Long-Term Exposure to Air Pollution and Increased Risk of Membranous Nephropathy in China

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ABSTRACT

The effect of air pollution on the changing pattern of glomerulopathy has not been studied. We estimated the profile of and temporal change in glomerular diseases in an 11-year renal biopsy series including 71,151 native biopsies at 938 hospitals spanning 282 cities in China from 2004 to 2014, and examined the association of long-term exposure to fine particulate matter of <2.5 μm ($PM_{2.5}$) with glomerulopathy. After age and region standardization, we identified IgA nephropathy as the leading type of glomerulopathy, with a frequency of 28.1%, followed by membranous nephropathy (MN), with a frequency of 23.4%. Notably, the adjusted odds for MN increased 13% annually over the 11-year study period, whereas the proportions of other major glomerulopathies remained stable. During the study period, 3-year average $PM_{2.5}$ exposure varied among the 282 cities, ranging from 6 to 114 $\mu g/m^3$ (mean, 52.6 $\mu g/m^3$). Each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration associated with 14% higher odds for MN (odds ratio, 1.14; 95% confidence interval, 1.10 to 1.18) in regions with $PM_{2.5}$ concentration >70 $\mu g/m^3$. We also found that higher 3-year average air quality index was associated with increased risk of MN. In conclusion, in this large renal biopsy series, the frequency of MN increased over the study period, and long-term exposure to high levels of $PM_{2.5}$ was associated with an increased risk of MN.

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Glomerular disease remains the leading cause of ESRD in Asia.[1–3] Published studies have shown geographical and racial variations in the patterns of glomerular diseases.[4–9] IgA nephropathy (IgAN) is the most common primary glomerulopathy in Asia, Europe, Australia, and some regions of the United States.[6,9–14] However, recent studies, mostly from Europe and Australia, have suggested a temporal change in the pattern of glomerular disease. In these studies, FSGS is increasing in incidence and has emerged as the most common

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primary glomerulopathy in some countries.[6,13,15] The temporal change in the pattern of primary glomerulopathy, especially within comparable ethnic groups in different countries, suggests the presence of unidentified environmental factors that have clinically significant effects on primary glomerular disease. However, no published studies have evaluated the effect of environmental factors on the changing pattern of glomerular diseases.

China comprises 20% of the world population. With rapid developments in its economy and urbanization, especially during the past decade, air pollution has become a public health problem in some cities.[16] Exposure to air pollution, especially particulate matter of <2.5 μm ($PM_{2.5}$), has been associated with increased death and incidence of cardiovascular events.[17–19] Animal studies have shown that exposure to fine particulate promotes the production of autoantibodies and immune complexes and results in immune dysregulation[20,21] which is implicated in the pathogenesis of some glomerulopathies. These findings led us to hypothesize that long-term exposure to air pollution may cause temporal changes in the profile of glomerulopathy in China. To date, the nationwide trend and composition of glomerulopathies has not been described, although several single-center biopsy series have reported the frequency of glomerular disease in China.[11,22]

In this study, we analyzed data from an 11-year renal biopsy series including 71,151 patients from 938 hospitals in 282 cities across China, encompassing all age groups and both tertiary and community hospitals, to evaluate the nationwide composition and secular pattern of glomerular diseases. We further examined the association between long-term exposure to $PM_{2.5}$ and specific types of glomerular diseases.

RESULTS

Study Participants

The study sample consisted of 71,151 independent cases with biopsy-proven glomerular diseases, from 938 hospitals across China (Supplemental Figure 1). The demographic and clinical characteristics of the series are presented in Table 1. The study population comprised mainly young to middle-aged adults (89%), with an average age of 37.3 years, split equally in gender but imbalanced in geographical presentation, hospital level, and year of biopsy. Over the study period, the numbers of biopsy patients and hospitals performing biopsy significantly increased. The percentage of patients aged >65 years increased from 3.3% in the period 2004 to 2006, to 6.0% in the period 2013 to 2014. Nephrotic syndrome (45.4%) and urinary abnormality (40.4%) were the most common indications for biopsy. The percentage of patients that received a biopsy due to nephrotic syndrome gradually increased, while those that were performed due to urinary abnormality decreased during the study period.

Composition and Secular Pattern of Glomerulopathy

Of the 70,626 patients with single glomerular disease, 77.5% had primary glomerulopathy. The disease spectrum varied with age (Table 2). After age and region standardization, IgAN was the most common glomerulopathy during the study period, accounting for 36.3% of the primary glomerulopathies, followed by membranous nephropathy (MN; 30.2%). MN was the leading cause of nephrotic syndrome in adults aged >40 years, while minimal change disease (MCD) was the most common histologic diagnosis among those aged ≤ 39 years (Table 3).

