

Short-term effect of air pollution on asthma patient visits in Shanghai area and assessment of economic costs

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ABSTRACT

Backgrounds: Shanghai, in China, is one of the highest incidence cities for asthma morbidity. However, few studies have systemically explored the association of ambient air pollutants and asthma patients with economic costs.

Objectives: The study researched the link of short-term ambient air pollutants exposure and asthma patients in Shanghai. Furthermore, the economic cost was also assessed.

Methods: We applied the generalized additive model (GAM) to analyze the association between ambient air pollutants and asthma patients with economic costs assessment.

Results: We investigated a total of 7200 asthma patient visits (inhabitant in Shanghai). A $10 \mu\text{g m}^{-3}$ increase in the current day concentrations of SO_2 , CO, NO_2 , PM_{10} , O_3 and $\text{PM}_{2.5}$ corresponded to increase of 3.79% [95% CI: 0.84%, 6.83%], 0.27% [95% CI: 0.14%, 0.40%], 0.63% [95% CI: -0.81%, 2.10%], 1.11% [95% CI: 0.38%, 1.85%], 0.23% [95% CI: 0.31%, 0.78%] and 1.27% [95% CI: 0.29%, 2.26%] in daily asthma patient visits. In economic cost level, the economic cost of asthma patients were attributed to ambient air pollutants (SO_2 , CO, NO_2 , PM_{10} , O_3 and $\text{PM}_{2.5}$) with 197 million USD losses per year. Among, the economic cost of asthma patient visits were attributed to SO_2 , CO, NO_2 , PM_{10} , O_3 and $\text{PM}_{2.5}$ with 101.30, 7.46, 17.15, 30.18, 6.39 and 34.50 million USD loss per year, respectively.

Conclusions: Short-term exposure to SO_2 , CO, NO_2 , PM_{10} , O_3 and $\text{PM}_{2.5}$ were linked to asthma patient visits increase in Shanghai areas. The economic cost of asthma patient visits were attributed to ambient air pollutants (SO_2 , CO, O_3 , PM_{10} , NO_2 and $\text{PM}_{2.5}$) with 197 million USD losses per year. The study strengthen our fundamental comprehending of impacts of ambient air pollutants on human health and economy burden.

1. Introduction

Air pollution adversely affects human health, including morbidity and mortality (Chiang et al., 2016; Li and Lin, 2014). Asthma is a kind of lung inflammatory disorder that affects all ages' people, and causes morbidity and mortality increase of human being (Athanasio, 2012; Rincon and Irvin, 2012). Globally, approximately 300 million people have asthma disease and a sustainedly increase in adults and children, which has been witnessed in recent decades. For example, the asthma patients have reached about 30 million in China in 2010 (D'Amato et al., 2015; Ober and Yao, 2011). The economic burden of asthma is considerable and associated with hospitalization, medications, and potential years of work lost due to morbidity and mortality (Einarson et al., 2016; Stirbulov et al., 2016). Obviously, asthma has imposed a heavy economic burden over past decade.

Many epidemiologic studies demonstrated an association of air pollution and asthma risks, which lead to the hospital patients increase

(Loyo-Berrios et al., 2007; Makra et al., 2012; Raun et al., 2014). Further, evidences have showed that ambient air pollutant also might induce new-onset asthma (Guarnieri and Balmes, 2014; Jeebhay et al., 2014). For example, previous cohort study found that traffic-related emission can cause asthma onset in children (Jerrett et al., 2008). Modig L et al. shows that vehicle exhaust also lead to asthma onset among adults (Modig et al., 2009). Not all researches support a casual association of asthma and air pollution (Guarnieri and Balmes, 2014). With real-time monitoring of $\text{PM}_{2.5}$ in 2013, China newly supplemented the average concentrations of CO, O_3 and $\text{PM}_{2.5}$ as new indicators to assess air quality. Thus, investigating the impacts of ambient air pollutants on asthma patients have become a practical and significant possibility.

Kan et al. showed that NO_2 and SO_2 were significantly associated with emergency visits and hospital outpatient in Shanghai, and that exposure to SO_2 and NO_2 have an adverse health effect (Cai et al., 2014; Li et al., 2016; Meng et al., 2013). Shanghai is characterized by the

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northwest trade winds over the Mainland China, the southeast summer monsoon trade winds from the Western Pacific ocean. The boom of industrialization in Shanghai has led to a excessive release of ambient air pollutants (Cao et al., 2009). Levels of atmospheric PM have continually increased because of a rapid increase of motor vehicles, the expansion of urban area and the illegal biomass burning (Cao et al., 2015; Hu et al., 2016; Zhang et al., 2015). Thus, exploration of the relationship of air pollution and asthma in Shanghai area is significant.

In this study, we researched the relationship of asthma patient visits and ambient air pollutants: SO₂, CO, NO₂, PM₁₀, O₃ and PM_{2.5} in Shanghai, China. We also assessed the effect of asthma patient visits on economic cost.

2. Materials & methods

2.1. Study area

Shanghai, is locating to the Yangtze River Delta in east China where has a distinct seasons, moderate subtropical climate and abundant rainfall. Shanghai had a population of 24.26 million in 2014 with an area of 6341 km², including 8 urban districts with area of 259 km² in Shanghai. These urban districts include Luwan, Yangpu, Pudong, Hongkou, Putuo, Xuhui, Jing'an and Qingpu (Fig. S1). These urban districts were investigated due to sufficient ambient air pollutants monitoring data.

2.2. Asthma patient visits

Data was extracted from Shanghai Pulmonary Hospital (asthma patient counts of 7200), which is a large of samples behaving random episodes. These data were selected because of representation. Asthma patient means that the clinic visits are related with respiratory disease symptoms. Samples are confirmed or suspected to asthma. The samples were selected according to the code in International Classification of Diseases (ICD), 10th revision (ICD-10) for all patients with asthma (ICD-10: J45, J45.0, J45.9, J 45.1). The samples information, including date of admission, diagnostic and residential address, were used in this study. The respiratory disease patients who lived in study areas were confirmed through the residential address.

2.3. Environmental data

Daily 8 h average for O₃ and daily 24 h average for SO₂, CO, NO₂, PM₁₀ and PM_{2.5} were acquired in Shanghai Environmental Monitoring Center (SEMC) during 22 January 2014–31 October 2015. The daily concentrations for these pollutants were obtained from the available monitoring data of eight fixed-site station. These fixed-site stations avoid the effect of industrial source or traffic. Moreover, the stations should also avoid furnaces, waste-burning boiled and buildings. Thus, the gathering data reflects the overall level of urban air pollution. If a station had more than 20% of the values missing for the all period of analysis, these data should be excluded. The meteorological data, including relative humidity and daily average temperature, were extracted at Shanghai Meteorological Bureau (SMB). The data was collected base on World Meteorological Organization standard. We promise that the data was authenticity and representative.

