**Depression and anxiety with exposure to ozone and particulate matter: an epidemiological claims data analysis**

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**Abstract**

**Background:** Depression and anxiety have complex etiologies and are associated with a significant burden of disease. Although air pollution has been hypothesized as a possible risk factor of these disorders, the associations are still under-investigated. We aimed to analyze associations between long-term exposure to ambient ozone and particulate matter with diameter < 10 µm (PM10) and diagnoses of depression and anxiety in a general population.

**Methods:** We utilized data from a large statutory health insurance company from Saxony, Germany. Information on outpatient clinical diagnoses of depression and anxiety was available for the years 2005 to 2014. We assigned ambient ozone and PM10 estimates to residential districts of 1.13 million individuals aged 16 and older. Depression and anxiety were defined as diagnoses counts. Associations with depression and anxiety were assessed using adjusted generalized estimating equations models.

**Results:** In the ten-year study period, the observed prevalences of depression and anxiety were 7.40% and 3.82%, respectively. In the two-pollutant model, 10 more days with a maximum 8-hour average ozone concentration exceeding 120 µg/m³ resulted in a relative risk (RR) of 1.010 with 95% confidence interval (CI) (1.005, 1.014) for depression and an RR of 1.007 (95% CI (1.000, 1.014)) for anxiety. The effect estimates of PM10 for depression and anxiety were 1.180 (95% CI (1.160, 1.201)) and 1.176 (95% CI (1.148, 1.205)) per 10 µg/m³ increase in PM10 concentration, respectively.

**Conclusions:** Our findings indicate that increased levels of ambient ozone and PM10 may elevate the risk of a depression or anxiety diagnosis in the general population. However, given the lack of data on individual air pollutant exposure and socioeconomic status, our results should be interpreted with caution. Further well-designed epidemiological studies should replicate our findings.

**Keywords**

Air Pollution; Ozone; Particulate Matter; Adult; Depressive Disorder; Anxiety Disorders

**Highlights**

We conducted a semi-individual study with 1.13 million Germans aged 16 and older

We observed associations of increased ozone and PM10 with depression and anxiety

Air pollution might contribute to the etiology of mental disorders

Confounding by socioeconomic status cannot be ruled out in this study

1. **Introduction**

Depressive disorder, hereafter referred to as depression, is a common illness. On a global scale, the aggregated estimated lifetime prevalence of depression is 10.8% [1]. In 2017, 43.0 million years lived with disability (YLDs) were due to major depressive disorder and dysthymia leaving depression the third leading cause of burden of disease worldwide [2]. Anxiety, short for anxiety disorders, has a global estimated lifetime prevalence of 12.9% [3] and accounted for 27.1 million YLDs in 2017 [2]. This made it the second largest contributor to the mental disorder-related burden of disease.

While the burden caused by depression and anxiety when occurring in isolation is already significant, these two disorders are frequently comorbid in addition [4-6]. Indeed, it has been estimated that two thirds of depression patients also have an anxiety disorder, and more than one third of patients with panic disorder or generalized anxiety disorder also suffer from depression [5]. A study also indicated that 72% of lifetime anxiety cases had a history of depression, while 48% of lifetime depression cases had anxiety [7]. This comorbidity pattern of depression and anxiety is often associated with more severe symptoms and unfavorable prognosis [8]. Such a pattern might be a reflection of some common pathophysiological mechanisms [9-13].

Nevertheless, the etiology of depression and anxiety remains unclear. For instance, familial aggregation of anxiety is substantial [14]; however, heritability accounts only for 30% to 50% of observed cases [15] which indicates that other factors must play a role. Besides genetic and biological influences [16-19], relevant determinants include sociodemographic correlates and socioeconomic circumstances [20-22] as well as physical environmental factors [23, 24]. In particular, exposure to ambient air pollutants is hypothesized to be associated with depression and anxiety [25-27].

Although the adverse health effects of particulate matter (PM), as a typical ambient pollutant, have been extensively investigated, associations with depression were surprisingly inconsistent across published studies. The statistically significant associations observed in two systematic reviews [28, 29] were not replicated by the latest systematic review [30], in which the sophisticated inverse variance heterogeneity model was adopted for meta-analysis [31, 32]. Thus, it is still not clear whether PM increases the risk of depression. Also, considering PM and anxiety, the small number of studies [25, 27, 33-38] warrants further research.