There was a remarkable rising trend in the frequency of MN over the period 2004 to 2014, while the frequencies of the other major glomerulopathies remained stable (Figure 1). The rising trend in MN was observed among all age groups and in all regions (Supplemental Figure 2). Estimated by a generalized additive model with adjustments for age, gender, geographic region, pathologic laboratory, level of hospital for biopsy, and clinical syndrome, the frequency of MN doubled from 2004 (12.2%) to 2014 (24.9%). On average, the odds of MN increased by 13% annually (odds ratio [OR], 1.13; 95% confidence interval [95% CI], 1.12 to 1.15).

During the year of 2014, a total of 399 patients with biopsy-proven MN without features of secondary disease had been tested for glomerular deposits of phospholipase A2 receptor, of which 332 (83%) were positive, validating the diagnosis of primary MN.

Air Pollution and Increased Frequency of MN

Frequency of MN varied greatly among geographical regions (Figure 2A). In our study, the frequency of MN was higher in the northern region, especially in Hebei province, the most polluted area in China (Figure 2B). This finding led us to hypothesize that air pollution might be associated with increased risk of MN. The 3-year average $PM_{2.5}$ derived from the aerosol optical depth (AOD) data[23] among the 282 cities ranged from 6 to 114 $\mu g/m^3$ from 2004 to 2014 (Supplemental Table 1). The study-wide mean $PM_{2.5}$ level increased from 45.9 $\mu g/m^3$ in 2004 to 55.7 $\mu g/m^3$ in 2008 and was slightly reduced afterwards. The average annual increase in $PM_{2.5}$ concentration ($PM_{2.5}$ slope) was 0.85 $\mu g/m^3$ per year, with the highest increase (3.2 $\mu g/m^3$ per year) observed in the cities in Hebei province.

Higher levels of $PM_{2.5}$ exposure were associated with an increased risk of MN after adjusting for confounders including age, gender, geographic region, level of hospital for biopsy, pathologic laboratory, clinical syndrome, and year of biopsy (Figure 2C). The relationship appeared to be nonlinear: each increase of 10 $\mu g/m^3$ was associated with 14% higher odds for MN (OR, 1.14; 95% CI, 1.10 to 1.18) at $PM_{2.5}$ concentration above 70 $\mu g/m^3$; the curve was flat at $PM_{2.5}$ below 70 $\mu g/m^3$ (OR, 1.02; 95% CI, 0.99 to 1.04). The annual increase in odds for MN was greater in the cities with a higher $PM_{2.5}$ slope even after adjusting for geographic region (P=0.03) (Figure 2D, Supplemental Figure 3). Assuming a causal relationship, 15.2% of MN in China could be attributable to $PM_{2.5}$ air pollution exposure.

As a validation to the exposure measurement, similar associations of MN with 3-year average air quality index

