doi: 10.13241/j.cnki.pmb.2018.06.036

张家口市大气颗粒物 $PM_{2.5}$、PM_{10} 浓度与慢性阻塞性肺疾病住院人次的关系研究 *

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摘要 目的：研究张家口市大气颗粒物对慢性阻塞性肺疾病（COPD）的影响，并分析大气颗粒物对不同特征人群的影响。**方法：**从张家口市医保办公室获取张家口市 2013 年 1 月 1 日 -2015 年 12 月 31 日两家三甲医院 COPD 患者的住院病历资料，从中国环境监测总站网站获取大气污染物的监测数据，从张家口市气象局获取气象资料。建立广义相加模型(GAM)，在控制长期趋势、星期几效应和温湿度影响后，应用条件 Logitic 回归方法评估 $PM_{2.5}$、PM_{10} 对 COPD 住院人次的影响。根据患者不同特征（性别、年龄、季节）进行分层分析，评估颗粒物污染的高危人群。**结果：**研究纳入两家三甲医院，共 1984 例住院 COPD 患者，其中男性患者 1258 例（63.4%）、女性患者 726 例（36.6%），≥ 75 岁患者 678 例（34.2%），60~75 岁患者 936 例（47.2%）、≦60 岁患者 370 例（18.6%）。2013-2015 年 $PM_{2.5}$、PM_{10} 年均浓度分别为 [（36.54± 20.34）μg/m³、（84.37± 52.54）μg/m³]，[（34.50± 27.08）μg/m³、（78.43± 69.78）μg/m³]，[（32.04± 21.35）μg/m³、（75.46± 50.02）μg/m³]，两者在移动平均滞后 3d 时，对 COPD 的影响最大，即 $PM_{2.5}$ 每增加 10 μg/m³，COPD 住院人次增加 1.90%（95%CI:1.002-1.033，P<0.05），PM_{10} 每增加 10 μg/m³，COPD 住院人次增加 2.10%（95%CI:1.005-1.045，P<0.05）。分层分析结果显示：$PM_{2.5}$、PM_{10} 每升高 10 μg/m³，女性 COPD 患者住院人次增加 1.09%、1.14%，差异具有统计学意义（P<0.05）；≥ 75 岁患者，COPD 住院人次增加 1.03%、0.99%，差异具有统计学意义（P<0.05）；而年龄≦60 岁、60~75 岁、男性以及季节分层分析中，$PM_{2.5}$、PM_{10} 浓度与 COPD 住院人次无统计学意义（P>0.05）。**结论：**颗粒物污染会增加 COPD 住院率，≥ 75 岁的老年患者及女性患者更敏感。

关键词：空气污染；肺疾病；慢性阻塞性；颗粒物；广义相加模型

中图分类号：R563 **文献标识码：**A **文章编号：**1673-6273（2018）06-1167-05

Relationship Between Concentration of Airborne Particulate Matter $PM_{2.5}$ and PM_{10} and Number of Inpatients with Chronic Obstructive Pulmonary Disease in Zhangjiakou City*

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ABSTRACT Objective: To study the effects of airborne particulate matter on chronic obstructive pulmonary disease (COPD) in Zhangjiakou city, and to analyze the effects of airborne particulate matter on population with different characteristics. **Methods:** The inpatient records of COPD patients in 2 top three hospitals in Zhangjiakou city from January 1, 2013 to December 31, 2015 were obtained from Zhangjiakou medical insurance office; air pollution monitoring data were obtained from the China environmental monitoring station website; meteorological data were obtained from Zhangjiakou Meteorological Bureau. A generalized additive model (GAM) was established, and after controlling long-term trends, week effects, and temperature and humidity effects, the conditional Logitic regression method was used to assess the effect of $PM_{2.5}$ and PM_{10} on the number of inpatients of COPD. Based on different characteristics of the patients (sex, age, season), stratified analyses were performed to assess high-risk population of particulate contamination. **Results:** A total of 1984 inpatients with COPD from 2 top three hospitals were enrolled in this study, among them, there were 1258 male patients (63.4%), 726 female patients (36.6%), 678 patients over 75 (34.2%), 936 patients over 60~75 (47.2%), and 370 patients (18.6%) below 60 years old. The yearly average concentration of $PM_{2.5}$ and PM_{10} from 2013 to 2015 years was [(36.54± 20.34)

