Impact of Exposure to Ambient Fine Particulate Matter Pollution on Adults with Knee Osteoarthritis

Hongbo Chen 1,2, Junhui Wu 1*, Mengying Wang 1, Siyue Wang 1, Jiating Wang 1, Huan Yu 1, Yonghua Hu 1,3,* and Shaoemei Shang 2,*

1 Department of Epidemiology and Biostatistics, School of Public Health, Peking University, No. 38 Xueyuan Road, Beijing 100191, China; chenhongbo@bjmu.edu.cn (H.C.); jhsophie@163.com (J.W.); mywang@bjmu.edu.cn (M.W.); siyue.wang@pku.edu.cn (S.W.); jiating@pku.edu.cn (J.W.); yuhh@pku.edu.cn (H.Y.)
2 School of Nursing, Peking University, China, No. 38 Xueyuan Road, Beijing 100191, China
3 Medical Informatics Center, Peking University, No. 38 Xueyuan Road, Beijing 100191, China
* Correspondence: yhhu@bjmu.edu.cn (Y.H.); shangshaomei@126.com (S.S.)

Abstract: The impact of exposure to fine particulate matter (PM$_{2.5}$) on the incidence of knee osteoarthritis is unclear, especially in Beijing which is a highly polluted city. We conducted a time-series study to examine the correlation between PM$_{2.5}$ exposure and outpatient visits for knee osteoarthritis in Beijing. Changes (in percentage) in the number of outpatient visits corresponding to every 10-µg/m$^3$ increase in the PM$_{2.5}$ concentration were determined using a generalized additive quasi-Poisson model. There were records of 9,797,446 outpatient visits for knee osteoarthritis in the study period from 1 January 2010 to 31 December 2017. The daily concentration of PM$_{2.5}$ was 86.8 (74.3) µg/m$^3$ over this period. A 10-µg/m$^3$ increase in PM$_{2.5}$ concentrations on lag days 0–3 was associated with a 1.41% (95% confidence interval: 1.40–1.41%) increase in outpatient visits for knee osteoarthritis. Females and patients aged above 65 years were more sensitive to the adverse effects of PM$_{2.5}$ exposure. The present findings demonstrate that short-term exposure to PM$_{2.5}$ resulted in an increase in the number of outpatient visits for knee osteoarthritis in Beijing. The findings shed light on the effects of air pollution on knee osteoarthritis and could guide risk-mitigating strategies in cities such as Beijing.

Keywords: knee osteoarthritis; fine particulate matter; air pollution; outpatients; time-series; China

1. Introduction

Knee osteoarthritis is a common joint disease that is associated with pain, loss of function and disability, and reduced quality of life [1]. Knee osteoarthritis affects approximately 250 million people globally, and the global prevalence of symptomatic knee osteoarthritis is 10.0–16.0% in adults aged above 60 years [2–5]. In 2016, China ranked tenth with regard to the number of years lived with disability (YLDs) as a result of osteoarthritis [6], and the Nordic nations ranked fifth with regard to the rate of increase in YLDs associated with osteoarthritis [7]. In fact, knee osteoarthritis is the most common kind of osteoarthritis, accounting for 87% of YLDs associated with osteoarthritis. In China, the number of total knee arthroplasty cases in 2018 was 249,000, which were associated with a total cost of about 12.948 billion yuan [8], making this disease a serious burden for the healthcare system. Therefore, it is important to understand the causative factors and mitigate the risk of knee osteoarthritis in the Chinese population.

The 2015 Global Burden of Diseases, Injuries, and Risk Factors Study (GBD 2015) identified air pollution as one of the main causes of the increase in global disease burden, especially in low- and middle-income countries [9]. Accordingly, in the last few years, mounting evidence has linked indoor/outdoor air pollution to musculoskeletal disease [10–13], and previous epidemiological studies have shown that environmental factors,
especially environmental pollution, may be specifically associated with an increased risk of knee osteoarthritis [14,15]. With regard to the underlying mechanism, air pollutants may cause oxidative stress in the lung, and this may lead to the production of a large number of antibodies and pro-inflammatory cytokines. Alternatively, air pollutants could also be genotoxic and induce epigenetic changes that may lead to cartilage erosion and synovial inflammation [16] and eventually cause the development of musculoskeletal disease [14]. In particular, fine particulate matter or PM$_{2.5}$, which is defined as particulate matter that has an aerodynamic diameter of $\leq 2.5$ µm, is the most harmful to human health, and it ranks fifth in the list of mortality risk factors [17]. Studies have confirmed that PM$_{2.5}$ is a risk factor for heart failure, asthma, ischemic stroke, allergic rhinitis, and other diseases [18–21]. In terms of musculoskeletal diseases, previous studies have indicated that exposure to high levels of PM$_{2.5}$ could increase the risk of osteoarthritis [15,22]. However, most of these previous studies used cell lines or animal models, or small population samples. Thus, there is a lack of large-scale population studies that explore the effect of PM$_{2.5}$ exposure on the risk of osteoarthritis.

