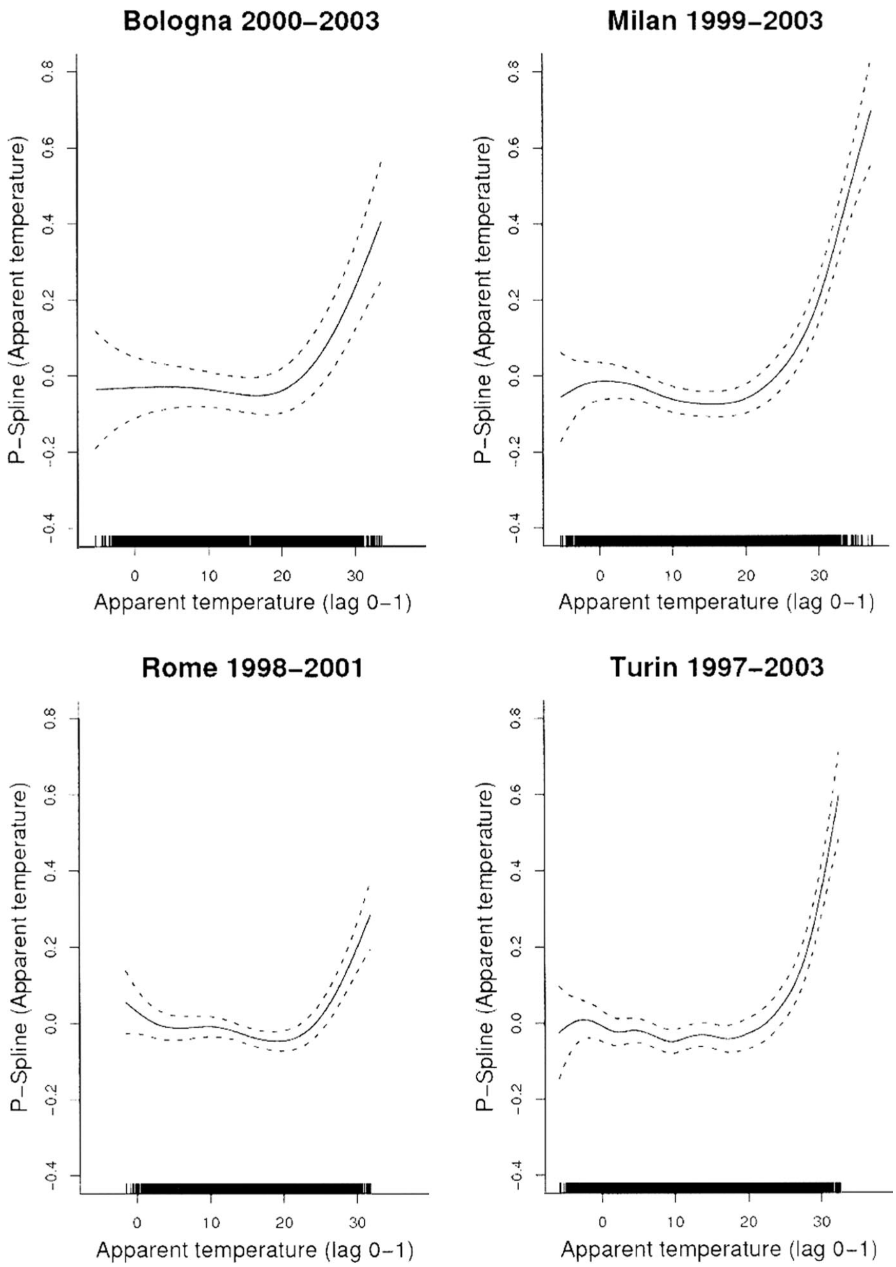

FIGURE 1. Relationship between mean apparent temperature (lag 0–1) and all noninjury mortality, age 35+ years, 1997–2003, 4 cities in Italy. The curves show penalized splines of apparent temperature from city-specific case-crossover models. The models control for seasonal and long-term time trend (by design), day of the week (by design), population decrease during the summer period, holidays, influenza epidemics, PM_{10} (lag 0–1), and barometric pressure (lag 0). The x-axes represent apparent temperature; the y-axes represent the natural logarithms of risks of death centered at zero.