* 基金项目：河北省 2017 年度医学科学研究重点课题（20170184）
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（收稿日期：2017-07-20 接受日期：2017-08-13）

μg/m³, (84.37± 52.54)μg/m³], [(34.50± 27.08)μg/m³, (78.43± 69.78)μg/m³], [(32.04± 21.35)μg/m³,(75.46± 50.02)μg/m³]; the effect of both on COPD was the greatest when they moved average lags 3d, that was to say, with an increase of per 10 μg/m³ of $PM_{2.5}$, the number of inpatients with COPD was increased by 1.90% (95%CI:1.002-1.033, P<0.05), with an increase of per 10 μg/m³ of PM_{10}, the number of inpatients with COPD was increased by 2.10% (95%CI:1.005-1.045, P<0.05). The results of stratified analysis showed that $PM_{2.5}$ and PM_{10} was increased by per 10 μg/m³, and the number of female inpatients with COPD was increased by 1.09% and 1.14%, the difference was statistically significant (P<0.05). For more than 75 years old patients, the number of inpatients with COPD was increased by 1.03% and 0.99%, the difference was statistically significant (P<0.05). But for the patients below 60, 60~75 years old, men and the seasonal stratification analysis, there were not statistical significance in $PM_{2.5}$ and PM_{10} concentrations and the number of inpatients with COPD (P>0.05). **Conclusion:** Particulate matter contamination can increases hospitalizations of COPD,and the patients over 75 and female patients are more sensitive to it.

Key words: Air pollution; Pulmonary disease; Chronic obstructive; Particulate matter; Generalized additive model

Chinese Library Classification(CLC): R563 Document code: A

Article ID: 1673-6273(2018)06-1167-05

前言

慢性阻塞性肺疾病（chronic obstructive pulmonary disease, COPD）是以气道高反应、不完全可逆的持续性气流阻塞为主的疾病[1,2]。COPD 是一种严重危害人类健康的常见病、多发病，具有病死率高、经济负担大等特点，已严重影响患者的生活质量[3]。COPD 患者肺结构与功能的损害与气道、肺血管、肺实质进行性发展的炎症呈正相关，吸烟、吸入颗粒性物质、环境污染是导致 COPD 发病的重要因素[4,5]。慢性阻塞性肺疾病急性加重（acute exacerbations of chronic obstructive pulmonary disease, AECOPD）是指 COPD 患者出现呼吸系统症状急性加重，包括呼吸困难加剧、咳痰增加等典型临床表现突然出现或超出日常状况的进行性加重[6,7]。COPD 患者每年出现 0.5~3.5 次急性加重[8]。AECOPD 已成为继心、脑血管疾病以外急性入院的第三大原因[9]。大气颗粒物（particulate matter, PM）是指大气中的各种固态颗粒和液态颗粒的总称[10]。PM_{10}、$PM_{2.5}$ 分别表示空气动力学直径小于 10 μm、2.5 μm 的颗粒物，又称为可吸入颗粒物、可吸入肺颗粒物[11]。目前，世界各界学者已开展大气颗粒物对人类呼吸道损害的研究，避免大气颗粒物对 COPD 的发生发展和急性加重的影响以及开展高危人群的预防工作刻不容缓[12]。随着大气污染问题的愈发严重，大气颗粒物的异质性明显，为研究空气污染与 COPD 发生发展的关系，并为控制大气颗粒物的含量提供可靠依据，本文共纳入张家口市两家三甲医院的 COPD 住院患者资料，分析大气颗粒物与 COPD 人群住院的关系，探讨大气颗粒物对 COPD 患者预后的影响。

1 资料与方法

1.1 患者资料

选取张家口市两家三甲医院 2013 年 1 月 1 日 -2015 年 12 月 31 日呼吸内科医疗保险报销范围内的 COPD 患者住院病历资料，数据来源于张家口市医保办公室。资料包括患者性别、年龄、入院日期、出院日期、合并症等。纳入标准：患者均符合中华医学会呼吸病学分会制定的《慢性阻塞性肺疾病诊治指南》中的诊断标准[13]，患者病历资料完整；排除标准：非张家口市 COPD 住院患者；肺部肿瘤患者；结缔组织病并长期服用糖皮质激素患者。