Table 1. Demographic and clinical characteristics of the biopsy series

Characteristics	2004–2006 *n*=4007	2007–2008 *n*=3335	2009–2010 *n*=6543	2011–2012 *n*=18,964	2013–2014 *n*=38,302	Total *n*=71,151
Gender						
Male	1935 (48.3)	1652 (49.5)	3179 (48.6)	9392 (49.5)	19,483 (50.9)	35,641 (50.1)
Female	2072 (51.7)	1683 (50.5)	3364 (51.4)	9572 (50.5)	18,819 (49.1)	35,510 (49.9)
Age, yr						
0–14	495 (12.3)	329 (9.9)	327 (5.0)	996 (5.3)	2018 (5.3)	4165 (5.9)
15–39	2175 (54.2)	1892 (56.7)	3845 (58.8)	9975 (52.6)	17,587 (45.9)	35,474 (49.9)
40–64	1205 (30.1)	994 (29.8)	2116 (32.4)	7125 (37.6)	16,415 (42.9)	27,855 (39.1)
65–99	132 (3.3)	120 (3.6)	255 (3.9)	868 (4.6)	2282 (6.0)	3657 (5.1)
Age, mean (SD)	33.2 (15.7)	33.6 (15.5)	35.3 (15.1)	36.6 (15.5)	38.8 (16.1)	37.3 (15.9)
Region						
Central	694 (17.4)	541 (16.4)	807 (14.0)	2871 (15.3)	5057 (13.4)	9970 (14.3)
East	1729 (43.3)	1201 (36.5)	1299 (22.5)	3877 (20.6)	8604 (22.8)	16,710 (24.0)
North	0 (0.0)	0 (0.0)	1 (0.0)	746 (4.0)	3829 (10.1)	4576 (6.6)
South	1525 (38.2)	1144 (34.7)	2995 (51.9)	7894 (42.0)	12,539 (33.2)	26,097 (37.5)
West	42 (1.1)	407 (12.4)	670 (11.6)	3427 (18.2)	7756 (20.5)	12,302 (17.7)
Hospital level						
Tertiary class A	3703 (92.9)	3000 (91.1)	4673 (81.0)	14,106 (75.0)	29,040 (76.9)	54,522 (78.3)
Tertiary class B	121 (3.0)	85 (2.6)	296 (5.1)	2372 (12.6)	4529 (12.0)	7403 (10.6)
Secondary	163 (4.1)	208 (6.3)	803 (13.9)	2337 (12.4)	4216 (11.2)	7727 (11.1)
Hospital, *N*	50	42	139	507	800	938
Clinical syndrome						
NS	1094 (27.3)	1100 (33.0)	2641 (40.4)	8838 (46.6)	18,626 (48.6)	32,299 (45.4)
NS+AKI	95 (2.4)	127 (3.8)	211 (3.2)	643 (3.4)	1167 (3.0)	2243 (3.2)
AKI	97 (2.4)	61 (1.8)	138 (2.1)	318 (1.7)	708 (1.8)	1322 (1.9)
Progressive CKD	613 (15.3)	488 (14.6)	748 (11.4)	1498 (7.9)	3188 (8.3)	6535 (9.2)
Proteinuria	1685 (42.1)	1294 (38.8)	2522 (38.5)	6968 (36.7)	13,567 (35.4)	26,036 (36.6)
Isolated hematuria	423 (10.6)	265 (7.9)	283 (4.3)	699 (3.7)	1046 (2.7)	2716 (3.8)

All cells are expressed as *N* (% within year strata). NS, nephrotic syndrome.

(AQI) during 2012 to 2014 and average $PM_{2.5}$ level measured by local monitors during 2014 were also observed (Figure 2, E and F).

DISCUSSION

To our knowledge, this is the first and the largest study of a nationwide biopsy series to examine the effect of air pollution on the changing pattern of glomerular diseases in China. Among 71,151 native renal biopsies encompassing all age groups from both tertiary and community hospitals across the country, we found a remarkable rise in the proportion of MN over a period of 11 years from 2004 to 2014. We also found that long-term (3-year average) exposure to high levels of $PM_{2.5}$ was associated with an increased risk of idiopathic MN, an autoimmune glomerulonephropathy involving the formation of circulating autoantibodies and immune complex deposits in the kidney.[24]

In this study, we compared the frequencies of various glomerular diseases among age groups and clinical syndromes. IgAN was the most frequent glomerular disease with an age- and region-standardized frequency of 28.1% during the study period, accounting for 36.3% of all primary glomerulopathies. This is consistent with other studies from Asia, Australia, Europe, and some regions of the United States.[11–14] Interestingly, MN emerged as the most frequent biopsy finding in patients aged >40 years. An age- and region-standardized frequency of MN was recorded in 23.4% of all biopsies, second in frequency to IgAN. A high frequency of MN has been reported in multiple studies of the elderly, especially those aged >65 years.[5,10,25] In our series, nephrotic syndrome was the indication for biopsy in 45.4% of the population. MN was the leading cause of nephrotic syndrome in adults aged >40 years, while MCD was the most common histologic diagnosis among those aged ≤39 years.

An important finding from this study is the remarkable rising trend in the frequency of MN over the past decade. From 2004 to 2014, the adjusted frequency of MN increased from 12.2% to 24.9% in this Chinese population. The risk for MN increased 13% annually in a regression analysis with adjustments for the confounders, including age and clinical characteristics. Projected from this trend, MN would soon pass IgAN to become the leading type of nephropathy in China. Although these results need to be interpreted in the context of an increasingly aggressive diagnostic approach to glomerular disease, this is unlikely to be the main cause for the increasing trend in MN frequency due to the following reasons. First, in