2.4. Statistical analysis

During 22th January 2014–30th October 2015, amount of 7200 asthma patient visits were counted. A time-series method is often used to explore the link of ambient air pollutants and health outcome (Huang et al., 2016). The link of ambient air pollutants and asthma patients were investigated by Generalized additive model (GAM) in this study. The data of holidays and weekends were deleted because it is not open in these days. Ambient air pollutants were acquired from SEMC, which

is representative. Relative humidity and daily average temperature were collected from SMB.

Multiple linear regression models were applied to research the associations of asthma patient visits and the concentrations of ambient air pollutants (SO₂, CO, NO₂, PM₁₀, O₃ and PM_{2.5}) to which the patients were exposed (Zheng et al., 2015). After the consideration of underlying confounders and impact modifiers, the whole models were controlled for testing period, temperature, relative humidity.

To determine the potential non-linear exposure-response relationships, GAMs were used to estimate the internal connection of ambient air pollutants and asthma patient visits by examining the degrees of freedom of the fluent connection for every variable as one part of the model fixation procedure. The regulation variables were similar to those obtained by the linear regression. When we selected the final models for each ambient air pollutants, the potential confounding and modifying effect was examined. To avoid potential multi-collinearity of air pollutants, two-pollutant models were fitted to examine co-dependency according to the correlation structure.

Pearson correlation coefficient was calculated to explore the relationship of ambient air pollutants. GAM was applied to analyze the relationship of ambient air pollutants and asthma patient visits because of the co-variant of meteorological conditions in this study. We set up the models and then selected the pollutant's variables and analyze their impacts on asthma patient visits. We explored the impact of ambient air pollutants with different lag structures on asthma patient visits, including single-day lag (e.g. Lag 0) and multi-day lag (e.g. Lag 01). For instance, in single-day pollutant concentration, a Lag 0 means the pollutant concentration effect in current-day, and a Lag 1 means the concentration in previous-day. In multi-day Lag models, Lag 01 refers to 2 days moving mean of pollutants concentration of the current and previous day, and Lag 02 means 3-day moving average of ambient air pollutants concentration of the current and previous 2 days. We explored the impacts of single-pollutant and multi-pollutant on asthma patient. The 95% confidence interval (CI) was estimated as follows:

$$(Q_1 - Q_2) \pm 1.96 \times \sqrt{(SE_1^2 + SE_2^2)} \quad (1)$$

where Q₁ and Q₂ are the estimates, and SE₁ and SE₂ are the standard errors (Cao et al., 2009).

The analyses were carried out in R 2.11.1 through the GAM model (R Development Core Team, 2011). In order to compare with previous studies, we show per 10 µg m⁻³ increase of ambient air pollutants concentration as the percent change in asthma patient visits.

3. Results

3.1. Influence of ambient air pollutants on asthma patient visits

Table 1 summarizes the asthma patient counts and environmental variables. Daily average concentrations were 50.5 µg m⁻³ for PM_{2.5}, 68.3 µg m⁻³ for PM₁₀, 106 µg m⁻³ for O₃, 16.5 µg m⁻³ for SO₂, 43.7 µg m⁻³ for NO₂ and 780 µg m⁻³ for CO. Meanwhile, the relative humidity and daily mean temperature were 70% and 18 °C, which is showing the subtropical climate in Shanghai. In general, SO₂, CO, NO₂, PM₁₀, O₃ and PM_{2.5} had relative high correlated coefficients with each other except O₃ with SO₂, NO₂ and CO (Table 2).

Table 3 presents the single-pollutant model and multi-pollutant model results using exposure at current day (Lag 0). In two-pollutant model, the link of particulate matter (PM_{2.5} and PM₁₀) with asthma morbidity decrease and statistically insignificant, but remained positive (except PM_{2.5} with CO), after adding gaseous pollutant (SO₂, CO or O₃). However, NO₂ adjustment increased the associations and rendered them significantly. A 10 µg m⁻³ increase in PM_{2.5} and PM₁₀, after adjustment for NO₂, were associated with a 1.44% [95% CI: 0.29, 2.60] and 1.28% [95% CI: 0.41, 2.15] increase of asthma morbidity.

Following the results of multi-pollutants, we study the relationships

Table 1

Summary Statistics of asthma patient visits, air pollutants and weather condition in Shanghai.

	Mean $\pm$ SD	Min	P(25)	Median	P(75)	Max
Asthma patient visits	15 $\pm$ 8	0	8	13	21	40
Air pollutants concentrations						
PM _{2.5} ($\mu\text{g m}^{-3}$)	51 $\pm$ 31	5	28	42	66	199
PM ₁₀ ($\mu\text{g m}^{-3}$)	69 $\pm$ 39	6	42	57	86	261
O ₃ ($\mu\text{g m}^{-3}$)	106 $\pm$ 43	14	76	101	131	265
SO ₂ ($\mu\text{g m}^{-3}$)	16 $\pm$ 9	6	11	13	19	75
NO ₂ ($\mu\text{g m}^{-3}$)	44 $\pm$ 19	6	30	40	53	139
CO ($\mu\text{g m}^{-3}$)	780 $\pm$ 260	360	600	700	900	2200
Meteorological measures						
Temperature ($^{\circ}\text{C}$)	18 $\pm$ 8	– 1	12	20	24	34
Humidity (%)	70 $\pm$ 14	28	60	72	80	99

24-h average for PM_{2.5}, PM₁₀, SO₂, NO₂, CO; 8-h average for O₃.

SD: standard deviation.

Table 2

Correlation coefficients between daily air pollutant concentrations in Shanghai.

	PM _{2.5}	PM ₁₀	O ₃	SO ₂	NO ₂	CO
PM _{2.5}	1.00					
PM ₁₀	0.90	1.00				
O ₃	0.10	0.12	1.00			
SO ₂	0.73	0.79	– 0.15	1.00		
NO ₂	0.69	0.69	– 0.16	0.77	1.00	
CO	0.86	0.76	– 0.11	0.74	0.75	1.00

Significant Pearson correlation coefficients ($r > 0.6$) are marked bold.

between PM_{2.5} and O₃ to asthma patient visits (Fig. 1). The number of asthma patient presented a weak increase with increased concentrations of single PM or single O₃, respectively, but strong increase with increased both concentrations of O₃ and PM together in high pollutant concentration (PM_{2.5} more than $150 \mu\text{g m}^{-3}$ and O₃ more than $200 \mu\text{g m}^{-3}$). This showed that PM_{2.5} and O₃ have greater co-effect on asthma patient visits than single pollutant impact in high concentration of air pollutants.