Table 4 shows the combined results for 28 groups of diagnoses as a primary or secondary cause of hospital admission in the 2 years before death. Psychoses, depression, and conduction disorders of the heart were effect modifiers, with ORs of 1.70 (CI = 1.39–2.09), 1.71 (1.23–2.38), and 1.77 (1.38–2.27), respectively. Those with previous cerebrovascular diseases (12% of the total cases) also had a higher risk (1.46; 1.33–1.61) than those not affected. On the other hand, subjects with cancer had a lower relative risk of dying during hot days than subjects without cancer (1.20; 1.13–1.28). No noticeable positive or negative effect modification was detected for other conditions. The main findings of the study are summarized in Figure 2.

A number of sensitivity analyses have been conducted and the main results are reported in Table 5. Age could be a confounder responsible for some of the apparent effect mod-

TABLE 2. Risk of Dying on Days With 30°C in Mean Apparent Temperature (lag 0–1) versus Days With 20°C, by Age and Sex, for the 4 Cities Combined*

Age (years)	Men OR (95% CI)	Women OR (95% CI)	Total OR (95% CI)
35–64	1.09 (0.97–1.22)	1.17 (1.01–1.35)	1.12 (1.02–1.23)
65–74	*1.19 (1.02–1.39)*	1.34 (1.19–1.51)	*1.25 (1.12–1.38)*
75–84	1.28 (1.18–1.40)	*1.44 (1.30–1.59)*	1.36 (1.28–1.44)
85–94	1.40 (1.26–1.56)	*1.56 (1.41–1.71)*	*1.49 (1.37–1.63)*
95+	1.33 (0.91–1.94)	1.65 (1.37–1.97)	1.58 (1.34–1.85)
Total (35+)	1.24 (1.16–1.33)	*1.45 (1.37–1.52)*	1.34 (1.27–1.42)

*Results in italics are from random-effects models.

ification. However, it was difficult in our model to adjust for age because 3 age–temperature interaction terms would be needed in addition to the main effect modifier under focus, and the interpretation of the coefficients would not be straightforward. Therefore, we repeated all the analyses with a restriction to the population age 65+ years or age 75+ years. The results were quite similar to those found in the 35+ years age category, although the power was reduced especially in the 75+ years age group. In addition, the results were robust when the 2003 data were excluded from the analysis, indicating that the effects found were not merely the result of a specific heat wave. Finally, the inclusion of summer ozone as a confounder in the city-specific models did not change the risk estimates in a meaningful way.

DISCUSSION

We designed the study to identify subgroups vulnerable to heat, addressing a specific request from public health authorities seeking to better target social and medical intervention. We found that the following categories of people were at higher risk of dying on hot days: elderly, women, widows and widowers, and people with psychiatric conditions, depression, heart conduction disorders, and previous

TABLE 3. Risk of Dying on Days With 30°C in Mean Apparent Temperature (lag 0–1) versus Days With 20°C, by Age, Demographic Characteristics, Previous Hospital Admissions, and Place of Death; Combined Results for the 4 Cities*

	No.	Percent	OR (95% CI)	REM Index† (*P*)
Total (35+ years)	205,019	100	1.34 (1.27–1.42)	—
Sex				
Men	99,675	49	*1.24 (1.16–1.33)*	1.00
Women	105,344	51	*1.45 (1.37–1.52)*	1.17 (0.001)
Age (years)				
35–64	29,941	15	1.12 (1.02–1.23)	1.00
65–74	43,601	21	*1.25 (1.12–1.38)*	1.11 (0.140)
75–84	65,188	32	1.36 (1.28–1.44)	1.21 (0.000)
85–94	58,242	28	*1.49 (1.37–1.63)*	1.33 (0.000)
95+	8047	4	1.58 (1.34–1.85)	1.40 (0.000)
Marital status‡				
Married	48,576	46	1.21 (1.13–1.28)	1.00
Not married, widowed, divorced	56,491	54	*1.50 (1.33–1.69)*	1.24 (0.002)
Income (area level)				
<20th percentile	47,542	23	*1.38 (1.22–1.55)*	1.00
20th–50th percentile	60,833	30	*1.37 (1.25–1.49)*	0.99 (0.917)
50th–80th percentile	57,545	28	1.36 (1.27–1.45)	0.99 (0.847)
80th–100th percentile	37,841	19	1.30 (1.20–1.41)	0.95 (0.439)
Hospital admission in the 2 previous years (excluding last 28 d)				
No	74,132	36	*1.42 (1.34–1.51)*	1.00
Yes	130,887	64	*1.31 (1.23–1.39)*	0.92 (0.047)
Place of death				
Out of hospital	66,312	32	*1.37 (1.27–1.49)*	1.00
Discharged 2–28 d before death	14,631	7	*1.17 (0.99–1.37)*	0.85 (0.075)
In hospital (<60 d)	108,396	53	*1.32 (1.23–1.41)*	0.96 (0.412)
In hospital (≥60 d)	5251	3	1.43 (1.18–1.74)	1.04 (0.709)
Nursing home‡	10,423	5	1.61 (1.41–1.84)	1.17 (0.047)

