Short-term association between sulfur dioxide and daily mortality: The Public Health and Air Pollution in Asia (PAPA) study

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A B S T R A C T
Sulfur dioxide (SO2) has been associated with increased mortality and morbidity, but only few studies were conducted in Asian countries. Previous studies suggest that SO2 may have adverse health effects independent of other pollutants. In the Public Health and Air Pollution in Asia (PAPA) project, the short-term associations between ambient sulfur dioxide (SO2) and daily mortality were examined in Bangkok, Thailand, and three Chinese cities: Hong Kong, Shanghai, and Wuhan. Poisson regression models incorporating natural spline smoothing functions were used to adjust for seasonality and other time-varying covariates. Effect estimates were obtained for each city and then for the cities combined. The impact of alternative model specifications, such as lag structure of pollutants and degree of freedom (df) for time trend, on the estimated effects of SO2 were also examined. In both individual-city and combined analysis, significant effects of SO2 on total non-accidental and cardiopulmonary mortality were observed. An increase of 10 μg/m3 of 2-day moving average concentrations of SO2 corresponded to 1.00% [95% confidence interval (CI), 0.75–1.24], 1.09% (95% CI, 0.71–1.47), and 1.47% (95% CI, 0.85–2.08) increase of total, cardiovascular and respiratory mortality, respectively, in the combined analysis. Sensitivity analyzes suggested that these findings were generally insensitive to alternative model specifications. After adjustment for PM10 or O3, the effect of SO2 remained significant in three Chinese cities. However, adjustment for NO2 diminished the associations and rendered them statistically insignificant in all four cities. In conclusion, ambient SO2 concentration was associated with daily mortality in these four Asian cities. These associations may be attributable to SO2 serving as a surrogate of other substances. Our findings suggest that the role of outdoor exposure to SO2 should be investigated further in this region.

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1. Introduction

Ambient air pollution is a complex mixture composed of both suspended particulates and gaseous pollutants. Identification of specific pollutants contributing most to the health hazard of air pollution mixture may have important implications for environmental and social policies, and for local government in taking steps to protect the human health. Although the strongest evidence linking outdoor air pollutants with adverse health effects thus far is for solid particulates (Dockery, 2009), many researchers have reported associations for gaseous pollutants such as nitrogen dioxide (NO₂) (Burnett et al., 2004; Samoli et al., 2006), ozone (O₃) (Bell and Dominici, 2008; Bell et al., 2004), and sulfur dioxide (SO₂) (Stieb et al., 2002; Stieb et al., 2003). Recent multi-city analyses conducted in Europe provide further evidence supporting the short-term association of SO₂ with adverse health endpoints including both mortality (Katsouyanni et al., 1997) and morbidity (Suyner et al., 2003a, 2003b). SO₂ is a respiratory irritant and bronchoconstrictor, and has been associated with cardiovascular abnormalities including decrease in heart rate variability (Tunnicliffe et al., 2001), providing a mechanism by which SO₂ affects cardiorespiratory health. However, recent findings about the independent health effect of SO₂ remain inconsistent. For example, after adjusting for PM₁₀ (i.e. particles with size < 10 μm), Suyner et al. (2003b) reported associations of ambient SO₂ with cardiovascular admissions, particularly for ischemic heart diseases, in seven European cities; however, the SO₂ association with respiratory admission disappeared after adjustment for PM₁₀ in the same cities (Suyner et al., 2003a). Also, to our knowledge, there have been no multi-city studies of SO₂ in the Asian region.

In Asian developing countries, the characteristics of outdoor air pollution (e.g. air pollution level, chemical composition and size of particles, and fate and transport of pollutants), meteorological conditions and socio-demographic patterns are different from North America and Western Europe. However, there have been only a limited number of air pollution health studies conducted in this region (Health Effects Institute, 2004). Because of the wide use of high sulfur fuel (e.g. coal) and inefficient technology in removal of sulfur, the ambient SO₂ levels in Asian countries are much higher than in developed countries (Guttikunda et al., 2003). The objective of this paper is to examine the short-term associations between SO₂ and daily mortality in four Asian cities—Bangkok (BK), Thailand; Hong Kong (HK), China; Shanghai (SH), China; and Wuhan (WH), China. This study is a component of the joint Public Health and Air Pollution in Asia (PAPA) program supported by the Health Effects Institute (HEI) (Kan et al., 2008; Wong et al., 2008).