As one of the largest developing countries in the world, China is witnessing accelerated industrialization and urbanization, which have led to a surge in air pollution. In 2016, the majority, that is, 81% of China’s population was exposed to PM$_{2.5}$ concentrations higher than the limit of 35% µg/m$^3$ set by the State Environmental Protection Administration [23]. In 2017, 8,51,660 (7,12,002–9,90,271) deaths in China were attributable to PM$_{2.5}$ pollution [24]. The air pollution crisis is particularly severe in Beijing [25] and needs to be addressed urgently. Therefore, this time-series study investigates whether short-term exposure to outdoor PM$_{2.5}$ is correlated with the number of outpatient visits for knee osteoarthritis in Beijing, China. We believe that this is the first such large-scale study on the association between PM$_{2.5}$ exposure and knee osteoarthritis in China.

2. Materials and Methods

2.1. Data on Outpatient Visits for Knee Osteoarthritis

We collected outpatient data on visits for knee osteoarthritis between 1 January 2010, and 31 December 2017, from Beijing’s Medical Claims for Employees (BMCDE) database. The database contains records of the medical claims of patients who have been availed of Urban Employee Basic Medical Insurance. Medical insurance for urban employees is the main type of medical insurance in Beijing, since rural inhabitants only form a small percentage of the population and the rate of employment is high. By the end of 2017, the number of beneficiaries included in the BMCDE database was 17.7 million, which is equivalent to nearly 80% of the city’s permanent residents. The database includes demographic data (sex and age), medical records (hospital name, hospital level, and dates of consultation), diagnosis in Chinese and diagnosis according to the criteria of the International Classification of Diseases (10th Revision [ICD-10]), diagnosis dates, and treatment costs. Detailed information from the database can be found in previous relevant studies [26,27].

This study is exempt from ethical approval since the BMCDE database does not contain any identifying information about the beneficiaries, and any traceable information we used was encrypted.

2.2. Environmental Data

Temperature and humidity data were obtained from the Chinese Meteorological Bureau. Hourly data were obtained for PM$_{2.5}$ concentration from an open-source report released by the US Embassy. According to previous studies, the PM$_{2.5}$ levels monitored by the US Embassy are roughly representative of the levels in the whole city, and can, therefore, be considered as proxy values for population exposure within a range of 40 km of the monitoring station [19,20,28]. This radius covers the majority of the tertiary hospitals, that is, 97.8% (44/45), and also the majority of the secondary hospitals (79.3% [69/87]) [29]. Previous literature has demonstrated the reliability of data from monitoring sites of the US
Embassy [19,30]. Real-time data on PM$_{2.5}$ concentrations were published by the national air quality monitoring network of China only from 2013. As a result, for the purpose of this study, the data were only obtained from the US Embassy. Specifically, we examined the correlation of the daily average concentration of PM$_{2.5}$ with the number of daily visits for knee osteoarthritis according to meteorological conditions.

2.3. Statistical Analysis

We conducted a time-series analysis of PM$_{2.5}$ exposure and outpatient visits for knee osteoarthritis (adjusted for meteorological factors). According to previous methods used for exploring the relationship between air pollution and health, a generalized additive quasi-Poisson model with the following formula was applied [29,31,32].

$$\log[E(Y_t)] = \alpha + \beta PM_{2.5} + \text{public holiday} + \text{day of the week} + ps(\text{calendar time, } 7 \text{ per year}) + ps(\text{temperature, } 6) + ps(\text{relative humidity, } 3)$$

In the above equation, E($Y_t$) is the anticipated number of daily adult outpatient visits for knee osteoarthritis on day $t$, and $ps()$ represents a penalized spline function. Public holidays and the day of the week were considered as categorical variables and were adjusted for. $\beta$ denotes the log value of the relative risk of knee osteoarthritis-related morbidity for every unit rise in the concentration of PM$_{2.5}$, and $\alpha$ denotes the intercept term. In order to verify the robustness of the results, we set various degrees of freedom for calendar time, relative humidity, and temperature based on findings from previous studies, and conducted sensitivity analysis on the results for different degrees of freedom [31].

Separate models were created for each lag day, from the day of outpatient visit (lag 0 days) to three days before the visit (lag 3 days), as well as multiple-day lags (lag 0–1 day, lag 0–2 days, and lag 0–3 days) to explore the exposure–response association between PM$_{2.5}$ and outpatient consultations for knee osteoarthritis [33]. Stratified analyses were conducted to detect the impact of age, sex, and meteorological conditions on knee osteoarthritis risk [34].

The “mgcv” and “nlme” packages of R3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for the statistical analyses in our study. Percentage change in the daily number of outpatient visits for knee osteoarthritis corresponding to a 10 µg/m$^3$ increase in the PM$_{2.5}$ concentration was expressed as a percentage with the 95% confidence interval (CI). A two-tailed $p$ value of $<$0.05 was considered to indicate statistical significance. Categorical variables were represented by their percentage values, and continuous variables, by their mean ± standard deviation values.