Fig. 2 presents the exposure-response relationship for PM_{2.5}, PM₁₀, O₃ and SO₂ with asthma patient visits. For PM_{2.5} and asthma patient visits, the curve tends to be slightly flat when PM_{2.5} concentration is higher. We found a J-shaped relationship of PM₁₀ and asthma patient visits. Even below the levels of current air quality standard in residential area of China (24 h average: $75 \mu\text{g m}^{-3}$ for PM_{2.5} and $150 \mu\text{g m}^{-3}$ for PM₁₀), we still can find obvious health effects for PM_{2.5} and PM₁₀. In addition, the bumpy exposure-response relationship was observed between O₃ and asthma patient visits, then the curve was slightly flat with the ambient pollutant concentration increase. For SO₂, the exposure-response relationships similar to those of PM₁₀ were observed. We can still observed apparent health effect of SO₂, PM_{2.5}, O₃ and PM₁₀ from curves. The exposure-response curves of NO₂ and CO were not presented because not significant associations were found.

Table 4 presents the results of single-lag day (Lag 0 - Lag 6) and cumulative exposure models (Lag 01 and Lag 06) for the percent increase in asthma patient visits per $10 \mu\text{g m}^{-3}$. A $10 \mu\text{g m}^{-3}$ increase in the current day (Lag 0) concentration of SO₂, CO, NO₂, PM₁₀, O₃ and PM_{2.5} corresponded to 3.79% [95% CI: 0.84%, 6.83%], 0.27% [95% CI: 0.14%, 0.40%], 0.63% [95% CI: – 0.81%, 2.10%], 1.11% [95% CI: 0.38%, 1.85%], 0.23% [95% CI: 0.31%, 0.78%] and 1.27% [95% CI: 0.29%, 2.26%] increase of asthma patient visits. Significantly relationships were found for some lag structures of ambient air pollutants. Asthma patient visit was significantly related with Lag 01 pollution for PM₁₀ and CO. Ambient air pollutants did not present any statistically significant association with asthma morbidity in Lag 02 analysis.

Table 3

The increase in asthma morbidity associated with an increase of $10 \mu\text{g m}^{-3}$ in air pollutants (PM_{2.5}, PM₁₀, O₃, SO₂, NO₂, CO) in Shanghai Pulmonary Hospital, in single- and multi-pollutant models adjusted for co-pollutants.

Model choice	Air pollutants	Asthma morbidity		
		Increase%	95% CI	
Single-pollutant model	PM _{2.5}	1.27	0.29	2.26
	PM ₁₀	1.11	0.38	1.85
	O ₃	0.23	– 0.31	0.78
	SO ₂	3.79	0.84	6.83
	NO ₂	0.63	– 0.82	2.1
	CO	0.27	0.14	0.4
	PM _{2.5} with PM ₁₀	0.03	– 1.77	1.85
Multi-pollutant model	PM _{2.5} with O ₃	1.24	0.25	2.24
	PM _{2.5} with SO ₂	0.8	– 0.43	2.05
	PM _{2.5} with NO ₂	1.44	0.29	2.6
	PM _{2.5} with CO	– 0.62	– 2.07	0.85
	PM ₁₀ with O ₃	1.10	0.36	1.85
	PM ₁₀ with SO ₂	0.89	– 0.11	1.90
	PM ₁₀ with NO ₂	1.28	0.41	2.15
	PM ₁₀ with CO	0.24	– 0.67	1.16
	O ₃ with SO ₂	0.36	– 0.19	0.91
	O ₃ with NO ₂	0.28	– 0.27	0.83
	O ₃ with CO	0.42	– 0.12	0.97
	SO ₂ with NO ₂	5.33	1.34	9.49
	SO ₂ with CO	0.07	– 3.48	3.75
	NO ₂ with CO	– 1.76	– 3.50	0.01
	PM _{2.5} with PM ₁₀	1.09	– 0.26	2.48
	PM _{2.5} with O ₃	0.16	– 0.39	0.71
	PM _{2.5} with SO ₂	2.30	– 1.37	6.11
	PM _{2.5} with NO ₂	– 0.47	– 2.14	1.23
	PM _{2.5} with CO	0.33	0.14	0.53
	PM ₁₀ with O ₃	0.02	– 0.52	0.58
	PM ₁₀ with SO ₂	1.29	– 2.64	5.38
	PM ₁₀ with NO ₂	– 0.59	– 2.29	1.13
	PM ₁₀ with CO	0.26	0.09	0.42
	O ₃ with SO ₂	4.12	1.12	7.22
	O ₃ with NO ₂	0.7	– 0.71	2.25
	O ₃ with CO	0.29	0.15	0.42
	SO ₂ with NO ₂	– 1.10	– 3.02	0.84
	SO ₂ with CO	0.27	0.11	0.43
	NO ₂ with CO	0.36	0.21	0.53

Black bold: $p < 0.05$.

CI: confidence interval.

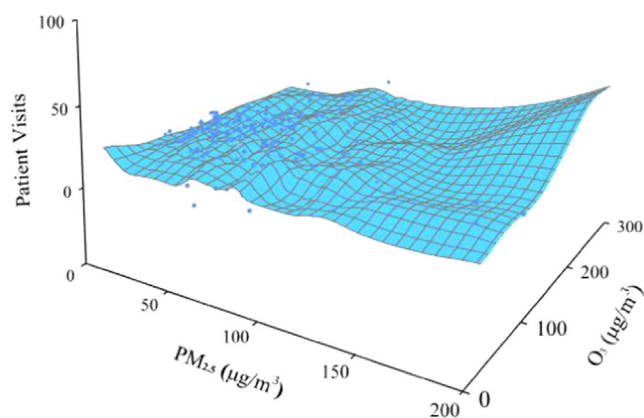


Fig. 1. The joint influence of PM_{2.5} and O₃ on asthma patient visits.