2. Materials and methods

2.1. Data

The study periods were 1999–2003 for Bangkok, 1996–2002 for Hong Kong, and 2001–2004 for both Shanghai and Wuhan. The sources of mortality data were the Ministry of Public Health, Bangkok; the Census and Statistics Department, Hong Kong; the Shanghai Municipal Center of Disease Control and Prevention, Shanghai; and the Wuhan Center for Disease Prevention and Control, Wuhan. The causes of death were coded according to International Classification of Diseases, Revision 9 (ICD-9) or 10 (ICD-10). The mortality data were classified into deaths due to total non-accidental causes (ICD-9 800-999; ICD-10 A00-R99), cardiovascular disease (ICD-9 390-459; ICD-10 I00-I99), and respiratory disease (ICD-9 460-519; ICD-10 J00-J99).

The sources of air pollutant concentrations were the Pollution Control Department, Ministry of Natural Resources and Environment, Bangkok (10 air monitoring stations); the Environmental Protection Department, Hong Kong (8 stations); the Shanghai Environmental Monitoring Center, Shanghai (6 stations); and the Wuhan Environmental Monitoring Center, Wuhan (6 stations). Air quality indicators included SO₂ particulate matter with aerodynamic diameter of 10 μm or less (PM₁₀), nitrogen dioxide (NO₂), and ozone (O₃). 24-h average concentrations for SO₂, PM₁₀, NO₂, and maximal 8-h mean concentrations for O₃ were collected. For the calculation of 24-h mean concentrations of PM₁₀, SO₂ and NO₂, as well as maximal 8-h mean NO₂ concentrations, at least 75% of the 1-h values must be available on that particular day. If a station had more than 25% of the values missing for the whole period of analysis, the entire station was excluded from the analysis. In each city, the location of monitoring stations were not in the direct vicinity of traffic or of industrial sources, and were mandated not to be influenced by local pollution sources and should also avoid buildings, or housing large emitters such as coal-, waste-, or oil-burning boilers, furnaces, and incinerators. Thus, the monitoring results should reflect the general background urban air pollution level rather than local sources such as traffic or industrial combustion.

To allow adjustment for the effect of weather on mortality, meteorological data (daily mean temperature and humidity) were obtained at each city. All the death, air pollution and meteorological data were validated by an independent auditing team assigned by the HEI. The team checked samples of the original death certificates and monitoring records, and validated the generation process of death, air pollution and weather data used for the statistical analysis in each city. The data quality was assured to be satisfactory and thus the differences in measurement errors may be minimal.

2.2. Statistical analysis

The single-city analytical method was developed and commonly adopted by the four teams in a common protocol that comprises a communication network between the four teams and the Health Effects Institute International Scientific Oversight Committee (ISOC), specification for selection of monitoring stations, quality assurance or quality control for the data collection, health outcomes and air pollutants to be included in the analysis (Wong et al., 2008). The protocol also developed the methods to standardize data management including compilation of daily data. The methods were tailor made to suit the local situation, including the specifications for selection of monitoring stations and quality assurance and quality control procedures for data collection on health outcomes and air pollutants to be included in the analysis. Generalized linear modeling was used to model daily health outcomes, with natural spline smoothers (Burnett et al., 2004; Wood, 2006) for filtering out seasonal patterns and long-term trends in daily mortality, as well as temperature and relative humidity. The partial autocorrelation function (PACF) was used to guide the selection of degree of freedom (df) for time trend in the core models. When the absolute magnitude of the PACF plot was less than 0.1 for the first 2 lag days, the core models were regarded as adequate. If this criterion was not met, other methods were used to reduce autocorrelation, such as the inclusion of explanatory variables to model influenza epidemics and the addition of auto-regression terms. If there were special periods with extra variations for which the core model could not account, an additional spline smoother would be included. Also, an adjustment for the day of the week and dichotomous variables relevant to individual cities if available, such as public holidays (Hong Kong) and extreme weather conditions (Wuhan), was included. Residuals of the core models were examined to check whether there were discernable patterns and autocorrelation by means of residual plots and PACF plots.