3. Results

3.1. Demographic Information

Table 1 presents the demographic data for outpatient visits for knee osteoarthritis. A total of 9,797,446 adult knee osteoarthritis outpatient visits were observed in the BMCDE database between 1 January 2010, and 31 December 2017, and 59.87% of the consultations were recorded in the cool season, that is, November to April. Additionally, 63.61% of the outpatients were female and 63.84% were elderly ($\geq$65 years).

| Variable          | All Year | Cool Season | Warm Season |
|-------------------|----------|-------------|-------------|
| Outpatient visits | 9,797,446| 5,865,689   | 3,931,757   |
| Sex               |          |             |             |
| Male(%)           | 3,565,162(36.39) | 2,140,860 (36.50) | 1,424,302 (36.23) |
| Female(%)         | 6,232,284 (63.61)| 3,724,829 (63.50) | 2,507,455 (63.77) |
| Age(year)         |          |             |             |
| 18–64(%)          | 6,254,770 (63.84)| 3,733,856 (63.66) | 2,520,914 (64.12) |
| $\geq$65(%)       | 3,542,676 (36.16)| 2,131,833 (36.34) | 1,410,843 (35.88) |
3.2. Daily Values of PM$_{2.5}$, Outpatient Visits for Knee Osteoarthritis, Temperature, and Humidity

Table 2 presents the mean (SD) values for daily knee osteoarthritis outpatient visits, PM$_{2.5}$ concentration, temperature, and relative humidity. The daily number of outpatient visits was 3354 (3700), and it ranged from 108 to 30,125. The daily PM$_{2.5}$ value was 86.8 (74.3) µg/m$^3$, and it ranged from 1.0 µg/m$^3$ to 537.3 µg/m$^3$. Over the study period of 2922 days, the daily PM$_{2.5}$ value was below the limit of 25 µg/m$^3$ set by the air quality guidelines of WHO only on 509 (17.4%) days [35]. The daily temperature was 14.6 °C (11.3 °C), and relative humidity, 51.8% (20.2%).

| Variable | Mean ± SD | Minimum | Percentile 25th | Percentile 50th | Percentile 75th | Maximum | IQR |
|----------|-----------|---------|----------------|----------------|----------------|---------|-----|
| Daily outpatient visits | 3354 ± 3700 | 108 | 324 | 2406 | 4684 | 30,125 | 4360 |
| PM$_{2.5}$(µg/m$^3$) | 86.8 ± 74.3 | 1.0 | 33.3 | 66.5 | 115.0 | 537.3 | 81.7 |
| Daily outpatient visits during the cool season | 3457 ± 4074 | 108 | 116 | 2324 | 4960 | 30,125 | 4844 |
| Daily outpatient visits during the warm season | 3212 ± 3103 | 133 | 942 | 2492 | 4287 | 14,596 | 3345 |
| Temperature (°C) | 14.6 ± 11.3 | −14.3 | 2.6 | 15.1 | 24.0 | 34.5 | 21.4 |
| Relative humidity (%) | 51.8 ± 20.2 | 8 | 35 | 52 | 68 | 88 | 33 |

IQR: interquartile range, SD: standard deviation.

3.3. Changes in the Number of Outpatient Visits According to PM$_{2.5}$ Concentration

Table 3 shows the percentage changes in outpatient visits for knee osteoarthritis corresponding to each 10-µg/m$^3$ rise in PM$_{2.5}$ concentration for different lag days and intervals. The data were adjusted for temperature, relative humidity, day of the week, and public holidays, and the results showed that a 10-µg/m$^3$ increase in PM$_{2.5}$ corresponded to an increase of 1.20% (95% CI, 1.20–1.21%) in the number of outpatient visits on the same day. A lag of one day resulted in an increase of 0.61% (95% CI, 0.61–0.62%) in the daily number of visits, and a lag of two days was associated with an increase of 0.59% (95% CI, 0.59–0.59%). Furthermore, based on the percentage increase in outpatient visits for different lag intervals, the PM$_{2.5}$ concentration was found to have a significant cumulative effect that was the highest for a lag interval of zero to three days (1.41%; 95% CI, 1.40–1.41%). These findings indicate a strong exposure-response relationship between the PM$_{2.5}$ concentration and daily number of outpatient visits for knee osteoarthritis.

| Lag Day | Percentage Change | 95% Confidence Interval | p |
|---------|-------------------|-------------------------|---|
| Lag 0 day | 1.20 | 1.20–1.21 | <0.001 |
| Lag 1 day | 0.61 | 0.61–0.62 | <0.001 |
| Lag 2 day | 0.59 | 0.59–0.59 | <0.001 |
| Lag 3 day | 0.54 | 0.54–0.55 | <0.001 |
| Lag 0–1 days | 1.22 | 1.21–1.22 | <0.001 |
| Lag 0–2 days | 1.32 | 1.31–1.32 | <0.001 |
| Lag 0–3 days | 1.41 | 1.40–1.41 | <0.001 |