Table 2. Glomerulopathies by age strata

Glomerulopathy Type	Biopsy, *N*	*N* (% within Age Strata)					Std. Freq. %
		0–14 yr	15–39 yr	40–64 yr	65–99 yr	All Ages	
Primary							
IgAN	19,959	709 (17.2)	12,719 (36.0)	6258 (22.7)	273 (7.5)	19,959 (28.3)	28.1
MN	14,929	135 (3.3)	4386 (12.4)	8781 (31.9)	1627 (45.0)	14,929 (21.1)	23.4
MCD	11,810	841 (20.4)	7018 (19.9)	3460 (12.6)	491 (13.6)	11,810 (16.7)	17.1
FSGS	3811	238 (5.8)	1829 (5.2)	1498 (5.4)	246 (6.8)	3811 (5.4)	5.5
MsPGN	2321	213 (5.2)	1033 (2.9)	1003 (3.6)	72 (2.0)	2321 (3.3)	3.2
MPGN	485	10 (0.2)	142 (0.4)	274 (1.0)	59 (1.6)	485 (0.7)	0.7
Secondary							
Lupus GN	6013	335 (8.1)	3872 (11.0)	1739 (6.3)	67 (1.9)	6013 (8.5)	7.4
Purpura GN	2308	791 (19.1)	1011 (2.9)	430 (1.6)	76 (2.1)	2308 (3.3)	3.4
TBMN	1600	432 (10.5)	592 (1.7)	557 (2.0)	19 (0.5)	1600 (2.3)	2.0
DN	1235	0 (0.0)	176 (0.5)	925 (3.4)	134 (3.7)	1235 (1.7)	1.7
HBVAN	1032	29 (0.7)	533 (1.5)	439 (1.6)	31 (0.9)	1032 (1.5)	1.4
Amyloidosis	536	0 (0.0)	18 (0.1)	352 (1.3)	166 (4.6)	536 (0.8)	0.8
Unclassified	1013	108 (2.6)	474 (1.3)	393 (1.4)	38 (1.1)	1013 (1.4)	1.4

Std. Freq., age- and region-standardized frequency; MsPGN, mesangial proliferative GN; MPGN, membranoproliferative GN (type 1); Lupus GN, lupus nephritis; Purpura GN, Henoch-Schonlein purpura nephritis; TBMN, thin basement membrane nephropathy; DN, diabetic nephropathy; HBVAN, hepatitis B virus-associated nephritis.

Table 3. Top glomerulopathies by clinical syndromes and age groups

Clinical Syndrome	*N*	Top 1	Top 2	Top 3
0–14 yr				
NS	1598	MCD (45.6)	IgAN (14.0)	FSGS (10.1)
NS+AKI	68	MCD (39.7)	Lupus GN (17.6)	EnPGN (11.8)
AKI	46	EnPGN (30.4)	Lupus GN (28.3)	IgAN (8.7)
Progressive CKD	80	IgAN (20.0)	FSGS (18.8)	Lupus GN (15.0)
Proteinuria	1689	Purpura GN (35.9)	IgAN (20.7)	Lupus GN (9.9)
Isolated hematuria	650	TBMN (57.4)	IgAN (17.2)	Purpura GN (8.8)
15–39 yr				
NS	14,891	MCD (40.7)	MN (22.0)	IgAN (13.0)
NS+AKI	1035	MCD (40.7)	Lupus GN (26.7)	IgAN (10.1)
AKI	572	Lupus GN (32.2)	IgAN (22.6)	MHPT (12.8)
Progressive CKD	2807	IgAN (64.3)	FSGS (8.3)	Lupus GN (6.8)
Proteinuria	14,729	IgAN (55.0)	Lupus GN (11.4)	MN (7.1)
Isolated hematuria	1275	IgAN (50.1)	TBMN (35.8)	Purpura GN (4.0)
40–64 yr				
NS	13,309	MN (50.4)	MCD (19.7)	IgAN (7.4)
NS+AKI	908	MCD (46.4)	Lupus GN (14.4)	FSGS (9.1)
AKI	557	AASV (22.6)	Lupus GN (18.9)	IgAN (12.7)
Progressive CKD	3151	IgAN (51.1)	FSGS (10.1)	DN (6.0)
Proteinuria	8907	IgAN (37.3)	MN (20.9)	MsPGN (9.5)
Isolated hematuria	737	TBMN (55.8)	IgAN (27.0)	Lupus GN (3.3)
65–99 yr				
NS	2276	MN (58.0)	MCD (15.2)	Amyloidosis (6.1)
NS+AKI	210	MCD (45.7)	MN (14.8)	FSGS (12.9)
AKI	131	AASV (35.1)	CreGN (19.1)	Anti-GBM (6.9)
Progressive CKD	392	IgAN (23.2)	FSGS (12.8)	MN (11.5)
Proteinuria	579	MN (39.0)	IgAN (13.8)	MsPGN (8.6)
Isolated hematuria	29	TBMN (44.8)	IgAN (31.0)	AASV (10.3)