SO₂ concentrations were entered into the core model to assess its health effects in each city. Combined estimates of SO₂ on daily mortality were calculated using a fixed- or random-effects model. Estimates were weighted by the inverse of the sum of within- and between-study variance. Homogeneity tests were performed by means of Chi-square tests for the differences in sum of squares of individual and weighted average of the estimates.

Because the assumption of the linearity between the log of mortality and SO₂ may not be justified, the same non-linear function with non-linear effects of SO₂ was used to graphically describe their relationships. Test of non-linearity was assessed by testing the change of deviance between a non-linear pollutant (smoothed) model with 3 df and linear pollutant (unsmoothed) model with 1 df.

Single-day lag models were reported to underestimate the cumulative effect of air pollution on mortality (Dockery, 2009); therefore, 2-day moving average of current and previous day concentrations (lag 01) were used in our main analyses. As a sensitivity analysis, the effects of SO₂ with different lag structures, including current day (lag 0) and 5-day average of lags 0–4 (lag 04), were also examined.

Given that it is not easy to determine the optimal values of df for time trend, sensitivity analyses were conducted to test the impact of alternative df values on the estimated effect of SO₂. Also, both single- and multi-pollutant models were fitted to assess the stability of SO₂ effect estimate; up to two pollutants were included per model.

All analyzes were conducted in R 2.5.1 using the MGCV package (R Development Core Team, 2007). Cross-checking of results between teams was performed by pairing up the teams; Hong Kong was assigned to pair with Wuhan, and Bangkok was assigned to pair with Shanghai.
3. Results

Table 1 summarizes the mortality and air pollution data in all four cities. In our research periods (1999–2003 for Bangkok, 1996–2002 for Hong Kong, and 2001–2004 for both Shanghai and Wuhan), the mean daily death numbers for all non-accidental causes, cardiovascular causes and respiratory causes were 94.8, 13.4 and 8.1, respectively, for Bangkok; 84.2, 23.8, and 16.2 for Hong Kong; 119.0, 44.2 and 14.3 for Shanghai; and 61.0, 27.8, and 7.0 for Wuhan (Table 1). Among all deaths, cardiorespiratory causes accounted for 23% in Bangkok, 49% in Hong Kong, 57% in Shanghai, and 57% in Wuhan. The concentrations of SO2 were similar in Bangkok and Hong Kong, and were lower than both Shanghai and Wuhan (Table 1). The relatively higher levels of SO2 in Shanghai (mean: 44.7 µg/m³) and Wuhan (mean: 39.2 µg/m³) might be due to the significant local contribution of power plants in the two cities. Bangkok (mean: 13.2 µg/m³) and Hong Kong (mean: 17.8 µg/m³) had levels that were less than half of those of Wuhan and Shanghai. The SO2 levels in the two Mainland Chinese cities were 2–3 times higher than in European cities (Sunyer et al., 2003a, 2003b). SO2 had much higher correlation coefficients with PM10 and NO2 in Shanghai and Wuhan than in Bangkok and Hong Kong (Table 2). In all four cities, SO2 was weakly correlated with O3.

We found significant associations between SO2 levels and daily mortality from all causes and from cardiorespiratory diseases in each of the four cities (Table 3). An increase of 10 µg/m³ of 2-day moving average concentrations of SO2 corresponds to 1.61% [95% confidence interval (CI), 0.08–3.16], 0.87% [95% CI, 0.38–1.36], 0.95% [95% CI, 0.62–1.28], and 1.19% [95% CI, 0.65–1.74] increase in the confidence interval in the concentration–response curve of Hong Kong. For Shanghai and Wuhan, respectively, SO2 had significant associations with cardiovascular and respiratory mortality only in three Chinese cities, but not in Bangkok.