Figure 1 shows the exposure-response relationship of PM$_{2.5}$ concentrations with the number of daily outpatient visits for knee osteoarthritis. A clear concentration-response curve was observed for PM$_{2.5}$ and outpatient visits for knee osteoarthritis.
Figure 1. Exposure-response relationship of PM$_{2.5}$ concentrations with the number of daily outpatient visits for knee osteoarthritis. The concentration-response curve (solid line) is shown for the three degrees of freedom of the daily mean concentrations of PM$_{2.5}$ and the log-transformed value of the relative risk (after adjustment for temperature, relative humidity, public holiday, and day of the week) of outpatient visits for knee osteoarthritis between 1 January 2010, and 31 December 2017, in Beijing, China. The dotted lines indicate the 95% confidence intervals.

3.4. Influence of Age, Gender, and Season on Changes in the Number of Outpatient Visits

As shown in Table 4, the association between PM$_{2.5}$ and knee OA outpatient visits was greater in patients aged 65 and over (1.59%, 95% CI: 1.58–1.60%) than in younger age groups (1.28%, 95% CI: 1.28–1.29%). Additionally, the estimated effect of PM$_{2.5}$ was lower in men (1.36%, 95% CI: 1.35–1.37%) than in women (1.41%, 95% CI: 1.40–1.42%). With regard to seasonal influence, the estimated value was higher in the warm season (2.76%, 95% CI: 2.75–2.78%).

Table 4. Gender-, age-, and season-dependent differences in the percentage change in the number of outpatient visits for knee osteoarthritis corresponding to a 10-µg/m$^3$ increase in the same-day PM$_{2.5}$ concentration.

| Subgroups   | Percentage Change | 95% Confidence Interval | $^a$ p  |
|-------------|-------------------|-------------------------|--------|
| Sex         |                   |                         |        |
| Male        | 1.36              | 1.35–1.37               | <0.001 |
| Female      | 1.41              | 1.40–1.42               | <0.001 |
| Age(year)   |                   |                         |        |
| 18–64       | 1.28              | 1.28–1.29               | <0.001 |
| ≥65         | 1.59              | 1.58–1.60               | <0.001 |
| Season      |                   |                         |        |
| Cool        | 0.75              | 0.74–0.76               | <0.001 |
| Warm        | 2.76              | 2.75–2.78               | <0.001 |

$^a$ p value according to the Z-test for differences between the two risk estimates derived from subgroup analyses.

3.5. Reliability of the Data

Sensitivity analysis (Table 5) showed that after the introduction of variations in the degree of freedom for calendar time, temperature, and relative humidity, the estimated
change in the number of outpatient visits did not change significantly. Thus, the relationship derived between PM$_{2.5}$ and outpatient visits for knee osteoarthritis was reliable.

Table 5. Percentage change in the number of outpatient visits for knee osteoarthritis in response to variations in calendar time, temperature, and relative humidity.

| Variable          | df | Percentage Change | 95% Confidence Interval       | p Value |
|-------------------|----|-------------------|-------------------------------|---------|
| Calendar time     | 6  | 1.40              | 1.39–1.40                     | <0.001  |
|                   | 7 * | 1.41              | 1.40–1.41                     | <0.001  |
|                   | 8  | 1.25              | 1.24–1.25                     | <0.001  |
|                   | 9  | 1.25              | 1.24–1.26                     | <0.001  |
| Temperature       | 5  | 1.44              | 1.43–1.45                     | <0.001  |
|                   | 6 * | 1.41              | 1.40–1.41                     | <0.001  |
|                   | 7  | 1.33              | 1.32–1.33                     | <0.001  |
|                   | 8  | 1.37              | 1.36–1.37                     | <0.001  |
| Relative humidity | 3 * | 1.41              | 1.40–1.41                     | <0.001  |
|                   | 4  | 1.42              | 1.41–1.42                     | <0.001  |
|                   | 5  | 1.42              | 1.41–1.42                     | <0.001  |
|                   | 6  | 1.42              | 1.41–1.43                     | <0.001  |

* The degree of freedom (df) value used in this study model.

4. Discussion

The present study was the first large-scale one conducted in Beijing, China, on the short-term effects of PM$_{2.5}$ exposure on outpatient visits for knee osteoarthritis in China. After some confounding variables, including temperature, relative humidity, day of the week, calendar time, and public holidays, were adjusted for, every 10-µg/m$^3$ rise in PM$_{2.5}$ led to a 1.41% (95% CI = 1.40–1.41%) increase in the number of outpatient visits when there was a lag of zero to three days between the exposure and the visit. This effect of exposure to PM$_{2.5}$ was prominent in women and patients over 65 years.