For ambient ozone, an air pollutant and potent oxidant, the situation is worse. Only a handful of published studies investigated the association between ozone and depression or depressive symptoms [39-45]. The existing research is heterogeneous in terms of study designs, study participants, exposure assessment, outcome definitions, and drawn conclusions. Two recent systematic reviews synthesized the relationship between ozone and depression [29, 30]. Meta-analyses of short-term ozone exposure failed to uncover a significant association with depression, and a meta-analysis of long-term exposure scenarios was not possible [29, 30] because there were only two studies [44, 46] . The association between ozone and depression should be further explored in well-designed studies with large populations, improved exposure assessment methods, and standard case definitions. To our knowledge there have been no studies on ozone and anxiety.

The present study is based on a large proportion of the general population above 16 years of age, residing in Saxony, Germany. We explored the association between long-term exposure to ambient ozone and depression and anxiety and also tested the association between PM and these two disorders.

1. **Materials and Methods**
	1. Study settings and case definition

We undertook a semi-individual study [47] utilizing pseudonymized claims data for the years from 2005 to 2014 from a large German statutory health insurance company (AOK PLUS) that covers about 50% of the population of the federal state of Saxony, Germany [48]. Saxony is in eastern Germany, with an area of 18,415 km2 and a population of approximately four million. The AOK data include information from outpatient care about diagnoses, medical procedures and prescriptions, as well as age, sex, and residential district of the beneficiaries [49]. Here, a residential district is defined as the combined region of all five-digit postal code regions with the same four leading digits. There are 186 residential districts with areas ranging from 4.3 to 408.3 km2 covering all of Saxony [50]. The information on outpatients has quarterly resolution, where quarters go from January to March, April to June, July to September, and October to December. To ensure that study subjects were at least 16 years old at the study baseline, only individuals that were born before 1990 were included in the study. Those who died, changed insurance company, or moved outside their residential district within the 10-year observation period were excluded.

The study is in accordance with Good Practice in Secondary Data Analysis [51]. Consent on data transmission and analysis was obtained from the Saxon State Ministry for Social Affairs and Consumer Protection. More details on the AOK PLUS database in general are available elsewhere [49, 50, 52].

Diagnoses of depression and anxiety were done according to ICD-10-GM, the German modification of the 10th version of the international statistical classification of diseases and related health problems. Any outpatient who received an F32 or F33 diagnosis from a physician was defined as a depression case in the quarter of the diagnosis [53, 54]. Similarly, any outpatient who received an F40 or F41 diagnosis was defined as having anxiety in the given quarter. We excluded individuals who received the same diagnosis of depression or anxiety for every quarter over the entire ten-year period.

* 1. Ambient ozone and PM10 exposure

Data on ozone and PM with an aerodynamic diameter < 10 µm (PM10) were provided by the German Environment Agency (Umweltbundesamt, UBA for short). The data were specifically modeled for Germany to a resolution of 2 km2 by Optimal Interpolation using air pollutant and meteorological measurements from 150 German monitoring stations [55, 56].

Since ozone concentrations are highly variable, we used a more robust metric - number of days with a maximum 8-hour average concentration exceeding 120 µg/m3. UBA introduced this metric to define a threshold beyond which ozone concentrations were deemed harmful for human health [57]. We have employed the same metric in our previous study [44]. The original ozone data had a time resolution of one hour. In a first step, we computed the 8-hour moving average for every hour, i.e., the average of hour of interest and the preceding 7 hours, taken from the previous calendar day if necessary. In a second step, we identified the maximum 8-hour average concentration for every calendar day. Finally, we counted, for every quarter, the number of days with a maximum 8-hour average concentration exceeding 120 µg/m³. Since the seasonal fluctuations of PM concentrations are much less pronounced than those of ozone, we used annual average PM10 concentrations in µg/m³ as exposure metric.

The calculation of the quarter ozone metrics from hourly concentrations over the 10-year period was performed in Python 3.4. Mean district-wide values were calculated for both ozone and PM10. The assignment of ozone and PM10 estimates to residential districts, i.e., the calculation of district mean values, was performed in ArcGIS Geographical Information System (ArcMap 10.4, ESRI, Redlands, CA).

* 1. Statistical analysis

Since ozone levels are much higher in the warm season than in the cold season, we discarded the cold season and summed the values of the ozone metric over quarters 2 and 3, i.e., from April to September, to obtain a single value for every year. This avoids confounding by seasonal effect.