3.2. Assessment of the economic cost of health effects attributed to the influence of ambient air pollutants on asthma patient visits

A Generalized Additive Model (GAM) based on Poisson regression was used to quantitatively estimate the economic cost. This method was first time to be used to assess the economic cost. This adjusted method is deduced reasonably. The specific formulas are as follows:

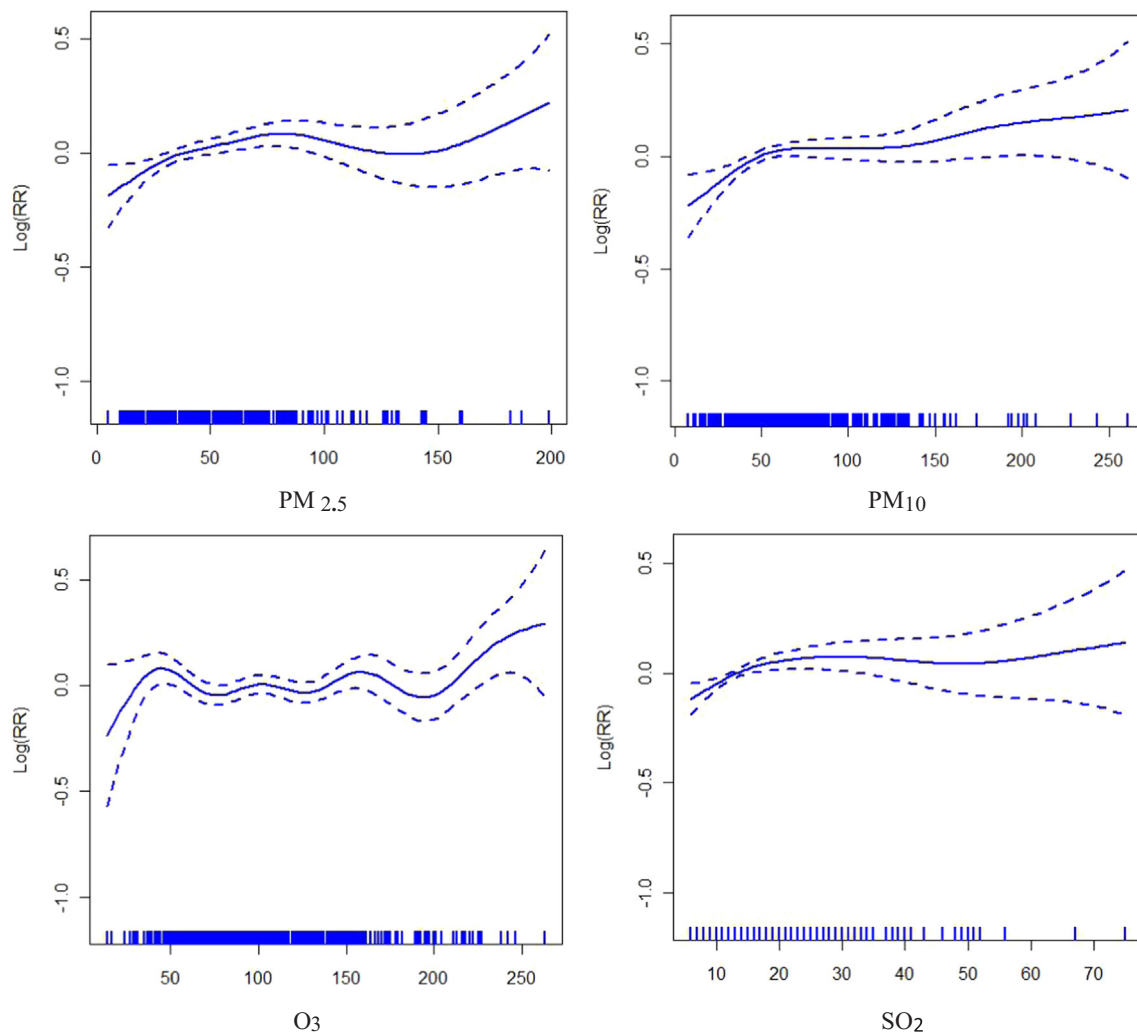


Fig. 2. Smoothing plots of pollutants against asthma patient visits. X-axis is pollutants concentrations. The estimated mean percent change in asthma patient visits is shown by the solid line, and the dotted lines represent twice the point-wise standard error. Current-day temperature and relative humidity were used with a df of 6 and 3, respectively.

Table 4

Percent increase (95% CI) of asthma patient visits, associated with $10 \mu\text{g}\cdot\text{m}^{-3}$ increase of pollutant concentrations in Shanghai Pulmonary Hospital.

	Lag(L)	PM _{2.5}	PM ₁₀	O ₃	SO ₂	NO ₂	CO
Asthma patient visits	L0	1.27 (0.29, 2.26)*	1.11 (0.38, 1.85)*	0.23 (-0.31, 0.78)	3.79 (0.84, 6.83)*	0.63 (-0.81, 2.10)	0.27 (0.14, 0.40)*
	L1	-0.20 (0.68, -1.08)	0.02 (-0.63, 0.68)	0.53 (-0.01, 1.08)	-0.63 (-3.32, 2.14)	-0.52 (-1.90, 0.86)	-0.07 (-0.19, 0.03)
	L2	-0.82 (-1.67, 0.02)	-0.53 (-1.20, 0.12)	0.42 (-0.11, 0.97)	-2.28 (-4.93, 0.44)	-0.69 (-2.06, 0.68)	-0.10 (-0.21, 0.01)
	L3	-0.89 (-1.71, -0.06)*	-0.44 (-1.08, 0.20)	0.23 (-0.30, 0.77)	-0.47 (-2.95, 2.07)	-0.47 (-1.77, 0.83)	-0.12 (-0.23, -0.02)*
	L4	-1.15 (-1.95, -0.34)	-0.57 (-1.20, 0.05)	0.01 (-0.52, 0.54)	-2.74 (-5.23, -0.19)*	-1.30 (-2.54, -0.01)*	-0.15 (-0.25, -0.05)*
	L5	0.16 (-0.65, 0.98)	0.07 (-0.55, 0.71)	-0.61 (-1.15, -0.06)*	1.26 (-1.30, 3.90)	1.05 (-0.20, 2.33)	-0.01 (-0.12, 0.08)
	L6	0.76 (-0.07, 1.59)	0.39 (-0.25, 1.04)	-0.53 (-1.08, 0.02)	1.08 (-1.50, 3.75)*	0.85 (-0.37, 2.10)	0.16 (0.07, 0.26)*
	L01	0.47 (-0.46, 1.41)	0.54 (-0.1, 1.25)*	0.39 (-0.15, 0.94)	1.40 (-1.42, 4.32)	0.05 (-1.37, 1.49)	0.08 (-0.04, 0.20)*
	L02	0.09 (-0.82, 1.02)	0.18 (-0.51, 0.88)	0.43 (-0.10, 0.98)	0.27 (-2.52, 3.15)	-0.13 (-1.56, 1.30)	0.04 (-0.08, 0.16)

* $p < 0.05$

Table 5

The economic cost of asthma patient visits attribute to the air pollutants (PM_{2.5}, PM₁₀, NO₂, SO₂, CO, O₃).