1.2 大气污染资料

从中国环境监测总站网站获取 2013 年 1 月 1 日至 2015 年 12 月 31 日期间张家口市空气污染物的数据资料，主要涵盖 $PM_{2.5}$、PM_{10}、SO_2、CO、NO_2、O_3 的日均浓度。

1.3 气象资料

从张家口市气象局气象数据网接收的地面站获取气象资料，包括日平均气温、日平均相对湿度。

1.4 方法

建立广义相加模型（generalized additive model,GAM），模型中包括温度、湿度及可吸入颗粒物浓度。在控制长期趋势、星期几效应和温湿度影响后，采用滞后模型，观察当天（lag0）以及滞后 1-5d（lag1-5）大气污染物对张家口市居民 COPD 住院的影响，分析大气污染物与 COPD 住院人数的关系，以 OR 值表示最佳滞后期[14,15]。将其他大气污染物 SO_2、CO、NO_2、O_3 纳入双污染物模型，以评估颗粒物对健康影响的稳定性。避免敏感性人群对结果的影响，本研究按照患者性别、年龄以及季节进行分层分析。

1.5 统计学方法

应用条件 Logitic 回归方法，每日 COPD 住院人数为权重，应用 SPSS17.0 进行统计分析，分析污染物浓度增加 10 μg/m³，COPD 住院人次增加的百分比，以 ER%作为效应指标，以双侧 P<0.05 为差异具有统计学意义。

2 结果

2.1 描述性分析

2.1.1 病历资料的描述性分析 2013 年 1 月 1 日至 2015 年 12 月 31 日期间，本研究共纳入张家口市 COPD 住院患者 1984 例，其中男性患者 1258 例（63.4%）、女性患者 726 例（36.6%）；≥75 岁患者 678 例（34.2%），60~75 岁患者 936 例（47.2%）、≦60 岁患者 370 例（18.6%）；冷季（10 月～次年 3 月）患者为 1207 例（60.8%）、暖季（4 月 ~9 月）患者为 777 例（39.2%）。

2.1.2 大气污染物及气象资料的描述性分析 张家口市 2013 年 ~2015 年大气污染物中，$PM_{2.5}$、PM_{10}、SO_2、CO、NO_2、O_3、温度及湿度的年均数据如表 1 所示，与我国现行的《环境空气质量标准》（GB3095-2012）相比较，张家口市 2013~2015 年大气污染物水平均高于国家空气质量二级标准（$PM_{2.5}$:35μg/m³，PM_{10}:

70 μg/m³),主要污染物为颗粒物。

表 1 2013 年 ~2015 年大气污染物及气象资料数据($\bar{x}\pm s$)

Table 1 Air pollutants data and meteorological data during 2013-2015($\bar{x}\pm s$)

Project	2013	2014	2015
$PM_{2.5}$/(μg/m³)	36.54± 20.34	34.50± 27.08	32.04± 21.35
PM_{10}/(μg/m³)	84.37± 52.54	78.43± 69.78	75.46± 50.02
SO_2/(μg/m³)	36.79± 25.14	52.17± 33.65	30.49± 21.89
CO/(μg/m³)	0.69± 0.31	1.12± 0.53	0.81± 0.46
NO_2/(μg/m³)	26.78± 10.84	27.69± 13.74	25.47± 13.02
O_3/(μg/m³)	107.1± 45.43	83.92± 36.71	96.45± 42.34
Temperature/(℃)	12.67± 10.04	13.01± 10.13	12.84± 10.13
Humidity(%)	0.59± 0.21	0.63± 0.19	0.60± 0.18

2.2 GAM 拟合的结果

2.2.1 单污染物模型 分别考察当天及滞后 1-5d(lag0~lag5)污染物的健康效应,具体数值见表 2。$PM_{2.5}$ 及 PM_{10} 在滞后 3d 时,对 COPD 入院人数有影响。$PM_{2.5}$ 每升高 10 μg/m³, 3d 后居民每日 COPD 住院人次增加 1.90%(95%CI:1.002-1.033,P<0.05);PM_{10} 每升高 10 μg/m³,3d 后居民每日 COPD 住院人次增加 2.10%(95% CI:1.005-1.045,P<0.05)。其他滞后时间点的 $PM_{2.5}$、PM_{10} 浓度与 COPD 住院人次的相关性无统计学意义(P>0.05)。