The bracketed numbers indicate percentage within age and clinical syndrome strata. NS, nephrotic syndrome; lupus GN, lupus nephritis; EnPGN, endocapillary proliferative GN; purpura GN, Henoch-Schonlein purpura nephritis; TBMN, thin basement membrane nephropathy; MHPT, malignant hypertension; AASV, anti-neutrophil cytoplasmic antibody associated systemic vasculitis; DN, diabetic nephropathy; MsPGN, mesangial proliferative GN; CreGN, crescentic GN; Anti-GBM, anti-glomerular basement membrane antibody disease.

our regression analysis of the trend, we adjusted for confounders including age, gender, region, clinical syndrome, pathologic laboratory, and hospital level for biopsy. Hence, the effects of aging and increased frequency in nephrotic syndrome in the biopsy population were already controlled. Second, the proportion of other major biopsy-proven glomerulopathies remained fairly stable during the study period, and the proportion of secondary MN, such as lupus nephritis and hepatitis B-associated nephritis, did not show a similar trend in the same population. Consistent with the previous reports,[26] most of the MN in our study were phospholipase A2 receptor-related, validating the diagnosis of primary MN. Third, there has been consistency in both the pathologic procedures and interpretations of biopsy specimens in the pathologic centers in charge of histologic diagnosis, and there were no substantial changes in the diagnosis of MN or differentiation of MN from other primary glomerular disease over the study period.

The large biopsy series with a wide coverage of 282 cities across China allowed us to examine the effect of exposure to air pollution on the risk of MN in the country. From 2004 to 2014, 3-year average levels of AOD-derived $PM_{2.5}$ in the study cities have been increasing up to a plateau in 2008 (Supplemental Table 1). In 2008,

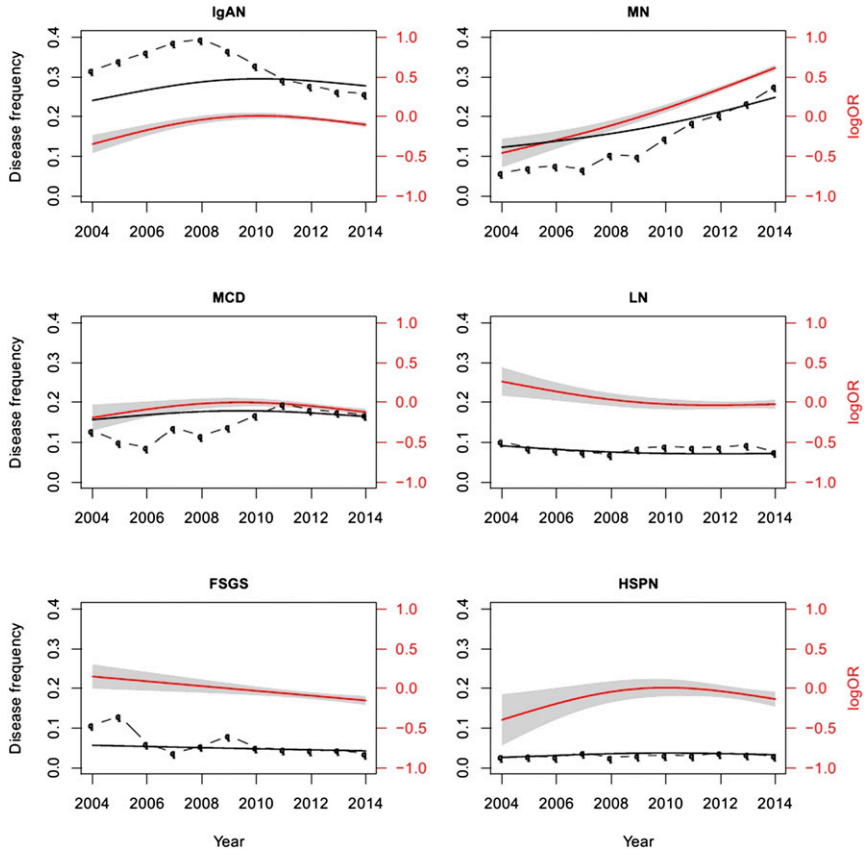

Figure 1. Trends in frequency of the most common glomerulopathies in China from 2004 to 2014. Open circles represent the unadjusted disease proportions among all glomerulopathies. Solid lines indicate the disease proportions estimated from generalized additive logistic models adjusted for age, gender, clinical syndromes, hospital type, pathologic laboratory, and region and weighted by regional population. Red lines and the corresponding gray zones, specify the ORs of the disease and their 95% CIs estimated from the generalized additive model with year 2009 as the reference.