Air pollutants	PM _{2.5}	PM ₁₀	O ₃	SO ₂	NO ₂	CO
β – value (10 ^{−3})	1.27	1.11	0.23	3.72	0.63	0.27
Economic cost (million \$) a year	34.50	30.18	6.39	101.30	17.15	7.46

(conditions: P_t – 12million persons, f_t – 7.57%, 75\$/person/day).

$$E = (f_t - f_o) \times P_t \quad (2)$$

$$\frac{f_t}{f_o} = RR \quad (3)$$

$$E = \left(\frac{RR - 1}{RR} \right) \times f_t \times P_t \quad (4)$$

$$RR = \exp(\beta) \quad (5)$$

$$E = \left(\frac{\exp(\beta) - 1}{\exp(\beta)} \right) \times f_t \times P_t \quad (6)$$

Where E is the excess number of asthma; f_t is the asthma morbidity in current air pollution; f_o is the asthma morbidity; P_t is the number of residents; β is the estimate.

Shanghai is the highest asthma morbidity (7.57%) in 2015. The economic cost of asthma patient visits attributed to ambient air pollutants (SO₂, CO, O₃, PM₁₀, NO₂ and PM_{2.5}) was ~ 197 million USD per year. Among, the economic cost of asthma patient visits attribute to SO₂, CO, NO₂, PM₁₀, O₃ and PM_{2.5} were 101.30, 7.46, 17.15, 30.18, 6.39 and 34.50 million USD per year, respectively (Table 5). The highest economic loss was estimated to occur for SO₂ effect.

4. Discussions

This time-series study showed that ambient air pollutants were closely linked to asthma and cause hugely economic cost burden in Shanghai, China. To our knowledge, this is the first systemic research to examine the potential detrimental impacts of ambient air pollutant on new onset asthma-related hospital patient visits and analyze economical cost in Shanghai area.

Many epidemiological studies have assessed an important link of ambient air pollutants and increased asthma risk (Delfino et al., 2014; Lam et al., 2016; Nastos et al., 2010; Tetreault et al., 2016). Recently, Michael Guarnieri and John R Balmes provided a systematic review of ambient air pollutants and asthma (Guarnieri and Balmes, 2014). Many ambient air pollutants were related to asthma, but the strength of the evidence is variable. In Michael Guarnieri's analysis, ambient air pollutants can lead to exacerbation of pre-existing asthma (Guarnieri and Balmes, 2014). Our study showed a 10 $\mu\text{g m}^{-3}$ increase in the current day concentrations of SO₂, CO, NO₂, PM₁₀, O₃ and PM_{2.5} corresponded to increase of 3.79% [95% CI: 0.84%, 6.83%], 0.27% [95% CI: 0.14%, 0.40%], 0.63% [95% CI: − 0.81%, 2.10%], 1.11% [95% CI: 0.38%, 1.85%], 0.23% [95% CI: 0.31%, 0.78%] and 1.27% [95% CI: 0.29%, 2.26%] in daily asthma patient visits, respectively. Several studies also suggested a contribution of ambient air pollutants to new-onset asthma (Jeebhay et al., 2014).

We observed different effect estimates using different lag structure in Shanghai (Fig. S2 and Fig. S3) than previous studies in other cities (Meng et al., 2010; Newman et al., 2014; Pan et al., 2014). For example, In Ding's case-crossover analysis, a 10 $\mu\text{g m}^{-3}$ increase in current day concentrations of SO₂, CO, NO₂, PM₁₀, O₃ and PM_{2.5} were associated with 1.008 (1.001–1.014), 1.000 (0.999–1.000), 1.009 (0.997–1.020), 1.002 (1.001–1.004), 0.999 (0.994–1.003) and 1.003 (1.000–1.005) relative risk for asthma in Chongqing (Ding et al., 2017). Several potential factors contribute to the heterogeneity. First, Shanghai is the fastest-growing metropolis with relatively high levels of ambient air

pollutants. For instance, the annual mean concentrations of PM_{2.5} between 2014 and 2015 was 51 $\mu\text{g m}^{-3}$, which greatly exceed almost 5-fold the WHO (10 $\mu\text{g m}^{-3}$). Second, the different characteristics of ambient air pollutants occur in Shanghai (e.g. transport of pollutants, particle composition) (Chen et al., 2008). Third, the socio-demographic status of local residents may be different, such as structure or disease pattern (Chen et al., 2012).

Understanding the exposure-response relationship is important for the evaluation of human health. This study showed that the risks of asthma could linearly increase corresponding to the acute exposure to ambient air pollutants with no any appreciable thresholds. In China, the average national prevalence of asthma was estimated at 1% (from BBC report in 2015). In addition, an increased burden of asthma was estimated in the aging population. Further, air pollution-related burden of asthma can be deemed a significant human health problem in Shanghai, where ambient air pollutants levels were the highest and its impact may be higher than the low-income provinces (e.g. Guizhou, Yunnan). The local decision-makers may also be informed about our results, thus providing a rationale to improve public health. For example, patients with chronic asthma and other high-risk diseases can be educated to stay at home when ambient air pollutants levels are high.

We found statistically significant relationship of ambient air pollutants and asthma patient visits were at Lag 0. Similarly, Deng et al. found the strongest relationship of asthma and ambient air pollutants at Lag 0, with this effect diminishing at longer lag times (Deng et al., 2016). The mechanism underlying pathophysiology of asthma is still unclear, through several pathways have been implicated, including airway inflammation (e.g. O₃, NO₂ and PM_{2.5}), airway hyper-responsiveness (e.g. O₃ and NO₂) and oxidative stress (O₃, NO₂, O_x (= O₃ + NO₂) and PM_{2.5}). Therefore, exposures to these pollutants were significantly linked to increase asthma morbidity increase. Nevertheless, the mechanisms by which specific pollutants cause these effects are not clear completely (Baccarelli and Kaufman, 2011). Given the multi-linearity and variation in exposure measurement errors of these pollutants, the impact of damages on the exacerbation of asthma could not be separated. After adjustment for other pollutants, the link of asthma patient visits and ambient air pollutants remained significant, suggesting that gaseous pollutants (SO₂, NO₂, and CO) and particulate matter (PM_{2.5}, PM₁₀) may contribute differently to the underlying mechanism of pathophysiological asthma. However, the effects of gaseous pollutants decreased after adjustment of particulate matter (PM_{2.5}, PM₁₀). Gaseous pollutants reduce the association of particulate matter with asthma morbidity, and particulate matter may act as a surrogate of other pollutants which are correlated with other gaseous pollutants (e.g. NO₂).