表 2 单污染物模型结果

Table 2 Results of single pollutant model

Lag time(d)	Index	ERI%	OR	95%CI	P
0	$PM_{2.5}$	0.67	0.986	0.975-0.997	0.094
	PM_{10}	0.79	1.004	0.998-1.014	0.671
1	$PM_{2.5}$	0.69	1.002	0.987-1.013	0.076
	PM_{10}	0.92	1.005	0.996-1.014	0.241
2	$PM_{2.5}$	1.05	1.001	0.988-1.015	0.647
	PM_{10}	1.13	1.006	0.997-1.016	0.094
3	$PM_{2.5}$	1.90	1.019	1.002-1.033	0.031
	PM_{10}	2.10	1.021	1.005-1.045	0.019
4	$PM_{2.5}$	0.85	1.009	0.997-1.019	0.068
	PM_{10}	0.93	1.004	0.995-1.012	0.632
5	$PM_{2.5}$	1.08	1.006	0.996-1.011	0.730
	PM_{10}	0.99	1.007	0.997-1.016	0.061

2.2.2 双污染物模型 在 lag3 时, 分别调整了 SO_2、CO、NO_2、O_3 的浓度,考察 $PM_{2.5}$ 及 PM_{10} 效应是否稳健。结果表明,调整 NO_2 或 SO_2 后,$PM_{2.5}$ 效应仍有统计学意义(P<0.05);调整 CO 和 O_3 后,$PM_{2.5}$ 效应无统计学意义(P>0.05)。在调整 SO_2、CO、NO_2、O_3 后,PM_{10} 效应仍有统计学意义(P<0.05)。所以,PM_{10} 效应更稳健,结果见表 3。

2.3 分层分析结果

女性患者中,$PM_{2.5}$、PM_{10} 每升高 10 μg/m³,COPD 住院人次增加 1.09%、1.14%,差异具有统计学意义(P<0.05);在≥ 75 岁患者中,$PM_{2.5}$、PM_{10} 每升高 10 μg/m³,COPD 住院人次增加 1.03%、0.99%,差异具有统计学意义(P<0.05);而年龄≤60 岁、60~75 岁、男性以及季节分层分析中,$PM_{2.5}$、PM_{10} 浓度与 COPD 住院人次无统计学意义(P>0.05)。如表 4。

3 讨论

国外学者认为大气颗粒物之所以引起 COPD、哮喘等呼吸系统疾病,是因为其进入肺内后,肺泡巨噬细胞吞噬细颗粒物后,释放出与免疫功能相关的细胞因子和参与炎症反应,如 γ-干扰素(IFN-γ)、肿瘤坏死因子 β(TNF-β)和白细胞介素 -2、6、8等[16]。此类炎症因子或沉积于肺脏深部的颗粒物进一步作用于肺上皮细胞、内皮细胞及成纤维母细胞等,产生粘附因子及细胞因子,进而导致炎症细胞聚集,最终发生炎症反应[17,18]。另有

表 3 双污染物模型结果

Table 3 Results of double pollutants model

Indexes	ERI%	OR	95%CI	P
$PM_{2.5}$+SO_2	1.04	0.996	0.983-1.021	0.020
$PM_{2.5}$+CO	1.12	1.001	0.995-1.104	0.057
$PM_{2.5}$+NO_2	0.98	0.997	0.980-1.036	0.015
$PM_{2.5}$+O_3	1.02	0.999	0.982-1.026	0.063
PM_{10}+SO_2	1.32	1.002	0.989-1.021	0.004
PM_{10}+CO	1.07	1.011	0.996-1.043	0.005
PM_{10}+NO_2	1.21	1.009	0.997-1.041	0.006
PM_{10}+O_3	1.31	0.998	0.981-1.010	0.007

表 4 分层分析结果

Table 4 Results of stratified analysis

Classification		Index	ERI%	OR	95%CI	P
Gender	Male	$PM_{2.5}$	1.02	0.994	0.981-1.002	0.079
		PM_{10}	1.15	1.005	0.996-1.017	0.052
	Female	$PM_{2.5}$	1.09	1.010	0.993-1.025	0.021
		PM_{10}	1.14	1.012	0.987-1.031	0.009
Age(years)	≦60	$PM_{2.5}$	1.21	1.008	0.997-1.020	0.061
		PM_{10}	1.08	1.015	0.998-1.032	0.426
	60~75	$PM_{2.5}$	0.98	1.021	1.003-1.045	0.364
		PM_{10}	0.88	1.003	0.987-1.018	0.072
	≥ 75	$PM_{2.5}$	1.03	1.011	0.997-1.033	0.024
		PM_{10}	0.99	1.014	0.998-1.036	0.030
Season	Cold season	$PM_{2.5}$	1.12	0.997	0.982-1.007	0.052
	Warm season	PM_{10}	1.03	1.003	0.996-1.012	0.143