In the four-city combined analysis, there was no significant heterogeneity for the associations of SO2 with either total or cardiopulmonary mortality. An increase of 10 µg/m³ of 2-day moving average concentrations of SO2 corresponded to 1.00% [95% CI, 0.75–1.24], 1.09% [95% CI, 0.71–1.47], and 1.47% [95% CI, 0.85–2.08] increase of total non-accidental mortality in Bangkok, Hong Kong, Shanghai, and Wuhan, respectively. SO2 had significant associations with cardiovascular and respiratory mortality only in three Chinese cities, but not in Bangkok.

There were positive concentration–response relationships between total mortality and SO2 level in all four cities (Fig. 1). For Shanghai and Wuhan, an almost linear relationship was found. For Bangkok and Hong Kong, the relationship seemed to be J-shaped or U-shaped nonlinear for most of the SO2 levels, although tests for non-linearity were significant only in Hong Kong (p < 0.05). Lack of data at high SO2 concentrations may contribute to the inverted U-shaped and wider confidence interval in the concentration–response curve of Hong Kong.

The results for the effects of alternative lags on all-cause mortality are summarized in Fig. 2. For three Chinese cities, with a few exceptions, the lag 0–1 usually generated the highest effect estimates of SO2. However, for Bangkok, the effects of SO2 were similar using different lag structures. For the combined-analysis results, the lag 0–1 showed the highest effect estimates.

Within the range of 4–12, the change of df/yr for time trend does not substantially affect the estimated effects of SO2 (Fig. 3), suggesting that our findings are relatively robust in this aspect.

In the three Chinese cities, the associations of SO2 with total and cardiopulmonary mortality were only minimally altered by adding PM10 and O3 into the models (Fig. 4). However, adjustment for NO2 decreased the associations and rendered them statistically insignificant in these Chinese cities. In Bangkok, the effects of SO2 decreased and became statistically insignificant after adjustment for any co-pollutants.

For the results of the cross-checking, no discrepancies were found between the original estimates and the estimates obtained in the cross-checking assessment.

4. Discussion

This combined analysis summarizes the results from four Asian cities concerning the short-term effects of SO2 on daily mortality. Significant associations of SO2 with total and cardiopulmonary mortality were found, and these findings were generally insensitive to alternative model specifications. To our knowledge, this is the first multi-city analysis in Asia to report the acute health effect of SO2. Our findings are consistent with previous results of SO2 in the APHEA (Air Pollution and Health: a European Approach) (Katsouyanni et al., 1997) and APHEA-2 studies (Sunyer et al., 2003a, 2003b), although the estimated effect of SO2 on daily mortality in these four Asian cities were moderately larger than those found in other locations (Katsouyanni et al., 1997; Stieb et al., 2002, 2003). Lower proportion of cardiorespiratory deaths might contribute to the uncertain results for Bangkok (Table 3).

To provide an indication of the relative magnitude of the pollution concentrations in these four large Asian cities, we compared them to the 20 largest cities in the United States using data from 1987 to 1994 from the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) (Samet et al., 2000). Generally, in the PAPA cities, the concentrations of SO2 and PM10 were much higher than those reported in the United States (SO2 means of 13–45 µg/m³ in the cities of the PAPA study vs. 14 µg/m³ in

Table 1
Mean (and standard deviation) of daily mortality counts and air pollutant concentrations (µg/m³) per city.

<table>
<thead>
<tr>
<th></th>
<th>Total mortality (no.)</th>
<th>Cardiovascular mortality (no.)</th>
<th>Respiratory mortality (no.)</th>
<th>SO2 (µg/m³)</th>
<th>PM10 (µg/m³)</th>
<th>NO2 (µg/m³)</th>
<th>O3 (µg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangkok</td>
<td>94.8 (12.1)</td>
<td>13.4 (4.3)</td>
<td>8.1 (3.1)</td>
<td>13.2 (4.8)</td>
<td>52.0 (20.1)</td>
<td>44.7 (17.3)</td>
<td>59.4 (26.4)</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>84.2 (12.8)</td>
<td>23.8 (6.5)</td>
<td>16.2 (5.2)</td>
<td>17.8 (12.1)</td>
<td>51.6 (25.3)</td>
<td>58.7 (20.1)</td>
<td>36.7 (22.9)</td>
</tr>
<tr>
<td>Shanghai</td>
<td>119.0 (22.5)</td>
<td>44.2 (11.0)</td>
<td>14.3 (6.4)</td>
<td>44.7 (24.2)</td>
<td>102.0 (64.8)</td>
<td>66.6 (24.9)</td>
<td>61.4 (36.7)</td>
</tr>
<tr>
<td>Wuhan</td>
<td>61.0 (15.8)</td>
<td>27.8 (8.8)</td>
<td>7.0 (5.8)</td>
<td>39.2 (25.3)</td>
<td>141.8 (63.7)</td>
<td>51.8 (18.8)</td>
<td>85.7 (47)</td>
</tr>
</tbody>
</table>