A model was set up to estimate the economic burden for asthma effect in Shanghai, China. The economic costs of asthma patient visits that are attributed to SO₂, CO, NO₂, PM₁₀, O₃ and PM_{2.5} were 101.30, 7.46, 17.15, 30.18, 6.39 and 34.50 million USD per year, respectively. These values are the similar order of magnitude with previously cost estimates. For instance, a previous study in Beijing assessed a direct annual cost of 96.88 million USD in 2013 (Gao et al., 2015). Furthermore, in developed areas, Lewis et al. showed that the direct cost burden of asthma for people were estimated at 1151.23 million USD, 1258.12 million USD, and 1024.15 million USD for Spain, Sweden and the UK (Lewis et al., 2016). The detailed data was described in Table S1. These data show Shanghai also have a severe situation compared with other developed areas.

Our study has several strengths. First, many previous studies concerning the associations of air pollution and asthma, were studied in one term; the present study was the first systematic evaluation and confirmed the link of ambient air pollutants and asthma patient visits. The study also considered the effect of different lag days, association with single-pollutant and multi-pollutants, exposure-response analysis and relative risk assessment. Second, few studies based on asthma patient visits, which might be more sensitive to reflect the effects of air

pollution on asthma. Third, this study has also provided the assessment of the economic cost caused by the burden of asthma.

Nevertheless, several limitations of this research should also be stated. First, as many of the time-series studies previously, pollution exposure assessment introduces some degree of exposure measurement error, and thus estimates are biased downward. Second, the diagnosis of asthma patient visits made by Shanghai Pulmonary Hospital might not be completely consistent with other hospitals of Shanghai. Further work is still needed to confirm in terms of the study through using a larger sample size.

5. Conclusions

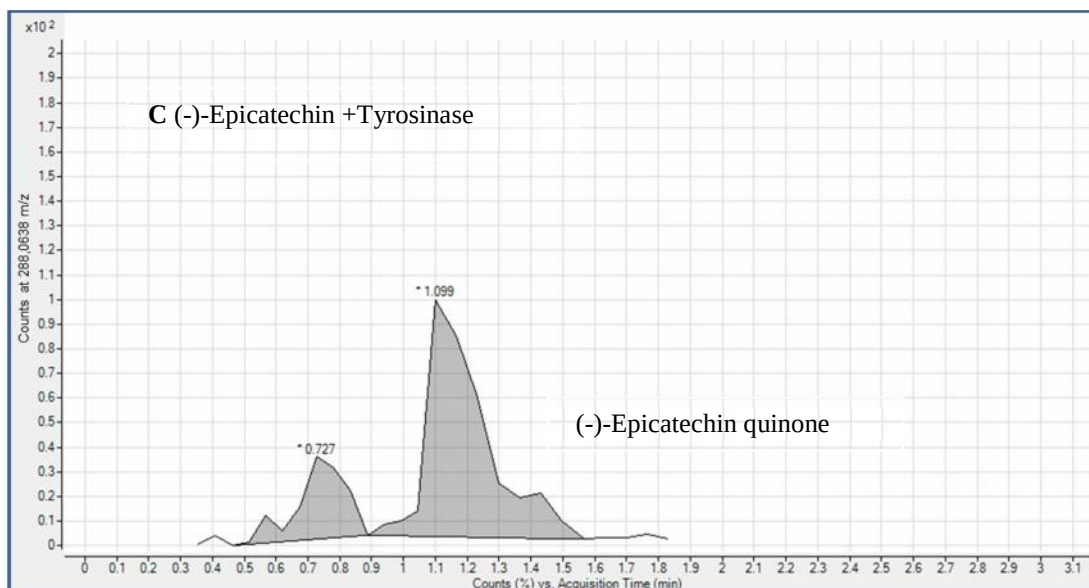
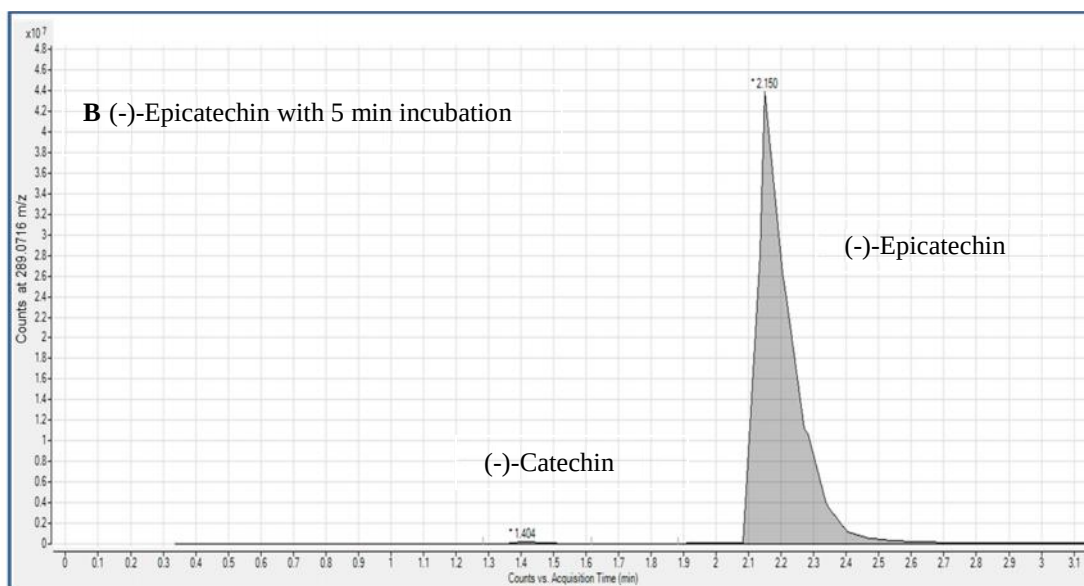
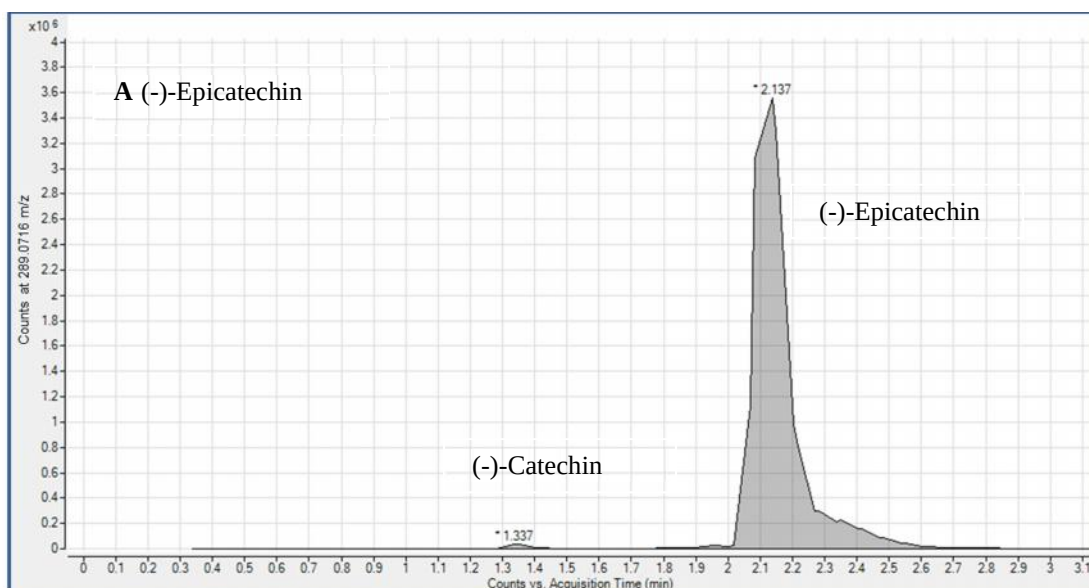
Short-term exposure to SO₂, CO, NO₂, PM₁₀, O₃ and PM_{2.5} were associated with asthma patient visits increase. The economic cost of asthma patient visits were attributed to SO₂, CO, NO₂, PM₁₀, O₃ and PM_{2.5} with 101.30, 7.46, 17.15, 30.18, 6.39 and 34.50 million USD losses per year, respectively. For further studies, the mechanisms by which pollutants induce asthma are needed to tackle with the independent or combined health effect of PM_{2.5}, PM₁₀, SO₂, NO₂, CO and O₃ for asthma morbidity.