In the same manner, for every outpatient, depression and anxiety diagnosis counts were summed over the same two quarters resulting in a warm season diagnosis count of 0, 1, or 2. Hence, we calculated person-warm-seasons of diagnosis of depression and anxiety for each year from 2005 to 2014.

Considering the longitudinal data structure of this study, we utilized generalized estimating equations (GEE) models [58] to analyze the associations between long-term exposure to pollutants and diagnoses counts of depression or anxiety. In the GEE models, we used a Poisson probability distribution with a logarithmic link function, an exchangeable correlation structure, and robust standard errors to compute the confidence intervals (CIs).

We built one-pollutant models incorporating the number of days with ozone levels exceeding 120 µg/m3 and the concentration of PM10, respectively. Additionally, since the two metrics were not highly correlated (Spearman correlation coefficient 0.279), we included them both to build two-pollutant models. As a sensitivity analysis, we investigated the associations between exposure and diagnosis of depression without anxiety and anxiety without depression by excluding individuals who were diagnosed with both depression and anxiety at the same time.

Due to the protection of personal information in the AOK PLUS data, the number of relevant covariates was limited. We used year of birth, sex, year of observation, and an estimate of individual access to healthcare that was based on a simplification of a standard method [59]. Since we only had information on residential district instead of exact addresses, we assumed that all addresses within a residential district were located at the centroid of the district. Access to healthcare was defined as the ratio of the number of general practitioners over the number of people in a 10-km circular buffer divided by the Saxony-wide general practitioner-over-people ratio, all based on information from 2011(Census year). A more detailed description of our method was published elsewhere [50].

Our analysis results are presented as relative risks (RRs) per 10-day increase in the ozone metric or 10-µg/m³ increase in PM10 concentration. All analyses that included claims data were undertaken by the center for evidence-based healthcare, TU Dresden (Technical University Dresden). Data management was done in Microsoft SQL Server 2007. Statistical analyses were performed with Stata (StataCrop. 2015. Stata Statistical Software: Release 15.1 College Station, TX: StataCorp LP). A figure was created using the *ggplot2* package [60] in R 3.5.2 [61].

1. **Results**
	1. Characteristics of participants and pollutants

Our analytic sample included 1,126,014 individuals. A characterization of the sample is given in Table 1. The study population included 10% more females than males and more older individuals with 61.2% being older than 46 years in 2005. In total, there were 11,260,140 person-warm-seasons (Table 2), 7.4% with a diagnosis of depression and 3.8% with a diagnosis of anxiety.

Tables 1 and 2

The characteristics of air pollutants are presented in Table 3. The 10-year average number of days with a maximum 8-hour average concentration exceeding 120 µg/m³ in the warm season (quarters 2 and 3, April to September) was 16 days in Saxony. The average concentration of ozone during the same quarters was 61.1 µg/m³. The 10-year mean of annual average PM10 concentrations was 19.9 µg/m³.

Table 3

* 1. Associations of ozone and PM10 with depression and anxiety

Table 4 shows results from GEE models presented as RRs with 95% CIs. We observed an association between ozone and depression that was consistent across one-pollutant and two-pollutant models. In the two-pollutant model, 10 more days with a maximum 8-hour average ozone concentration exceeding 120 µg/m³ increased the RR of diagnosis of depression by 1% (RR = 1.010, 95% CI (1.005, 1.014)). A similarly consistent association was found between ozone and anxiety with a RR of 1.007 in the two-pollutant model (95% CI (1.000, 1.014)).

The associations between PM10 and depression and anxiety were in the same direction as with ozone (Table 4). The effect estimates from two-pollutant models for depression and anxiety were 1.180 (95% CI (1.160, 1.201)) and 1.176 (95% CI (1.148, 1.205)) per 10-µg/m³ increase in PM10 concentration, respectively.

The results of sensitivity analyses are illustrated in Figure 1 and Table S1. The above associations with both ozone and PM10 persisted when we refined the outcomes and used depression without anxiety and anxiety without depression.

Table 4

* 1. Associations of covariates with depression and anxiety

We found a clear trend that all individuals born after 1930 had fewer diagnoses of depression compared to the reference group of individuals born before 1930, with the youngest generation having the fewest diagnoses (Table 4). There were more diagnoses of depression in the more recent years of observation. Males were 54% less likely to be diagnosed with depression. We saw no association with access to healthcare.