*Results in italics are from random-effects models.
†REM: relative effect modification index is calculated as the ratio between the specific OR and the OR from the reference category.
‡Milan and Turin only.

TABLE 4. Risk of Dying on Days With 30°C in Mean Apparent Temperature (lag 0–1) versus Days With 20°C, by 28 Groups of Diagnoses Figuring Either as the Primary or as a Secondary Contributing Cause of Hospital Admission in the 2 Yr Before Death, Excluding Last 4 Wk; Combined Results for the 4 Cities*

	Percent	OR (95% CI)	REM Index (*P*)
AIDS (ICD-9: 042)	0.4	1.08 (0.65–1.80)	0.80 (0.400)
Malignant neoplasms (ICD-9: 140–208)	28.2	1.20 (1.13–1.28)	0.85 (0.000)
Disorders of thyroid gland (ICD-9: 240–246)	1.9	1.49 (1.17–1.90)	1.11 (0.408)
Diabetes mellitus (ICD-9: 250)	9.9	*1.39 (1.21–1.59)*	1.03 (0.656)
Disorders of fluid, electrolyte, and acid-base balance (ICD-9: 276)	1.6	*1.27 (0.93–1.75)*	0.95 (0.741)
Obesity and other hyperalimentation (ICD-9: 278)	0.6	1.40 (0.90–2.20)	1.05 (0.845)
Anemias (ICD-9: 280–285)	8.8	1.24 (1.11–1.39)	0.91 (0.162)
Coagulation defects (ICD-9: 286–287)	1.0	*1.07 (0.64–1.77)*	0.79 (0.372)
Psychoses (ICD-9: 290–299)	3.9	*1.70 (1.39–2.09)*	1.28 (0.024)
Depression (ICD-9: 300.4, 301.1, 309.0, 309.1, 311)	1.0	1.71 (1.23–2.38)	1.28 (0.149)
Paralysis (ICD-9: 342–344)	1.3	1.45 (1.05–2.01)	1.08 (0.638)
Other disorders of the central nervous system (ICD-9: 330–341, 345–349)	4.7	*1.40 (1.20–1.64)*	1.05 (0.581)
Diseases of valves (ICD-9: 394.0–397.1, 424, 746.3–746.6, 093.2)	2.9	*1.30 (1.06–1.59)*	0.97 (0.740)
Hypertensive disease (ICD-9: 401–405)	16.3	1.26 (1.15–1.37)	0.93 (0.141)
Previous acute myocardial infarction (ICD-9: 410, 412)	4.1	1.31 (1.10–1.55)	0.97 (0.741)
Other ischemic heart diseases (ICD-9: 411, 413–414)	11.1	*1.34 (1.20–1.49)*	1.00 (0.972)
Diseases of pulmonary circulation (ICD-9: 415–417)	1.6	1.27 (0.96–1.69)	0.95 (0.703)
Conduction disorders (ICD-9: 426)	2.1	1.77 (1.38–2.27)	1.32 (0.032)
Cardiac dysrhythmias (ICD-9: 427)	11.4	*1.32 (1.18–1.48)*	0.98 (0.793)
Heart failure (ICD-9: 428)	9.5	1.26 (1.13–1.41)	0.93 (0.294)
Cerebrovascular diseases (ICD-9: 430–438)	12.2	1.46 (1.33–1.61)	1.10 (0.105)
Diseases of arteries, arterioles, and capillaries (ICD-9: 440–448)	5.7	*1.24 (1.04–1.47)*	0.92 (0.355)
Pneumonia (ICD-9: 480–486)	5.9	*1.28 (1.02–1.59)*	0.95 (0.641)
Chronic pulmonary diseases (ICD-9: 490–505)	10.7	1.25 (1.12–1.39)	0.92 (0.203)
Acute and chronic liver diseases (ICD-9: 570–572)	4.5	*1.19 (1.00–1.40)*	0.88 (0.150)
Renal failure (ICD-9: 584–588)	6.5	1.26 (1.10–1.43)	0.93 (0.322)
Diseases of the osteomuscular system (ICD-9: 710–739)	5.1	1.30 (1.12–1.52)	0.97 (0.701)
Fracture of femur (ICD-9: 820–821)	3.2	*1.42 (1.16–1.73)*	1.06 (0.591)