研究表示，大气颗粒物粒径小、比表面积大，易吸附多种有害物质并沉积在肺内，进而作用于巨噬细胞、I- 型肺泡上皮细胞、Ⅱ- 型肺泡上皮细胞，导致巨噬细胞吞噬功能减弱，趋向性亦发生改变，并能够使中性粒细胞聚集，肺泡通透性改变，最终引发炎症反应和氧化应激[19]。

粗颗粒物主要来源于地壳成分如硅、钙等，亦含有公路上轮胎成分及过渡金属等交通相关物质，此外，粗颗粒物中的内毒素和其他生物成分也可引起炎症反应 [20]。在体外及动物实验中，颗粒物能增强肺内巨噬细胞的吞噬功能，并促进免疫细胞分泌更多白细胞介素，导致炎症因子向炎症部位聚集并释放大量炎症介质，炎症介质的大量释放促进了 COPD 的发生发展[21,22]。

本研究表明，$PM_{2.5}$、PM_{10} 浓度升高，COPD 患者入院概率增大，两者均在滞后 3d 时，其浓度对 COPD 住院人次的影响具有统计学意义。在滞后第 3d 时，将大气污染物 SO_2、CO、NO_2、O_3 与 $PM_{2.5}$、PM_{10} 纳入双污染物模型，结果为调整 NO_2 或 SO_2 后，$PM_{2.5}$ 效应仍有统计学意义（P<0.05）；调整 CO 和 O_3 后，$PM_{2.5}$ 效应无统计学意义（P>0.05）。在调整 SO_2、CO、NO_2、O_3 后，PM_{10} 效应仍有统计学意义（P<0.05）。Malig BJ 等的关于大气颗粒物对呼吸系统疾病入院率的研究显示：大气粗颗粒物浓度每日升高 10 μg/m³，支气管哮喘急诊入院率增加 0.7%，COPD 急诊入院率增加 2.0%[23]。一项关于北京市大气细颗粒污染物与老年呼吸系统疾病急诊就医关系的研究显示，滞后 0 天对 COPD 急诊就医的 OR 值影响最大，细颗粒污染物日升高 10 μg/m³，其 OR 值为 1.035[24]。不同研究发现[25,26]，不同累积滞后的天数与大气污染对呼吸系统疾病就诊率的影响不尽相同，这可能与不同地区的大气污染物的组成成分及含量不尽相同有关，组成成分及浓度差异对机体免疫系统和呼吸系统疾病的发展过程的影响不同，也可能与各国家、各地区的气象条件及 COPD 的诊断标准和住院标准的差异有关。

本研究在性别分层的研究显示：$PM_{2.5}$、PM_{10} 的浓度在女性患者中更明显，其原因可能是我国女性吸烟比例较小，故女性患者对大气颗粒物较敏感[27]，另有学者认为，性别导致生理结构的差异，颗粒物的沉积模式不同而导致效应的差异[28]。年龄分层的研究显示：≥75 岁患者对大气颗粒物更敏感，由于老年人常常合并冠心病、糖尿病等基础疾病，并且免疫力低下，所以

此类人群对大气颗粒物更敏感[29,30]。

本研究存在一些局限性。首先,COPD 的诊断标准多样,急性加重的标准略有不同,有些 AECOPD 患者的维持治疗已不能缓解现有的症状,但由于路途遥远或医疗资源短缺等原因不能及时就诊,选择在家及个体门诊治疗,因而降低了实际入院人数,给统计工作带来不便。其次,COPD 患者从急性加重到入院治疗存在时间差异,难以准确估计患者与大气颗粒物的接触时间与滞后时间。最后,本研究仅纳入张家口市两家三甲医院,未能纳入其他就诊二级医院的患者,可能无法完全反映大气颗粒物对 COPD 住院人次的影响,故研究具有一定的局限性。

综上所述,大气颗粒物污染会增加 COPD 住院人次,≥ 75 岁的老年患者以及女性患者更敏感。

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