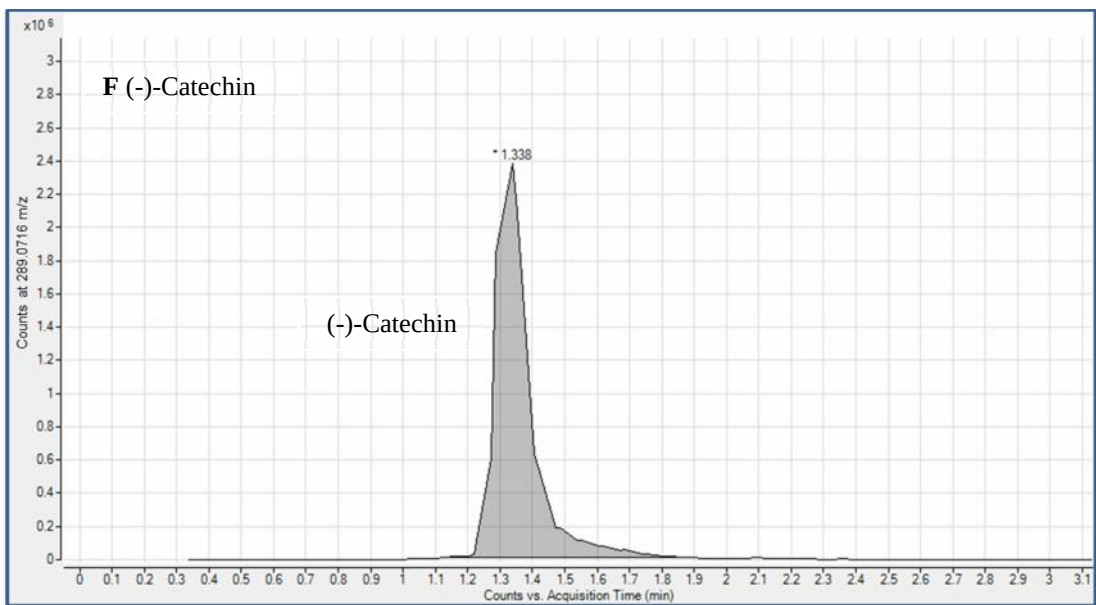
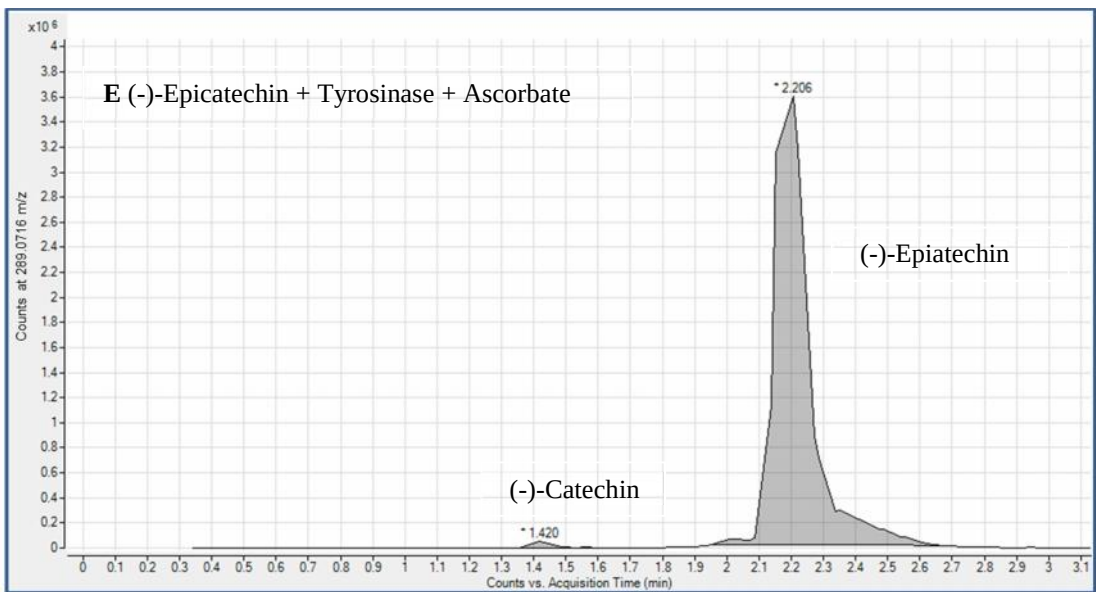
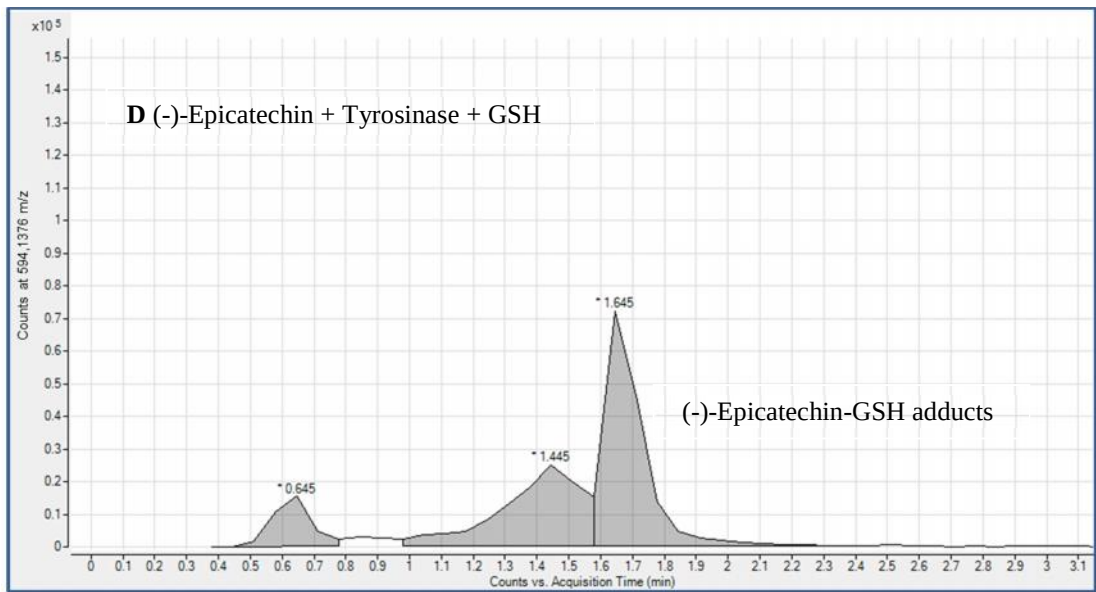
Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.ecoenv.2018.05.089>.