*Results in italics are from random-effects models.

cerebrovascular diseases. People who were in nursing homes or in the hospital, and thus receiving greater social or medical attention, did not seem to be protected against heat-related mortality.

The adverse effect of high temperatures on mortality has been well documented in the United States,[6,9,26] Europe,[7,27] and Italy.[14] We found an overall 34% increase of risk on days with mean apparent temperature of 30°C versus days with 20°C, similar to results in the other European studies but higher than U.S. estimates. O'Neill et al[10] found an overall 5% increase of risk when temperatures rise from 15°C to 29°C, much less than in the present study. However, most of the excess in their study was in out-of-hospital deaths (+10%), whereas no excess was observed for in-hospital mortality. The greater availability of air conditioning in the U.S. hospitals may reduce the excess of risk attributable to heat.[28]

Several studies found a higher effect of hot temperatures on mortality in the elderly,[26,27,29,30] and our results confirm the increasing trend of risk with age. Decreased sweating[31] and difficulty in thermoregulation with age[32] are the most important physiopathological factors. Our results, however, show an increase of risk even for the younger age group (35–64 years old), especially among women. O'Neill et al[10] found an excess mortality (at 29°C) for the $<$65 age group but no differences between the sexes. Other studies reported sex differences, with a higher excess in men during the 1995 heat wave in Chicago[33] and a higher excess in women in the 1995 heat wave in London.[4] In other cases, no effect modification by sex was found.[34,35] Vassallo et al[36] conducted a study among elderly patients living in an institution and found a higher risk of marginal hyperthermia in women than in men.

Excess mortality resulting from high temperatures has already been found in people residing in nursing homes with no air conditioning.[37–39] We found a greater risk for subjects living in nursing homes (OR = 1.61; CI = 1.41–1.84), which are mostly without air conditioning in Italy. In addition, we found that people who were in the hospital were also at risk for dying because of high temperatures (1.32; 1.27–1.40). A larger number of critically ill patients hospitalized during the heat wave might be the easiest interpretation of the finding. Our analysis, however, shows an increased heat-related mor-