Interestingly, the abovementioned associations were slightly different for anxiety. As with depression, younger generations had fewer diagnoses of anxiety. However, this trend was reversed for individuals born between 1930 and 1959 who had a higher risk of anxiety diagnoses than the reference category of individuals born before 1930. Associations of year of observation and sex with anxiety were in line with the ones found in depression. Unlike for depression, we found that individuals with better access to healthcare were more likely to get diagnosed with anxiety.

1. **Discussion**
	1. Main study findings

The results of our analyses based on 1.13 million individuals from the general population support the notion that long-term elevated ozone and PM10 levels increase the risk of depression and anxiety independently from each other. The findings were robust across different models. However, they should be interpreted with caution because we used semi-individual data and because we lacked information on other potential confounders, e.g., socioeconomic status (SES).

* 1. Interpretation and comparison with other studies

Our observed associations between ozone and depression mirror some previous results on long-term [46] and short-term ozone exposure [39-41, 45]. For instance, Kioumourtzoglou et al. [46] found that increased ozone concentrations from May to September were positively associated with depression onset in the United States based on 41,844 women with an average age of 67 years. Other studies, mainly on short-term ozone exposures, did not find any associations with depression. Szyszkowicz et al. [42] investigated associations between emergency department visits for depression in relation to air pollution in Canada and found no relationship for short-term ozone exposure using data on 27,047 emergency department visits. Wang et al. [43] analyzed data from an American cohort of 732 adults with a mean age of 78.1 years. They reported no significant associations between short-term exposure to ozone and depressive symptoms measured by questionnaires. Based on data from 2827 German adolescents aged 15 years, Zhao et al. [44] found no associations between short- or long-term exposure to ozone and questionnaire-based depressive symptoms.

Besides different study settings, different study populations, and different outcome definitions, different levels of ozone concentration across studies might explain the mixed previous results [44]. For comparison, we consider that a volumetric ozone concentration of 1 part per billion (ppb) is equivalent to a gravimetric concentration of 2 µg/m³. In our study, the average ozone concentration was 30.5 ppb. Kioumourtzoglou et al. [46] reported that their average ozone concentration was 31.9 ppb. In contrast, the study that observed no associations had an average ozone concentration of 21.6 ppb [44]. We should be aware though that various ozone metrics were used in different studies and that direct comparison might be inappropriate, especially when taking into account the possible non-linear, threshold-like or hormesis-like relationships between ozone exposure and health effects [62].

To the best of our knowledge, there are no studies on exposure to ambient ozone and anxiety. Therefore, we cannot compare our findings with others. Nevertheless, two controlled exposure studies [63, 64] partially and indirectly investigated the association of our interest. They explored the effect between different exposures to stress, mixtures of indoor air volatile organic compounds and their ozone oxidation products on anxiety symptoms of participants. The studies found that low negative affect subjects reported more severe anxiety when exposed to volatile organic compounds in combination with ozone [63].

There are many published studies on PM and depression. Yet no clear conclusion can be drawn from them. Even different systematic reviews generated inconsistent results [28-30]. Due to its large sample size and standardized diagnosis the present study adds to the available evidence and a further meta-analysis involving this study might change the current inconsistent results.

Few studies investigated the association between exposure to PM and anxiety. Five studies were in line with us and found that higher levels of PM increase the risk of anxiety [25, 27, 34, 36, 37] while three other studies did not find any association [33, 35, 38]. The current association between PM and anxiety is unresolved, although a systematic review [65] included two studies [25, 27] concluded the positive associations between PM2.5 and anxiety symptoms clinically relevant.

Despite the small effect estimates air pollution leads to a high burden of disease due to its ubiquitous nature which makes it a serious health concern all over the world. Our results indicate that increased levels of air pollutants may increase the risks of depression and anxiety in the general population exacerbating the already massive air pollution-related burden of disease [66].

Additionally, we observed other associations with depression and anxiety. The effect of year of birth and year of observation on depression are in line with the “from early childhood to late in life” prevalence of depression [67]. The lifetime prevalence of anxiety has a different pattern. Some phobias, especially social phobia and separation anxiety disorder, have an early age-of-onset pattern. Generalized anxiety disorder and some severe disorders like panic disorder have later ages of onset [68, 69]. The distinct age-of-onset distributions of the diverse anxiety disorders may explain the effects of year of birth, i.e., age. The higher risk of anxiety diagnoses in those born between 1930 and 1959 compared to the individuals born before 1930 might be due the fact that those born between 1930 and 1959 were more likely to experience the late age-of-onset anxiety disorders than any other generations. The younger generations were off-peak of the early age-of-onset disorders. The growing awareness of mental disorders over the years [70] explains why the number of diagnoses increases with year of observation. This study also confirmed that women have a higher risk of depression and anxiety [71-73]. Access to healthcare was associated with anxiety but not with depression. This could be due to the fact that, compared to depression, anxiety disorders are more often under-diagnosed, misdiagnosed, and inappropriately treated [74, 75]. It often requires a doctor specialized in mental health to diagnose an anxiety disorder. Individuals with access to more doctors are more likely to see a mental health specialist and thus the awareness, diagnosis, and treatment rate of anxiety can be higher in districts with more doctors.