There are very few studies about the impact of air pollution on the incidence of musculoskeletal diseases such as knee osteoarthritis and osteoporosis. According to one such report from Taiwan, individuals who are more likely to be exposed to air pollution have higher chances of developing osteoarthritis [15]. Another study conducted in the United States showed that the likelihood of hospital admissions for bone fractures at osteoporosis-related sites was higher in areas that had greater PM$_{2.5}$ levels [11]. In the context of China, a national-level longitudinal prospective study reported that adults over 45 years who have been exposed to indoor air pollution over a long time have an increased risk of developing arthritis [13]. Further, a cross-sectional survey in China’s Henan Province showed that every 1-µg/m$^3$ rise in PM$_{1}$, PM$_{2.5}$, PM$_{10}$, and NO$_2$ resulted in a 14.9%, 14.6%, 7.3%, and 16.5% higher risk of osteoporosis [12]. Similar findings have been reported in other studies too [36,37]. Earlier studies have indicated that a large proportion of patients with hip or knee osteoarthritis have osteoporosis too; thus, osteoporosis and osteoarthritis share similar mechanisms and epidemiology [11,38,39]. However, the abovementioned studies are limited by their small sample size and diagnostic methods, which might indicate limited statistical power. In contrast to these studies, our study uses a large sample size that is representative of the working population of Beijing and, therefore, makes an important contribution to the literature on this topic.

The mechanisms via which PM$_{2.5}$ induces osteoarthritis pathways are unclear. One of the main reasons for the increase in outpatient visits after short-term PM$_{2.5}$ exposure could be the increase in knee osteoarthritis-associated pain that results from serious air pollution [40]. With regard to the pathophysiological mechanisms, particulate matter may induce the production of reactive oxygen species [41], which could lead to systemic inflammation and the release of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6 [42,43]. In particular, IL-1β and TNF-α can stimulate IL-6 expression, and IL-6 is
a biomarker reflecting the severity of osteoarthritis [44,45]. Furthermore, an animal experiment on a rat model showed that exposure to particulate matter affects osteocalcin, cartilage oligomeric matrix protein, and N-telopeptides of type I collagen, resulting in decreased bone density, cartilage wear and structural damage, and development of osteoarthritis [14]. Unfortunately, no study has specifically examined the mechanisms by which PM$_{2.5}$ increases the risk of or exacerbates osteoarthritis.

With regard to the variables that influence the number of visits for knee osteoarthritis after PM$_{2.5}$ exposure, we found that being over 65 years old was a strong risk marker. Similarly, a study in Taiwan showed that in terms of the outpatient visit rate for musculoskeletal diseases, people over 65 years old are more likely to be affected by air pollution than those in younger age groups [15]. Based on these findings, it is recommended that elderly people living in Beijing restrict outdoor activities or take protective measures when going out to reduce exposure during periods of excessive PM$_{2.5}$ concentration. Another influential variable was the season, as outpatient visits for knee osteoarthritis had a stronger correlation with PM$_{2.5}$ concentration during spring than during summer. This is probably due to the fact that the environmental conditions in spring, when people are more likely to engage in outdoor activities and open windows for ventilation. This may increase the chances of exposure to pollutants. These findings indicate that it is important to be cautious about exposure to air pollutants even in the warm season. Finally, we observed that gender had a strong influence, as the effect of PM$_{2.5}$ was significantly stronger in women than in men. However, the underlying mechanism remains to be explored.

One of the biggest strengths of this study is its large population size and its location in Beijing, which has high air pollution levels and, therefore, is a source of comprehensive and representative data. Additionally, diagnosis was confirmed based on both the ICD-10 code and the corresponding Chinese criteria, so there is a lower risk of bias caused by inaccurate diagnosis and coding inaccuracy.

Some limitations of this study must be mentioned. Firstly, as the city of Beijing did not have a system for comprehensively monitoring all kinds of air pollutants until 2013, for the given study period, data could not be obtained about other pollutants (for example, NO$_2$, sulfur dioxide, carbon monoxide, ozone, and particulate matter with an aerodynamic diameter $\leq 10$ µm [PM$_{10}$]). Therefore, we could not determine the independent effect of PM$_{2.5}$. This is an important line of investigation for future studies. Secondly, although several studies have shown that the air pollution data provided by the US Embassy are reliable, the personal exposure data are estimated from a fixed monitor, which is prone to some degree of inaccuracy [46]. Finally, the findings of the subgroup analysis results may have limited statistical power due to the remarkably smaller sample size.

5. Conclusions

The present findings show that short-term exposure to PM$_{2.5}$ may be associated with adult outpatient visits for knee osteoarthritis. Importantly, women and elderly people are likely to be more susceptible to the effects of this pollutant. The comprehensive data from this large-scale study make an important contribution to understanding the impact of PM$_{2.5}$ pollution in China. In the future, it would be highly useful to determine the impact of other air pollutants and examine their independent effects.

Author Contributions: Y.H. and S.S. contributed to the study concept. Y.H. and S.S. had full access to all the data in this study and take responsibility for the integrity of the data. H.C. performed the data analysis and drafted the manuscript. J.W. (Junhui Wu), M.W. and S.W. contributed to the statistical analysis and creation of the tables. J.W. (Jiating Wang), and H.Y. revised the draft critically for important intellectual content. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The datasets generated and/or analyzed during the current study are owned by the government of China and are not publicly available, but are available from the corresponding author on reasonable request.