* Multi-year mean (and standard deviation) of pollutant concentrations.
comparisons of NO₂ and O₃ showed a fairly similar pattern. There were similarities as well as dissimilarities in effect estimates of SO₂ between these four cities. The estimates for Bangkok were relatively higher but less precise as compared with the three Chinese cities. The lack of precision in the Bangkok estimates may be due to a lack of variability in SO₂ (the SD of SO₂ in BK is 4.8 μg/m³ compared with 12.1–25.3 μg/m³ in the Chinese cities). When the effects were expressed per inter-quartile range increase, the estimates were very similar in the four cities (data not shown).

We did observe non-linear relationships between SO₂ and mortality risk in Bangkok and Hong Kong, although for most SO₂ concentrations, the concentration–response (C–R) relationship still appeared to be positive, and with concentration below 50 μg/m³ the concentration–response curve was similar to that in Bangkok. Higher effect estimates at lower concentration levels for SO₂ has also been reported from a Germany study (Wichmann et al., 2000). In this respect, one might postulate, with support from the biological mechanism, that scrubbing effects of the upper airway in response to SO₂ may be stronger at a higher concentration than at lower concentration for the pollutant (Schlesinger, 1999). We could not ignore that a non-linear relationship between SO₂ and mortality may be operating in some population and environment, e.g. Hong Kong. The C–R relation of a pollutant would be affected by the method being used, the susceptibility of the population being investigated, the toxicity nature of the pollutant, as well as the weather and social conditions under which the pollutant may be interacted. Therefore, the C–R relationships are subject to substantial uncertainty.

Table 3

<table>
<thead>
<tr>
<th></th>
<th>Bangkok</th>
<th>Hong Kong</th>
<th>Shanghai</th>
<th>Wuhan</th>
<th>Random effecta (4 cities)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ER</td>
<td>95% CI</td>
<td>ER</td>
<td>95% CI</td>
<td>ER</td>
</tr>
<tr>
<td>Total</td>
<td>1.61</td>
<td>(0.08, 3.16)</td>
<td>0.87</td>
<td>(0.38, 1.36)</td>
<td>0.95</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.77</td>
<td>(−2.98, 4.67)</td>
<td>1.19</td>
<td>(0.29, 2.10)</td>
<td>0.91</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1.66</td>
<td>(−3.69, 6.64)</td>
<td>1.28</td>
<td>(0.19, 2.39)</td>
<td>1.37</td>
</tr>
</tbody>
</table>

a Because of the lack of heterogeneity, the fixed and random effects are identical.
especially for those above the third quartile of air pollutant concentration. Further research is needed in these aspects.

After adjusting for PM$_{10}$ or O$_3$, the association of SO$_2$ remained significant in three Chinese studies (Fig. 3), suggesting that SO$_2$ is important for the air pollution mixture in China. Previously, the health effects of SO$_2$ were extensively reported in China. In Beijing, for example, Xu and coworkers found that it was SO$_2$, not total suspended particle (TSP), that was associated with daily mortality (Xu et al., 1994) and morbidity (Xu et al., 1995). In Chongqing, Venners et al. (2003) found that SO$_2$ had significant

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**Fig. 2.** Percent increase of total mortality associated with 10 μg/m$^3$ increase of SO$_2$, using different lag structures (lag 0, lag 01, and lag 04)—individual and combined effects. X-axis is lag structures. Y-axis is percent increase of total mortality.