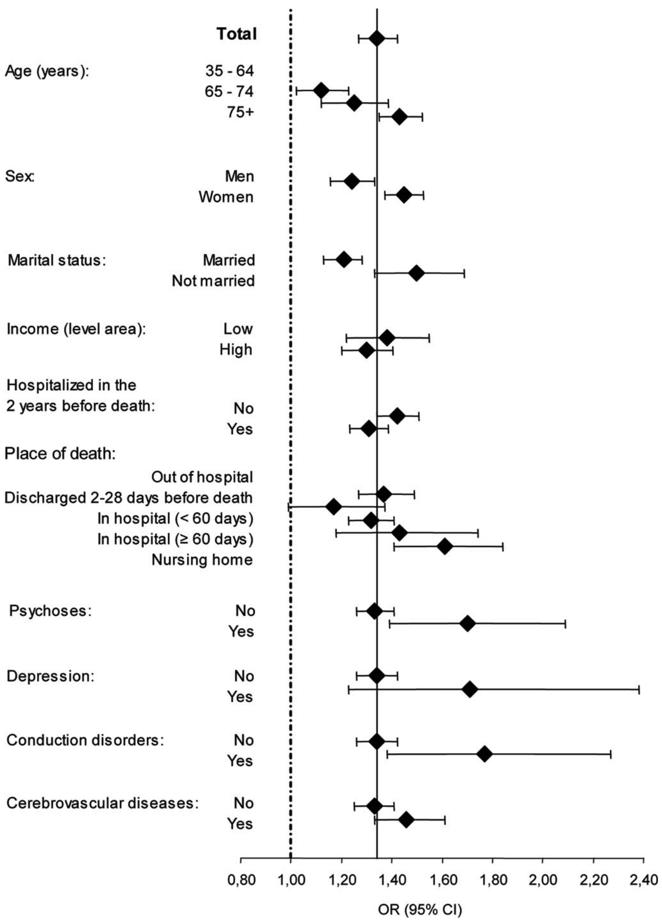

FIGURE 2. Forest plot of the main results: risk of dying on days with 30°C in mean apparent temperature (lag 0–1) versus days with 20°C by age, demographic characteristics, previous hospital admissions, place of death, and some groups of diagnoses figuring either as the primary cause or as a secondary contributing cause of hospital admission in the 2 years before death, excluding last 4 weeks (marital status and nursing home residence in Milan and Turin only).

tality even among those who were in the hospital before the heat wave (complete data not shown, available on request). Thus, air conditioners in health facilities may provide a means for the prevention of heat-related mortality.

The analysis of hospital admissions in the 2 years before death suggests that persons with specific chronic conditions are especially vulnerable to hot temperatures. Mortality was higher in patients affected by depression and psychiatric conditions, perhaps because of the use of medicines that alter thermoregulation ability.[38] The increased risk of dying of cerebrovascular diseases as a consequence of extreme heat has already been reported,[40] whereas our result of an augmented risk for patients affected by conduction disorders seems to be a new finding. Patients might need an increased heart rate during hot days, and if unable to support this need, this may lead to a fatal cardiac crisis.

The present study also found a risk of dying for people who were not hospitalized in the 2 years before death. The odds ratio in this group was 1.42 (CI = 1.34–1.51), whereas in hospitalized subjects, it was 1.31 (1.23–1.39). Thus, having been admitted to the hospital in the 2-year period before death (excluding last 28 days) does not seem to be a marker of susceptibility except for specific pathologies. Because the case-crossover design is only able to estimate *relative* effects, this result should not be interpreted as a protective effect but as a less-than-multiplicative one. In fact, the absolute risk of mortality for previously hospitalized subjects is presumably much higher than the risk for the nonhospitalized, and thus the relative contribution of apparent temperature on mortality turns out to be smaller in the first group.

Several strengths of the present study deserve consideration. This study involved 4 cities and more than 200,000 deaths in a fairly recent period that includes, for 3 of the 4 cities, the extremely hot summer of 2003. Record linkage of individual data from different sources offered the opportunity to exploit individual information that is rarely available in other European countries.

Some limitations must also be taken into account. The apparent temperature–mortality curves for the different cities are not identical, and these differences posed the problem of how to combine diverse information in a meta-analysis. Expressing the risk estimates as odds ratios of death resulting from high temperatures on days with temperatures of 30°C versus days with 20°C enables a straightforward synthesis of all the information available. Sensitivity analyses (results not shown) were performed varying the range from 20°–30°C, but no differences were noted from an effect-modification point of view. However, the heterogeneity among the curves makes the risk estimates more variable and limits the power when identifying specific effect modifiers.

The variables on clinical conditions are based on hospital admissions and suffer from the limits of accuracy of the source used.[41] Additional data could be useful to better define chronic susceptibility (individual habits, smoking status, obesity, and so on) and acute susceptibility (place of residence, assistance received, and so on). Such information is not available from current databases. In particular, further work is needed to investigate the clinical conditions that characterized the subjects in the few weeks before death.

In conclusion, increased public awareness of the health hazards from ambient temperature and regional- or city-specific programs to prevent heat-related deaths in the elderly are public health priorities in Europe. The elderly, women, widows/widowers, and subjects with psychiatric disorders, depression, heart conduction disorders, and previous stroke have been identified as especially vulnerable during extremely hot days. The findings can help focus community and individual prevention programs, as well as responses to heat emergencies, so that associated morbidity and mortality can be prevented. Supplying adequate temperature comfort in hospitals and nursing homes seems to be an immediate and simple measure against the health effects of heat.