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References

1. McAlindon, T.E.; Bannuru, R.; Sullivan, M.C.; Arden, N.K.; Berenbaum, F.; Bierma-Zeinstra, S.M.; Hawker, G.A.; Henrotin, Y.; Hunter, D.J.; Kawaguchi, H.; et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthr. Cartil. 2014, 22, 363–388. [CrossRef]

2. Cho, H.J.; Morey, V.; Kang, J.Y.; Kim, K.W.; Kim, T.K. Prevalence and Risk Factors of Spine, Shoulder, Hand, Hip, and Knee Osteoarthritis in Community-dwelling Koreans Older Than Age 65 Years. Clin. Orthop. Relat. Res. 2015, 473, 3307–3314. [CrossRef]

3. Helmick, C.G.; Felson, D.T.; Lawrence, R.C.; Gabriel, S.; Hirsch, R.; Kwoh, C.K.; Liang, M.H.; Kremer, H.M.; Mayes, M.D.; Merkel, P.A. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I. Arthritis Rheum 2008, 58, 15–25. [CrossRef]

4. Postler, A.; Ramos, A.L.; Goronzy, J.; Günther, K.P.; Lange, T.; Schmitt, J.; Zink, A.; Hoffmann, F. Prevalence and treatment of hip and knee osteoarthritis in people aged 60 years or older in Germany: An analysis based on health insurance claims data. Clin. Interv. Aging 2018, 13, 2339–2349. [CrossRef] [PubMed]

5. Guillemin, F.; Rat, A.C.; Mazieres, B.; Pouchot, J.; Fautrel, B.; Euller-Ziegler, L.; Fardellone, P.; Morvan, J.; Roux, C.H.; Verrouil, E.; et al. Prevalence of symptomatic hip and knee osteoarthritis: A two-phase population-based survey. Osteoarthr. Cartil. 2011, 19, 1314–1322. [CrossRef] [PubMed]

6. Zeng, X.Y.; Qi, J.L.; Yin, P.; Wang, L.J.; Liu, Y.N.; Liu, J.M.; Zhou, M.G.; Liang, X.F. Burden of Disease Reports in China and Provincial Administrative Regions from 1990 to 2016. Chin. Circ. J. 2018, 246, 7–18. (In Chinese)

7. Kiadaliri, A.A.; Lohmander, L.S.; Moradi-Lakeh, M.; Petersson, I.F.; Englund, M. High and rising burden of hip and knee osteoarthritis in the Nordic region, 1990–2015. Acta Orthop. 2018, 89, 177–183. [CrossRef] [PubMed]

8. Gao, X.R. How Many Artificial Knee and Hip Replacement Surgeries Did China do in 2018? What Is the Amount? (In Chinese). Available online: https://www.haodf.com/zhuanjiaguandian/gaoxurendr_7591652124.htm (accessed on 1 December 2020).

9. James, S.L.; Abate, K.H.; Agesa, K.M.; Alam, T.; Ballesteros, K.E.; Blacker, B.F.; Briant, P.S. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016, 388, 1659–1724.

10. Jandacka, D.; Uchytil, J.; Zahradnik, D.; Farana, R.; Vilimek, D.; Skypala, J.; Urbaczka, J.; Motyka, A.; Blaschova, D.; et al. Running and Physical Activity in an Air-Polluted Environment: The Biomechanical and Musculoskeletal Protocol for a Prospective Cohort Study 4HAIE (Healthy Aging in Industrial Environment-Program 4). Int. J. Environ. Res. Public Health 2020, 17, 9142. [CrossRef]

11. Nguyen, V.H. Environmental Air Pollution and the Risk of Osteoporosis and Bone Fractures. J. Prev. Med. Public Health 2018, 51, 215–216. [CrossRef]

12. Qiao, D.; Pan, J.; Chen, G.; Xiang, H.; Tu, R.; Zhang, X.; Dong, X.; Wang, Y.; Luo, Z.; Tian, H.; et al. Long-term exposure to air pollution might increase prevalence of osteoporosis in Chinese rural population. Environ. Res. 2020, 183, 109264. [CrossRef] [PubMed]

13. Deng, Y.; Gao, Q.; Yang, T.; Wu, B.; Liu, Y.; Liu, R. Indoor solid fuel use and incident arthritis among middle-aged and older adults in rural China: A nationwide population-based cohort study. Sci. Total Environ. 2021, 772, 145395. [CrossRef] [PubMed]

14. Peng, K.T.; Liu, J.F.; Chiang, Y.C.; Chen, P.C.; Chiang, M.H.; Shih, H.N.; Chang, P.J.; Lee, C.W. Particulate matter exposure aggravates osteoarthritis severity. Clin. Sci. 2019, 133, 2171–2187. [CrossRef] [PubMed]

15. Chau, T.T.; Wang, K.Y. An association between air pollution and daily most frequently visits of eighteen outpatient diseases in an industrial city. Sci. Rep. 2020, 10, 2321.