**Fig. 3.** Percent increase of total mortality associated with 10 μg/m$^3$ increase of 2-day moving average SO$_2$, using different df/yr for time trend.
which showed SO2 resulting from sulfur-rich fuels had a direct impact on cardiorespiratory deaths (Hedley et al., 2002). Outside China, similar independent effects of SO2 were presented in a European multi-city analysis (Katsouyanni et al., 1997; Sunyer et al., 2003a, 2003b). In Bangkok, the effect of SO2 became insignificant after adjustment for PM10 or O3. The discrepancy between the effects of SO2 in Bangkok and three Chinese cities might be caused by differences in the characteristics of local air pollution or patterns of exposure among local residents.

The effect estimate for SO2 decreased and became insignificant after adjustment for NO2 in all four cities (Fig. 4); however, SO2 or other pollutants (PM10 and O3) did not confound the effect of NO2 (data not shown). The fact that NO2 reduces the association of SO2 with daily mortality in our study may be because both pollutants probably come from the same source (i.e. fossil fuel combustion or diesel exhaust) or may increase together due to the meteorological conditions. SO2 may serve as a surrogate of other substances also correlated with NO2.

The biological mechanism by which exposure to SO2 may increase mortality is not well understood but has received considerable attention. SO2 is a known respiratory irritant and bronchoconstrictor, but its effects seem limited to patients with asthma and bronchitis, although sensitivity to exposure varies widely (Nowak et al., 1997). Previous study found a change in heart rate variability in humans associated with exposure to SO2 (200 ppb for 1 h) (Tunnicliffe et al., 2001), providing a mechanism which may be operating in the SO2 mortality associations. SO2 can be converted to sulfuric acid, which then can be carried into the small airways by inhalable particulates and impair lung function in children (Spengler et al., 1996). SO2 also contribute to particle formation; Zhang et al. (2000) found that concentration of SO2 in the air was closely associated with chronic disease mortality in Beijing.

Most air pollution epidemiologic studies, including ours, use ambient pollutant concentrations as surrogates of personal exposure. Given the correlations between SO2 and co-pollutants in the urban air, it is difficult to disentangle the specific effect of each pollutant. The observed health effects attributed to SO2 might actually be a result of exposures to fine particles or traffic-related emissions (Sarnat et al., 2001, 2005). Actually some authors have suggested that the pollutants measured and included in models of daily mortality might be better interpreted as indicators of the biologically relevant pollutant mixture and that the best indicators might vary in different geographic areas (Sarnat et al., 2001). To our knowledge, there have been no studies in Asian examining the associations between ambient SO2 concentrations, personal exposure to SO2 and personal PM exposure. We therefore cannot conclude that SO2 is a proxy of fine particle or the components of fine particle, or SO2 has a direct short-term effect on mortality.

Our analysis has strengths and limitations. These four Asian cities offer advantages for the study of the air pollution–mortality relationship in that they are generally very densely populated. As in most previous time-series studies, we simply averaged the monitoring results across various stations as the proxy for population exposure level to air pollution. The simple averaging method may raise a number of issues given that pollutant measurements can differ from monitoring location to monitoring location and that ambient monitoring results differ from personal exposure level to air pollutants (Sarnat et al., 2005). Numerous factors, such as air conditioning and ventilation rate between indoor and outdoor air, may affect the monitoring results from fixed stations as surrogates of personal exposure to air pollutants (Janssen et al., 2002). Because we were not able to measure the true population exposures in these four cities, we could not determine the direction of the bias and its impact on our conclusions.

In summary, we found significant associations of ambient SO2 concentrations with daily mortality in these four Asian cities. These associations were generally independent of PM10 and O3 but did not persist after adjustment for NO2. Our findings suggest that the role of outdoor exposure to SO2, especially the ambient-personal associations, should be investigated further in this region.

**Fig. 4.** Percent increase of mortality outcomes associated with 10 μg/m³ increase of 2-day moving average SO2 with single and two-pollutant models: S: single-pollutant model; C1: two-pollutant model (SO2+NO2); C2: two-pollutant model (SO2+PM10); C3: two-pollutant model (SO2+O3). (a) Total mortality; (b) cardiovascular mortality and (c) respiratory mortality.
Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2010.01.006.

Reference

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