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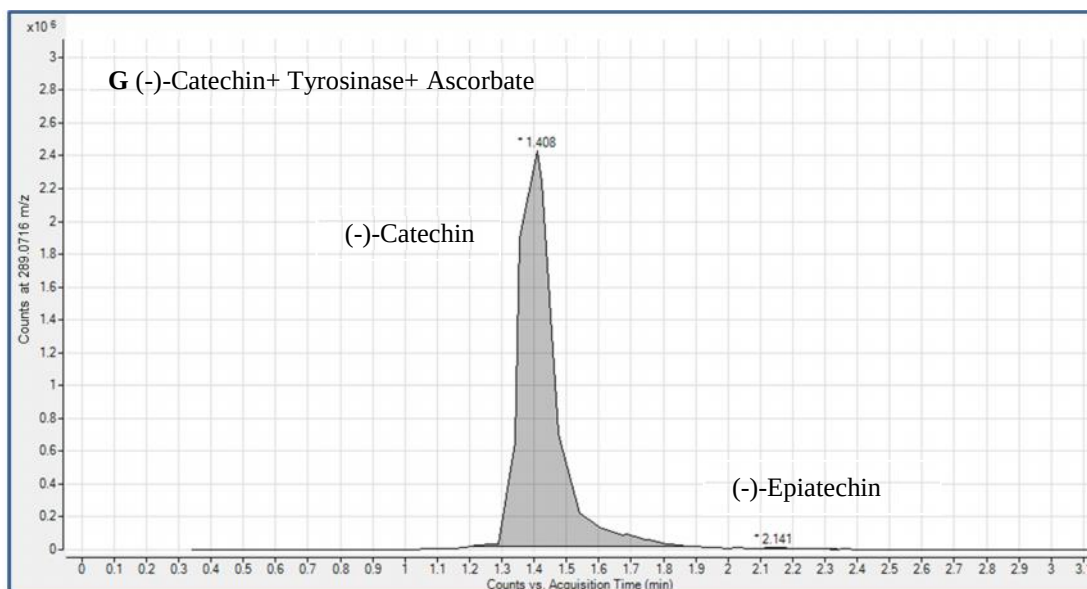


Fig. 1. LC/MS Chromatograms of the 50 μ M (-)-epicatechin calibration standard (A) and its incubation for 5 min (B), of the incubation mixture containing 50 μ M (-)-epicatechin and 10 U/mL tyrosinase (C), in presence of 100 μ M GSH (D) or 50 μ M ascorbate (E), of the 50 μ M (-)-catechin calibration standard (F), and of the incubation mixture containing 50 μ M (-)-catechin and of 15 U/mL tyrosinase and 50 μ M ascorbate (G). The incubation mixtures were injected into the UHPLC-Q-TOF/MS system 5 min after starting the reaction with tyrosinase. Traces of (-)-catechin (as evidenced by the shape of the “peak” of (-)-catechin, the concentration is below the Lower Limit of Quantification) were found in the (-)-epicatechin calibration standard (A), as well as in the incubation of (-)-epicatechin without (B) and with tyrosinase and ascorbate (E). Similarly, a trace of (-)-epicatechin was found in the incubation of (-)-catechin with tyrosinase in the presence of ascorbate (G). No (-)-epicatechin was detected in the (-)-catechin calibration standard (F). The presence of (-)-catechin in chromatogram E might indicate that there is some minor epimerization of (-)-epicatechin quinone. However, we also detected similar traces of (-)-catechin in chromatogram A and B that are probably formed by “spontaneous” epimerization, indicating that the (-)-catechin detected in chromatogram E might also be formed by “spontaneous” epimerization. Moreover, that only tiny traces of (-)-catechin were detected actually confirms the HPLC data that there is no substantial epimerization of the (-)-epicatechin to (-)-catechin.