16. Fernandez, J.C.; Martel, P.J.; Pelletier, J.P. The role of cytokines in osteoarthritis pathophysiology. Biochemistry 2002, 39, 237–246.

17. Cohen, A.J.; Brauer, M.; Burnett, R.; Anderson, H.R.; Frostad, J.; Estep, K.; Balakrishnan, K.; Brunekeet, B.; Dandona, L.; Dandona, R.; et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: An analysis of data from the Global Burden of Diseases Study 2015. Lancet 2017, 389, 1907–1918. [CrossRef]
18. Li, M.; Wu, Y.; Tian, Y.H.; Cao, Y.Y.; Song, J.; Huang, Z.; Wang, X.W.; Hu, Y.H. Association Between PM$_{2.5}$ and Daily Hospital Admissions for Heart Failure: A Time-Series Analysis in Beijing. *Int. J. Environ. Res. Public Health* 2018, 15, 2217. [CrossRef]

19. Tian, Y.; Xiang, X.; Juan, J.; Sun, K.; Song, J.; Cao, Y.; Hu, Y. Fine particulate air pollution and hospital visits for asthma in Beijing, China. *Environ. Pollut.* 2017, 230, 227–233. [CrossRef] [PubMed]

20. Tian, Y.; Xiang, X.; Wu, Y.; Cao, Y.; Song, J.; Sun, K.; Liu, H.; Hu, Y. Fine Particulate Air Pollution and First Hospital Admissions for Ischemic Stroke in Beijing, China. *Sci. Rep.* 2017, 7, 5897. [CrossRef] [PubMed]

21. Wang, M.Y.; Wang, S.Y.; Wang, X.W.; Tian, Y.H.; Wu, Y.; Cao, Y.Y.; Song, J.; Wu, T.; Hu, Y.H. The association between PM$_{2.5}$ exposure and daily outpatient visits for allergic rhinitis: Evidence from a seriously air-polluted environment. *Int. J. Biometeorol.* 2020, 64, 139–144. [CrossRef]

22. Liu, J.F.; Chi, M.C.; Lin, C.Y.; Lee, C.W.; Chang, T.M.; Han, C.K.; Huang, Y.L.; Fong, Y.C.; Chen, H.T.; Tang, C.H. PM$_{2.5}$ facilitates IL-6 production in human osteoarthritis synovial fibroblasts via ASK1 activation. *J. Cell. Physiol.* 2021, 236, 2205–2213. [CrossRef] [PubMed]

23. Song, C.; He, J.; Wu, L.; Jin, T.; Chen, X.; Li, R.; Ren, P.; Zhang, L.; Mao, H. Health burden attributable to ambient PM(2.5) in China. *Environ. Pollut.* 2017, 223, 575–586. [CrossRef] [PubMed]

24. Yin, P.; Brauer, M.; Cohen, A.J.; Wang, H.; Li, J.; Burnett, R.T.; Stanaway, J.D.; Causey, K.; Larson, S.; Godwin, W.; et al. The effect of air pollution on deaths, disease burden, and life expectancy across China and its provinces, 1990–2017: An analysis for the Global Burden of Disease Study 2017. *Lancet Planet Health* 2020, 4, e386–e398. [CrossRef]

25. Yin, H.; Pizzolo, M.; Xu, L. External costs of PM$_{2.5}$ pollution in Beijing, China: Uncertainty analysis of multiple health impacts and costs. *Environ. Pollut.* 2017, 226, 356–369. [CrossRef]

26. Wu, J.H.; Wu, Y.; Tian, Y.H.; Wu, Y.Q.; Hu, Y.H. Association between ambient fine particulate matter and adult hospital admissions for pneumonia in Beijing, China. *Atmos. Environ.* 2020, 231, 117497. [CrossRef]

27. Wu, Y.; Yang, C.; Xi, H.; Zhang, Y.; Hu, Y. Prescription of antibacterial agents for acute upper respiratory tract infections in Beijing, 2010–2012. *Eur. J. Clin. Pharmacol.* 2016, 72, 359–364. [CrossRef]

28. Wang, J.F.; Hu, M.G.; Xu, C.D.; Zhao, Y. Estimation of citywide air pollution in Beijing. *PLoS ONE* 2013, 8, e53400. [CrossRef]

29. Xie, W.; Li, G.; Zhao, D.; Wei, Z.; Wang, W.; Wang, M.; Li, G.; Liu, W.; Sun, J.; Jia, Z.; et al. Relationship between fine particulate air pollution and ischaemic heart disease morbidity and mortality. *Heart* 2015, 101, 257–263. [CrossRef]

30. Tian, Y.; Xiang, X.; Juan, J.; Song, J.; Cao, Y.; Huang, C.; Li, M.; Hu, Y. Short-term effects of ambient fine particulate matter pollution on hospital visits for chronic obstructive pulmonary disease in Beijing, China. *Environ. Health* 2018, 17, 21. [CrossRef]