We observed a higher prevalence of depression than of anxiety. The observed prevalence of anxiety in our study might be underestimated [76] due to the fact that many cases remain undetected by healthcare systems [74, 75]. Since both depression and anxiety are socially stigmatized, claims data are likely to underestimate the actual prevalences [77, 78]. Therefore, our results should be interpreted with caution.

* 1. Potential mechanisms

The suggested mechanisms linking ozone to mental disorders include the occurrence of oxidative stress or inflammation [79, 80], the dysregulation of the endocrine system or metabolism [81, 82], and the disturbance of neurotransmitters [83]. Rat experiments showed that ozone inhalation can induce depression-like effects and attenuate the antidepressant effects of antidepressant medications [84].

We assume that the abovementioned mechanisms might also play a role in the association between ozone and anxiety because the etiologies of depression and anxiety are related in terms of genetic predisposition [85], neuroinflammation [86], and endocrine function [87]. In the same animal study, rats showed anxiety-like effects after chronically inhaling ozone [84].

The mechanisms linking PM to depression are mostly related to inflammation and hormonal changes according to the systematic reviews [28-30]. They may also contribute to the pathophysiology of anxiety. Mice models have demonstrated that exposure of dim light at night and PM2.5 can upregulate neuroinflammatory cytokines, alter the hippocampal structure, and induce depressive-like responses [88]. Exposure to PM2.5 can cause cell apoptosis perturbing development of the cerebral cortex and provoking anxious and depressive behavior in mice offspring [89].

* 1. Strengths and limitations

Our study should be understood in the context of its limitations. Since we did not have house addresses, estimates of air pollution concentrations were assigned to residential districts and do not reflect individual exposure. Also, our claims data might not provide accurate prevalences or incidences of depression and anxiety. Given detailed personal data were unavailable due to data protection, we could adjust our analyses only for relatively few covariates. Although the longitudinal data structure allowed us to control for person-specific factors, residual confounding, especially by SES, cannot be totally ruled out. Another AOK data-based study faced the same challenge [90]. Furthermore, our study population was restricted to individuals who were alive and never changed their place of residence throughout the study period. This limits the generalizability of our results.

Our study has several strengths. First, we had a large number of subjects and multiple observations per subject. This gave us enough statistical power to detect even small effect sizes. Second, our results are less affected by information and selection bias since the claims data covers half the local population and medical data were collected in an indirect and automated fashion. We furthermore standardized our outcome definitions by using doctor diagnoses instead of questionnaire-based symptoms. Assessment exclusively based on questionnaires would likely have exaggerated disease prevalences [91]. Finally, two-pollutant models enabled us to conclude that both ozone and PM10 exposure can increase the risk of depression and anxiety independently from each other.

1. **Conclusions**

Our findings indicate that increased levels of ambient ozone and PM10 may elevate the risk of a depression or anxiety diagnosis in the general population. However, given the lack of data on individual air pollutant exposure and SES, our results should be interpreted with caution. Further well-designed epidemiological studies on the subject matter should replicate our findings. If confirmed, the clinical relevance of the observed associations needs to be determined in studies with clinical practice data.

**Abbreviations**

CI: confidence interval

ICD: international statistical classification of diseases and related health problems

IQR: interquartile range

PM2.5: particulate matter with an aerodynamic diameter < 2.5 µm

PM10: particulate matter with an aerodynamic diameter < 10 µm

ppb: parts per billion

RR: relative risk

UBA: Umweltbundesamt (German Environment Agency)

WHO: World Health Organization

YLD: years lived with disability

**Declarations**

**Ethics approval and consent to participate**

The consultation of an ethics committee and consent from participates is not required for analyses solely based on secondary data. The consent on data transmission and analysis was obtained from the Saxon State Ministry for Social Affairs and Consumer Protection.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The data that support the findings of this study are available from the authors (JS, FT). Due to data protection regulations, only aggregated data can be shared with the permission of AOK PLUS.