levels of $PM_{2.5}$ exposure varied from 8.1 to 110.5 $\mu g/m^3$ among the study cities with a mean of 55.6 $\mu g/m^3$. This level was much higher than that in many developed countries, such as the United States (mean, 12 $\mu g/m^3$), the United Kingdom (mean, 14 $\mu g/m^3$), and Japan (mean, 10 $\mu g/m^3$), and was comparable to developing countries such as India (mean, 59 $\mu g/m^3$).[27] Most importantly, we found that long-term exposure to high levels of $PM_{2.5}$ was associated with an increased risk of MN after controlling for confounders including age, gender, region, year of biopsy, pathologic laboratory, level of hospital for biopsy, and clinical syndrome. Each increase of 10 $\mu g/m^3$ was associated with 14% higher odds for MN (OR, 1.14; 95% CI, 1.10 to 1.18) in regions with $PM_{2.5}$ concentrations above 70 $\mu g/m^3$. Similar associations of MN with 3-year average AQI and $PM_{2.5}$ level measured by local monitors were also observed. The annual increase in odds for MN was greater in the cities with higher $PM_{2.5}$ slopes, even after adjusting for geographic region (P=0.03), though *per capita* disposable income, and educational and health care resources were comparable among these cities (Supplemental Table 2). Similarly, a previous study showed that neither education level nor household income significantly modified the relationship between air pollution and cardiovascular disease.[17] It is noteworthy that a rising trend in MN was also reported in India,[28] a country with a high level of environmental exposures. In comparison, MN was shown to be declining in other East Asian countries with low exposure levels, such as Japan[29] and Korea.[30]

The mechanism(s) by which long-term exposure to fine particulate air pollution may increase the risk of MN remains to be elucidated. MN has been recognized as an autoimmune disease characterized by the formation of circulating autoantibodies and subepithelial immune complex deposits in the kidney.[24] Animal studies have shown that exposure to fine particulate promotes the production of autoantibodies and immune-complexes.[20,21] It has been hypothesized that cytokines generated in the airways in response to air pollution can spill over into the circulation, influencing autoimmune responses and distant events.[31] Supporting this notion, air pollution increases the circulating levels of inflammation mediators such as TNF-α, IL-6, and plasminogen activator inhibitor-1,[21,32,33] and genetic polymorphisms in these cytokines are associated with the development of MN.[34–38] It would also be interesting to test the existence of any interactions between $PM_{2.5}$ exposure and the genetic polymorphisms implicated in MN.[39]

There were limitations in our study. First, our study was based on a renal biopsy series. Without registry data or sampling information for the biopsy specimens, we were not able to estimate the biopsy rate or incidence of glomerulopathy in the general population. However, under the setting of no temporal changes in the incidences of other glomerulopathies, an increased frequency of MN implies increased incidence of the disease. Second, information on patient residence was limited to the city level. As a result, we used citywide averages of $PM_{2.5}$ to approximate the individual exposures in the analysis, which may have led to an underestimation of the effect of $PM_{2.5}$. The large number of cities included in our study and the great variation in $PM_{2.5}$ levels among these cities should have helped to alleviate this problem. Third, the $PM_{2.5}$ data we used in the analysis was not directly measured but derived from the satellite AOD. However, we found similar patterns of association between MN and the ground-based $PM_{2.5}$ levels as well as AQIs in our analysis (Figure 2, E and F). A good agreement between AOD-derived and ground-based $PM_{2.5}$ levels has also been reported previously.[23] Finally, our study investigated the long-term (3-year) effect of $PM_{2.5}$ in a population with an unusually high level of exposure; the results