31. Dominič, F.; Peng, R.D.; Bell, M.L.; Pham, L.; McDermott, A.; Zeger, S.L.; Samet, J.M. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 2006, 295, 1127–1134. [CrossRef]

32. Kan, H.; London, S.J.; Chen, G.; Zhang, Y.H.; Song, G.X.; Zhao, N.Q.; Jiang, L.L.; Chen, B.H. Differentiating the effects of fine and coarse particles on daily mortality in Shanghai, China. *Environ. Int.* 2007, 33, 376–384. [CrossRef]

33. Bell, M.L.; Samet, J.M.; Dominič, F. Time-series studies of particulate matter. *Annu. Rev. Public Health* 2004, 25, 247–280. [CrossRef]

34. Altman, D.G.; Bland, J.M. Interaction revisited: The difference between two estimates. *BMJ* 2003, 326, 219. [CrossRef]

35. WHO. WHO’s global air-quality guidelines. *Lancet* 2006, 368, 1302.

36. Prada, D.; Zhong, J.; Colicino, E.; Zanobetti, A.; Schwartz, J.; Dagnacourt, N.; Fang, S.C.; Kroog, I.; Zmuda, J.M.; Holic, M.; et al. Association of air particulate pollution with bone loss over time and bone fracture risk: Analysis of data from two independent studies. *Lancet Planet Health* 2017, 1, e337–e347. [CrossRef]

37. Chang, K.H.; Chang, M.Y.; Muo, C.H.; Wu, T.N.; Hwang, B.F.; Chen, C.Y.; Lin, T.H.; Kao, C.H. Exposure to air pollution increases the risk of osteoporosis: A nationwide longitudinal study. *Medicine* 2015, 94, e733. [CrossRef]

38. Lingard, E.A.; Mitchell, S.Y.; Francis, R.M.; Rawlings, D.; Peaston, R.; Birrell, F.N.; McCaskie, A.W. The prevalence of osteoporosis in patients with severe hip and knee osteoarthritis awaiting joint arthroplasty. *Age Ageing* 2010, 39, 234–239. [CrossRef] [PubMed]

39. Domínguez, V.R.; Campos, G.C.; Plapler, P.G.; Rezende, M.R. Prevalence of osteoporosis in patients awaiting total hip arthroplasty. *Acta Ortop. Bras.* 2015, 23, 34–37. [CrossRef]

40. Ziadé, N.; Bouzamé, M.; Mrad-Nakhlié, M.; Karam, G.; Hmamouchi, I.; Abouqal, R.; Farah, W. Prospective correlational time-series analysis of the influence of weather and air pollution on joint pain in chronic rheumatic diseases. *Clin. Rheumatol.* (Online ahead of print). 2021. [CrossRef] [PubMed]

41. Pope, C.A.; Bhattacharyya, N.; Mccracken, J.P.; Applanalp, W.; Conklin, D.J.; O'Toole, T. Exposure to Fine Particulate Air Pollution Is Associated with Endothelial and Systemic Inflammation. *Circ. Res.* 2016, 119, 1204–1214. [CrossRef]

42. Osornio-Vargas, A.R.; Serrano, J.; Rojas-Bracho, L.; Miranda, J.; García-Cuellar, C.; Reyna, M.A.; Flores, G.; Zuk, M.; Quintero, M.; Vázquez, I.; et al. In vitro biological effects of airborne PM$_{2.5}$ and PM$_{10}$ from a semi-desert city on the Mexico-US border. *Chemosphere* 2011, 83, 618–626. [CrossRef] [PubMed]

43. Van Eeden, S.F.; Tan, W.C.; Suwa, T.; Mukae, H.; Terashima, T.; Fuji, T.; Qui, D.; Vincent, R.; Hogg, J.C. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM10). *Am. J. Respir. Crit. Care Med.* 2001, 164, 826–830. [CrossRef] [PubMed]

44. Wojdasiewicz, P.; Poniatowski, A.; Szuukiwicz, D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. *Mediators Inflamm.* 2014, 2014, 561459. [CrossRef] [PubMed]
45. Mori, T.; Miyamoto, T.; Yoshida, H.; Asakawa, M.; Kawasumi, M.; Kobayashi, T.; Morioka, H.; Chiba, K.; Toyama, Y.; Yoshimura, A. IL-1β and TNFα-initiated IL-6-STAT3 pathway is critical in mediating inflammatory cytokines and RANKL expression in inflammatory arthritis. *Int. Immunol.* 2011, 23, 701–712. [CrossRef]

46. Goldman, G.T.; Mulholland, J.A.; Russell, A.G.; Russell, A.G.; Strickland, M.J.; Klein, M.; Waller, L.A.; Tolbert, P.E. Impact of exposure measurement error in air pollution epidemiology: Effect of error type in time-series studies. *Environ. Health* 2011, 10, 61. [CrossRef]