**Conflict of interest**

Jochen Schmitt reports institutional funding for IITs from Sanofi, Novartis, ALK (ALK-Abelló), MSD (Merck Sharp & Dohme, or Merck & Co.), and Pfizer. The rest of the authors state no conflict of interest.

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**Authors' contributions**

JH, IM, FT, and TZ conceived the study. JS and FT contributed to the AOK PLUS data management. IM and CB contributed to the exposure data calculation. FT analyzed the data. TZ wrote the first draft of the manuscript. All authors involved in the result interpretation and text revision. All authors approved the final manuscript.

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Table 1. Characteristics of the study population

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Category | Population | Percentage (%) |
| Year of birth | Before 1930 | 83,098 | 7.38 |
|  | 1930-39 | 198,538 | 17.63 |
|  | 1940-49 | 182,843 | 16.24 |
|  | 1950-59 | 224,889 | 19.97 |
|  | 1960-69 | 209,741 | 18.63 |
|  | 1970-79 | 121,115 | 10.76 |
|  | 1980-89 | 105,790 | 9.40 |
| Sex | Female | 614,870 | 54.61 |
|  | Male | 511,144 | 45.39 |
| Access to healthcare\* | Mean ± SD | 1.003 ± 0.110 | - |
| Total |  | 1,126,014 | 100 |

Note:

Abbreviation: SD, standard deviation

\* Access to healthcare was defined as the ratio of the number of general practitioners over the number of people in a 10-km circular buffer divided by the Saxony-wide general practitioner-over-people ratio, all based on information from 2011.

Table 2. 10-year total person-warm-seasons of diagnoses of depression and anxiety

|  |  |  |  |
| --- | --- | --- | --- |
| Diagnosis | Count \* | Person-warm-seasons | Percentage (%) |
| Depression | 0 | 1,0426,832 | 92.60 |
|  | 1 | 323,132 | 2.87 |
|  | 2 | 510,176 | 4.53 |
| Anxiety | 0 | 10,829,823 | 96.18 |
|  | 1 | 213,599 | 1.90 |
|  | 2 | 216,718 | 1.92 |
| Total |  | 11,260,140 | 100 |

Note:

Abbreviation: SD, standard deviation

\* Depression and anxiety diagnosis counts were summed over the two quarters of the warm season (April to September) resulting in a diagnosis count of 0, 1, or 2.

Table 3. Descriptions of ozone and PM10 over the 10-year study period

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Air pollutant | Mean | SD | Min | Max | Median | IQR |
| Ozone-number of days *a*  | 16.024 | 6.987 | 0 | 40.250 | 15.667 | 9.333 |
| PM10-concentration *b*  | 19.999 | 2.718 | 12.533 | 30.450 | 19.800 | 3.480 |

Note:

Abbreviation: IQR, interquartile range; SD, standard deviation

1. 10-year average of number of days with maximum daily 8-h concentration exceeding 120 µg/m3 in the warm season (quarters 2 and 3, April to September)
2. 10-year average of annual average concentration (µg/m3)

Table 4. Adjusted associations of ozone and PM10 exposures with depression and anxiety