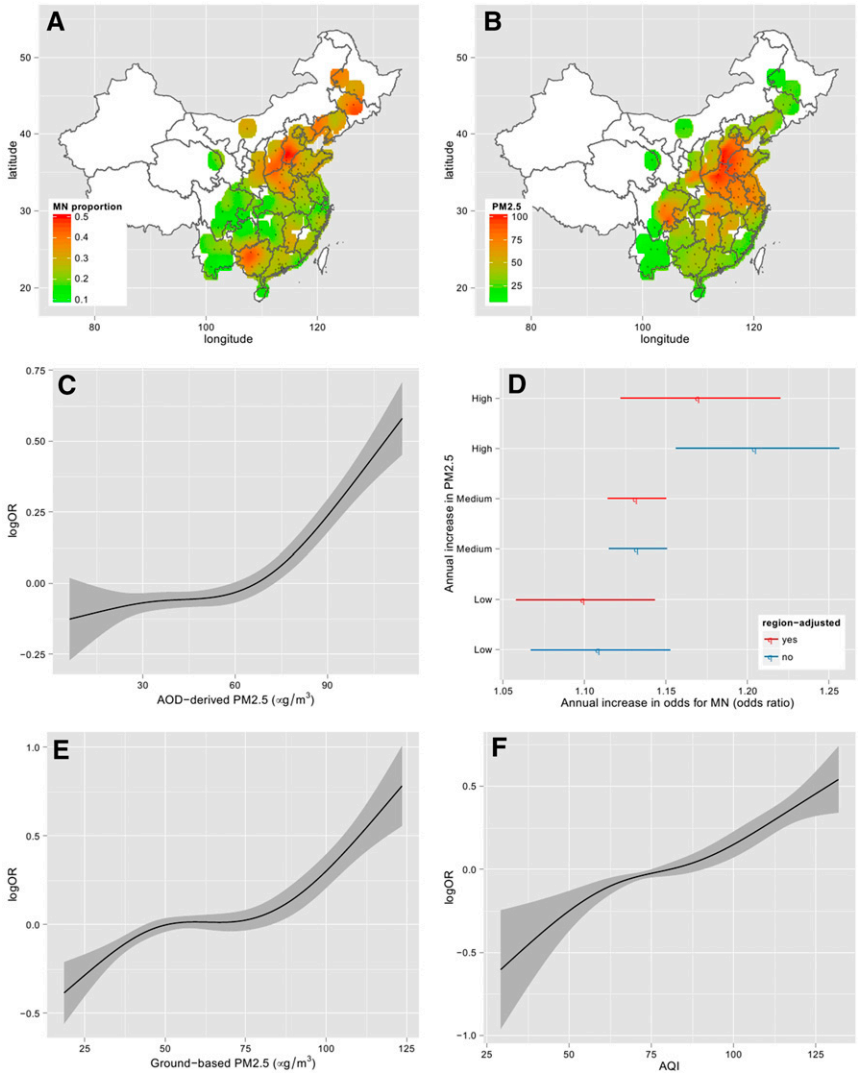

Figure 2. $PM_{2.5}$ was associated with odds for MN. (A) Two-dimensional smoothed map of the age- and gender-adjusted proportion of MN in 2014. Dots represent the locations of the hospitals performing the renal biopsies. (B) Map of 10-year average of $PM_{2.5}$ derived from satellite AOD. (C, E, and F) Smooth curves of the odds for MN along AOD-based $PM_{2.5}$ (C), ground-based $PM_{2.5}$ in 2014 (E), and average AQIs during 2012–2014 (F), respectively. The gray zones denote the 95% CI. (D) Average annual increases in odds for MN stratified by levels of $PM_{2.5}$ slope (rate of annual $PM_{2.5}$ increase), as estimated from the generalized additive models with adjustment for age, gender, clinical syndromes, hospital level, and pathologic laboratory, and with or without adjustment for region.

may not be ascribed to a short-term effect or generalized to a lower level of exposure.

We confirmed a significant rising trend in the frequency of MN, which in our data was second only to IgAN as the leading type of glomerular disease in China. We provided evidence for the association between long-term exposure to $PM_{2.5}$ and risk for MN, especially at a high level of exposure. Our results call for further investigation on this topic using animal models and population-based prospective cohort studies.

CONCISE METHODS

Data Source

We collected data from six central pathologic laboratories on 75,163 renal biopsies from 938 hospitals spanning 282 cities across China, over an 11-year period from January 2004 to December 2014. The data, which was extracted from referral records and pathologic reports of renal biopsies, included: age, gender, city of residence, date and hospital performing the biopsy, clinical syndrome, laboratory measurements, and histologic diagnosis. In the current analysis, we excluded the patients without histologic diagnosis (374), those with repeated biopsies (714) and kidney graft (250), and those with missing demographic or clinical data (927). We further excluded the patients with isolated tubulointerstitial renal diseases (1747). The remaining 71,151 independent native biopsies with glomerular disease were subsequently analyzed. The Medical Ethics Committee of Nanfang Hospital, Southern Medical University approved the study protocol and waived patient consent.