TABLE 5. Results of the Sensitivity Analyses; Risk of Dying on Days With 30°C in Mean Apparent Temperature (lag 0–1) versus Days With 20°C; Combined Results for the 4 Cities*

	Age Group 65+ Years		Age Group 75+ Years		Analysis Without Year 2003		Control for Ozone†	
Variables	**OR (95% CI)**	**REM Index (*P*)**	**OR (95% CI)**	**REM Index (*P*)**	**OR (95% CI)**	**REM Index (*P*)**	**OR (95% CI)**	**REM Index (*P*)**
Total	*1.39 (1.30–1.49)*	—	*1.43 (1.35–1.52)*	—	1.31 (1.26–1.36)	—	*1.33 (1.26–1.40)*	—
Sex								
Men	*1.28 (1.18–1.39)*	1.00	1.33 (1.24–1.42)	1.00	*1.22 (1.14–1.30)*	1.00	*1.23 (1.16–1.31)*	1.00
Women	*1.48 (1.39–1.59)*	1.16 (0.006)	*1.51 (1.40–1.63)*	1.14 (0.012)	1.41 (1.34–1.49)	1.16 (0.000)	1.43 (1.35–1.51)	1.16 (0.000)
Income (area level)								
20th percentile	*1.41 (1.23–1.63)*	1.00	*1.45 (1.27–1.65)*	1.00	*1.31 (1.21–1.43)*	1.00	*1.41 (1.25–1.60)*	1.00
80th–100th percentile	1.38 (1.27–1.50)	0.98 (0.770)	*1.45 (1.30–1.62)*	1.00 (0.987)	1.29 (1.18–1.41)	0.98 (0.786)	1.31 (1.20–1.43)	0.93 (0.350)
Hospital admission in the 2 previous years (excluding last 28 d)								
No	*1.45 (1.35–1.55)*	1.00	*1.45 (1.34–1.58)*	1.00	1.29 (1.23–1.35)	1.00	1.42 (1.33–1.51)	1.00
Yes	*1.36 (1.26–1.46)*	0.94 (0.224)	1.41 (1.34–1.49)	0.97 (0.582)	1.36 (1.28–1.45)	1.06 (0.144)	1.28 (1.22–1.35)	0.90 (0.013)
Place of death								
Out of hospital	*1.43 (1.31–1.56)*	1.00	*1.47 (1.36–1.59)*	1.00	1.32 (1.23–1.41)	1.00	*1.35 (1.23–1.47)*	1.00
Discharged 2–28 d before death	*1.23 (1.03–1.47)*	0.94 (0.224)	1.36 (1.15–1.61)	0.93 (0.419)	*1.07 (0.93–1.24)*	0.81 (0.010)	*1.12 (0.95–1.32)*	0.83 (0.057)
Nursing home‡	1.62 (1.42–1.86)	1.14 (0.119)	1.68 (1.45–1.94)	1.14 (0.113)	1.59 (1.37–1.85)	1.21 (0.024)	1.59 (1.35–1.86)	1.18 (0.079)
Hospital admissions in the 2 previous years (excluding last 28 d), by groups of diagnoses								
Psychoses	*1.75 (1.46–2.11)*	1.27 (0.018)	*1.67 (1.34–2.08)*	1.17 (0.170)	*1.62 (1.27–2.08)*	1.25 (0.082)	*1.68 (1.30–2.18)*	1.27 (0.074)
Depression	1.82 (1.26–2.63)	1.32 (0.150)	1.80 (1.14–2.84)	1.26 (0.331)	1.82 (1.26–2.62)	1.39 (0.081)	1.88 (1.29–2.74)	1.42 (0.074)
Conduction disorders	1.86 (1.44–2.40)	1.35 (0.029)	2.12 (1.60–2.82)	1.50 (0.007)	1.81 (1.39–2.36)	1.39 (0.017)	1.72 (1.31–2.27)	1.30 (0.069)
Cerebrovascular diseases	1.46 (1.32–1.61)	1.05 (0.411)	1.50 (1.34–1.67)	1.05 (0.411)	1.43 (1.29–1.59)	1.10 (0.088)	1.43 (1.28–1.59)	1.08 (0.204)

*Results in italics are from random effects models.
†Ozone is calculated as the maximum among daily 8-h running mean values (lag 0) and is controlled for the summer period (May–September).
‡Milan and Turin only.

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