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Diagnosis | One-pollutant model |  |  | One-pollutant model |  |  | Two-pollutant model |  |  |
|  |  | RR (95% CI) | P-value |  | RR (95% CI) | P-value |  | RR (95% CI) | P-value |
| Depression | Ozone-number of days  | 1.010 (1.005, 1.014) | 0.000 | - | - | - | Ozone-number of days  | 1.010 (1.005, 1.014) | 0.000 |
|  | - | - | - | PM10-concentration | 1.180 (1.160-1.200) | 0.000 | PM10-concentration | 1.180 (1.160, 1.201) | 0.000 |
|  | Year of birth |  |  | Year of birth |  |  | Year of birth |  |  |
|  |  Before 1930 (ref) | 1 | - |  Before 1930 (ref) | 1 | - |  Before 1930 (ref) | 1 | - |
|  |  1930-39 | 0.952 (0.932, 0.973) | 0.000 |  1930-39 | 0.954 (0.933-0.974) | 0.000 |  1930-39 | 0.954 (0.933, 0.974) | 0.000 |
|  |  1940-49 | 0.826 (0.808, 0.845) | 0.000 |  1940-49 | 0.828 (0.809-0.847) | 0.000 |  1940-49 | 0.828 (0.810, 0.847) | 0.000 |
|  |  1950-59 | 0.801 (0.784, 0.818) | 0.000 |  1950-59 | 0.804 (0.787-0.822) | 0.000 |  1950-59 | 0.804 (0.787, 0.822) | 0.000 |
|  |  1960-69 | 0.605 (0.591, 0.619) | 0.000 |  1960-69 | 0.607 (0.593-0.621) | 0.000 |  1960-69 | 0.607 (0.593, 0.621) | 0.000 |
|  |  1970-79 | 0.442 (0.430, 0.454) | 0.000 |  1970-79 | 0.443 (0.431-0.456) | 0.000 |  1970-79 | 0.443 (0.431, 0.456) | 0.000 |
|  |  1980-89 | 0.309 (0.300, 0.319) | 0.000 |  1980-89 | 0.310 (0.300-0.320) | 0.000 |  1980-89 | 0.310 (0.301, 0.320) | 0.000 |
|  | Year of observation |  |  | Year of observation |  |  | Year of observation |  |  |
|  |  2005 (ref) | 1 | - |  2005 (ref) | 1 | - |  2005 (ref) | 1 | - |
|  |  2006 | 1.069 (1.061, 1.077) | 0.000 |  2006 | 1.084 (1.077-1.092) | 0.000 |  2006 | 1.077 (1.069, 1.085) | 0.000 |
|  |  2007 | 1.162 (1.154, 1.171) | 0.000 |  2007 | 1.236 (1.223-1.248) | 0.000 |  2007 | 1.234 (1.222, 1.246) | 0.000 |
|  |  2008 | 1.275 (1.265, 1.285) | 0.000 |  2008 | 1.373 (1.357-1.388) | 0.000 |  2008 | 1.377 (1.361, 1.392) | 0.000 |
|  |  2009 | 1.450 (1.436, 1.465) | 0.000 |  2009 | 1.495 (1.481-1.509) | 0.000 |  2009 | 1.515 (1.498, 1.531) | 0.000 |
|  |  2010 | 1.562 (1.550, 1.575) | 0.000 |  2010 | 1.619 (1.605-1.634) | 0.000 |  2010 | 1.622 (1.607, 1.636) | 0.000 |
|  |  2011 | 1.642 (1.628, 1.657) | 0.000 |  2011 | 1.728 (1.710-1.746) | 0.000 |  2011 | 1.736 (1.718, 1.755) | 0.000 |
|  |  2012 | 1.775 (1.759, 1.793) | 0.000 |  2012 | 1.916 (1.892-1.940) | 0.000 |  2012 | 1.933 (1.908, 1.958) | 0.000 |
|  |  2013 | 1.886 (1.870, 1.903) | 0.000 |  2013 | 2.024 (2.000-2.238) | 0.000 |  2013 | 2.032 (2.009, 2.057) | 0.000 |
|  |  2014 | 2.070 (2.051, 2.089) | 0.000 |  2014 | 2.212 (2.187-2.238) | 0.000 |  2014 | 2.224 (2.198, 2.251) | 0.000 |
|  | Sex |  |  | Sex |  |  | Sex |  |  |
|  |  Female (ref) | 1 | - |  Female (ref) | 1 | - |  Female (ref) | 1 | - |
|  |  Male | 0.456 (0.300, 0.462) | 0.000 |  Male | 0.456 (0.445-0.462) | 0.000 |  Male | 0.456 (0.450, 0.462) | 0.000 |
|  | Access to healthcare  | 0.972 (0.923, 1.023) | 0.278 | Access to healthcare  | 0.971 (0.921-1.023) | 0.265 | Access to healthcare  | 0.971 (0.921, 1.022) | 0.262 |
| Anxiety | Ozone-number of days  | 1.008 (1.001, 1.015) | 0.023 | - | - | - | Ozone-number of days  | 1.007 (1.000, 1.014) | 0.037 |
|  | - | - | - | PM10-concentration | 1.177 (1.148-1.206) | 0.000 | PM10-concentration | 1.176 (1.148, 1.205) | 0.000 |