Histologic Specimens and Diagnosis

All renal biopsies were processed and assessed at six central pathologic laboratories. Biopsy specimens were routinely analyzed by light microscopy and immunohistologic assays. In addition, 64% of the biopsy specimens in the series were also examined by electron microscopy. The histologic results were interpreted by six leading histopathologists. The histologic findings were classified according to the "Revised Protocol for the Histological Typing of Glomerulopathy" (WHO,1995)[40] and categorized into primary, secondary, mixed (patients with two concurrent glomerular diseases), and unclassified glomerular diseases. The primary glomerular diseases included IgAN, MN, MCD, FSGS, mesangial proliferative GN, membranoproliferative GN type 1, and others.

Data on Air Pollution Exposure

We obtained the 3-year average $PM_{2.5}$ grid data from 2004 to 2012, derived from satellite AOD at a resolution of 0.1×0.1 degrees (longitude by latitude),[23] from the Socioeconomic Data and Applications Center, National Aeronautics and Space Administration. In the current study, we estimated long-term exposure to $PM_{2.5}$ as the mean of the 3-year average $PM_{2.5}$ levels prior to the year of biopsy within an area of 1×1 degrees centered on the city of residence. In years 2013 and 2014, the $PM_{2.5}$ data were not available and were substituted by the $PM_{2.5}$ data for 2012.

$PM_{2.5}$ data from local monitors in many cities were not publically available until late 2013. We were able to obtain monthly averages of locally measured $PM_{2.5}$ levels in 145 study cities during 2014, and

used the yearly average in the analysis. The 3-year average AQIs of 162 cities in China from 2012 to 2014 were calculated from the daily AQIs reported by the Ministry of Environmental Protection of China (http://datacenter.mep.gov.cn). AQI uses whichever pollutant is the highest on the day, so it is not specific to a single pollutant. Nevertheless, $PM_{2.5}$ was the principal pollutant on two thirds of the days with AQI≥100 during 2012 to 2014. The average AQIs of the cities without actual measurements were estimated by two-dimensional (longitude and latitude) smoothing of the AQI in nearby cities using the 'mgcv' R package.[41]

Statistical Analyses

We calculated the frequency of each glomerulopathy among all biopsy-proven glomerular diseases excluding mixed glomerular diseases. We used the age structure in the total biopsy population as the reference to calculate the age-adjusted frequency of each glomerulopathy in a region, and derived the overall standardized frequency as the average of all region-specific and age-adjusted frequencies weighted by the population sizes of the regions. We used a generalized additive logistic model to estimate the trend in frequency of each glomerulopathy (change in odds for the glomerulopathy and the corresponding proportion among patients with biopsy) during the study period with adjustments for age, gender, region, pathologic laboratory, hospital level, and clinical syndrome. We also used a generalized additive logistic model to estimate the effects of 3-year average $PM_{2.5}$ level on MN with adjustments for age, gender, region, pathologic laboratory, hospital level, year of biopsy, and clinical syndrome. We sought to confirm the association between air pollution and MN under the same statistical model, using the 3-year average AQI from 2012 to 2014 and the average $PM_{2.5}$ level measured by local monitors during 2014, respectively, as the pollution exposures, and limiting the biopsy series to 2012 to 2014. We estimated the population attributable fraction of $PM_{2.5}$ on MN empirically as the percentage of reduction in MN frequency under the generalized additive model if $PM_{2.5}$ exposure was reduced to 10 $\mu g/m^3$. We calculated the rate of annual change in $PM_{2.5}$ ($PM_{2.5}$ slope) in an area as the slope of a simple linear regression of $PM_{2.5}$ with calendar year during the period 2004–2012. We divided 282 cities into "low", "medium", and "high" groups by $PM_{2.5}$ levels and $PM_{2.5}$ slopes, respectively, using the corresponding 25th and 75th percentiles as the cutoffs. We compared the annual increases in odds for MN among different levels of $PM_{2.5}$ and $PM_{2.5}$ slope using the logistic regression model with adjustments for age, gender, region, pathologic laboratory, hospital level, and clinical syndrome. We used R version 3.2.0 for the statistical analyses, and, more specifically, the "mgcv" package version 1.8–6 for the generalized additive model.[41]

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DISCLOSURES

None.

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