|  | Year of birth |  |  | Year of birth |  |  | Year of birth |  |  |
|  |  Before 1930 (ref) | 1 | - |  Before 1930 (ref) | 1 | - |  Before 1930 (ref) | 1 | - |
|  |  1930-39 | 1.150 (1.112, 1.190) | 0.000 |  1930-39 | 1.153 (1.114-1.193) | 0.000 |  1930-39 | 1.153 (1.114, 1.193) | 0.000 |
|  |  1940-49 | 1.123 (1.084, 1.162) | 0.000 |  1940-49 | 1.126 (1.088-1.166) | 0.000 |  1940-49 | 1.126 (1.088, 1.170) | 0.000 |
|  |  1950-59 | 1.086 (1.050, 1.123) | 0.000 |  1950-59 | 1.092 (1.055-1.129) | 0.000 |  1950-59 | 1.092 (1.055, 1.129) | 0.000 |
|  |  1960-69 | 0.956 (0.924, 0.989) | 0.000 |  1960-69 | 0.959 (0.927-0.993) | 0.018 |  1960-69 | 0.960 (0.927, 0.993) | 0.000 |
|  |  1970-79 | 0.859 (0.827, 0.892) | 0.000 |  1970-79 | 0.861 (0.829-0.895) | 0.000 |  1970-79 | 0.861 (0.829, 0.895) | 0.000 |
|  |  1980-89 | 0.770 (0.741, 0.800) | 0.000 |  1980-89 | 0.772 (0.743-0.802) | 0.000 |  1980-89 | 0.772 (0.743, 0.803) | 0.000 |
|  | Year of observation |  |  | Year of observation |  |  | Year of observation |  |  |
|  |  2005 (ref) | 1 | - |  2005 (ref) | 1 | - |  2005 (ref) | 1 | - |
|  |  2006 | 1.027 (1.015, 1.038) | 0.000 |  2006 | 1.040 (1.029-1.051) | 0.000 |  2006 | 1.035 (1.023, 1.047) | 0.000 |
|  |  2007 | 1.087 (1.074, 1.099) | 0.000 |  2007 | 1.153 (1.137-1.170) | 0.000 |  2007 | 1.152 (1.135, 1.169) | 0.000 |
|  |  2008 | 1.182 (1.168, 1.197) | 0.000 |  2008 | 1.271 (1.250-1.292) | 0.000 |  2008 | 1.274 (1.253, 1.295) | 0.000 |
|  |  2009 | 1.361 (1.340, 1.381) | 0.000 |  2009 | 1.405 (1.385-1.424) | 0.000 |  2009 | 1.418 (1.395, 1.441) | 0.000 |
|  |  2010 | 1.506 (1.488, 1.525) | 0.000 |  2010 | 1.560 (1.540-1.581) | 0.000 |  2010 | 1.561 (1.540, 1.582) | 0.000 |
|  |  2011 | 1.589 (1.568, 1.610) | 0.000 |  2011 | 1.670 (1.645-1.696) | 0.000 |  2011 | 1.676 (1.651, 1.703) | 0.000 |
|  |  2012 | 1.753 (1.729, 1.778) | 0.000 |  2012 | 1.891 (1.857-1.925) | 0.000 |  2012 | 1.903 (1.868, 1.939) | 0.000 |
|  |  2013 | 1.862 (1.838, 1.886) | 0.000 |  2013 | 1.995 (1.962-2.029) | 0.000 |  2013 | 2.001 (1.968, 2.036) | 0.000 |
|  |  2014 | 2.042 (2.016, 2.070) | 0.000 |  2014 | 2.180 (2.145-2.217) | 0.000 |  2014 | 2.189 (2.152, 2.227) | 0.000 |
|  | Sex |  |  | Sex |  |  | Sex |  |  |
|  |  Female (ref) | 1 | - |  Female (ref) | 1 | - |  Female (ref) | 1 | - |
|  |  Male | 0.417 (0.410, 0.425) | 0.000 |  Male | 0.418  | 0.000 |  Male | 0.418 (0.410, 0.425) | 0.000 |
|  | Access to healthcare  | 1.186 (1.107, 1.271) | 0.000 | Access to healthcare  | 1.194 (1.113-1.281) | 0.000 | Access to healthcare  | 1.193 (1.112, 1.280) | 0.000 |

Note:

Abbreviation: CI, confidence interval; RR, relative risk; ref, reference category.

1. RRs and 95% CIs are scaled by 10-unit increase in specific metrics (days or µg/m3).
2. Ozone-number of days: Number of days with maximum daily 8-h concentration exceeding 120 µg/m3 in the warm season (April to September)
3. PM10-concentration: Annual average concentration (µg/m3)



Figure 1. Adjusted associations per 10-day increase in the number of days with maximum daily 8-h concentration exceeding 120 µg/m3 during the warm season (April to September) or per 10-µg/m3 increase in annual PM10 concentration; asterisks indicate P-values < 0.05