# Physical and Mental Health Impacts of Nitrogen Oxide

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Nitrogen oxides ($NO_x$) are gaseous pollutants contributing to pollution in their primary form and are also involved in reactions forming ground-level ozone and fine particulate matter. Thus, $NO_x$ is of great interest for targeted pollution reduction because of this cascade effect. To achieve a holistic understanding of the correlation between $NO_x$ and human health, both the physical and mental health implications must be accounted for. The following content is intended to be illustrative in nature, and not exhaustive of all research conducted in the field.

Keywords: air pollution ; air quality ; mental health ; nitrogen oxides ; NOx ; physical health

## 1. Nitrogen Oxides ($NO_x$) as a Targeted Pollutant

$NO_x$ is a ubiquitous pollutant due to its numerous sources (mainly from stationary and mobile fossil fuel combustion but also from natural causes such as lightning), its potential to be both a primary and secondary pollutant, and its documented impacts on human health.

$NO_x$ occurs primarily in one of two forms: nitric oxide (NO) and nitrogen dioxide ($NO_2$). NO is generally emitted as a primary pollutant, which photochemically reacts with free radicals in the atmosphere to form $NO_2$ [1][2]. There are instances where $NO_2$ is emitted as a primary pollutant, but more often than not, it occurs as a result of pre-existing NO [3]. The rate of secondary oxidation of NO into $NO_2$ depends on the solar radiation intensity, humidity, concentration, availability of free radicals, and airflow in the region of concern [4]. When no information is not provided, it can be assumed that the $NO_2$ concentration is essentially equivalent to the $NO_x$ concentration, since any NO in the atmosphere reacts quickly to form $NO_2$ [1][2].

NO and $NO_2$ can rapidly cycle back and forth in the atmosphere on a minute-by-minute timescale [5]. $NO_x$ is regarded as a short-lived air pollutant with an atmospheric lifetime on the order of a day [5], although this is typically shorter in the summer (<6 h [6][7]) due to higher ozone concentrations [7]. $NO_2$ buildup in the atmosphere can be visually seen hanging over many large urban centres as a brown haze on the horizon.

In some instances, nitrous acid (HONO) is also generated [4]. Water molecules in the atmosphere are able to dissolve the ambient $NO_2$ to form acidic compounds contributing to acid rain, putting ecosystems at risk of acidification. Additionally, $NO_2$ can be absorbed directly by plants causing damage or death of tissue, which can impact plant growth and yield [8].

$NO_x$, while a significant environmental pollutant on its own, also acts as a precursor for other air pollutants. $NO_x$ typically resides close to ground level in urban environments and, through a complex set of reactions, can react to form both ground-level ozone ($O_3$) and fine particulate matter ($PM_{2.5}$) in the form of secondary organic and inorganic aerosols (SOAs and SIAs, respectively). This, in turn, contributes to smog formation [9][10][11][12]. These reactions are cyclical in nature and can result in a buildup of $NO_x$ and $O_3$ at ground level. There is typically a lag time between when the concentration of $NO_x$ increases (during morning and evening rush hours) and when the concentration of $O_3$ increases (mid-morning and into the afternoon during peak solar intensities) [11].

## 2. Physical Health Impacts of $NO_x$

The main route of $NO_x$ exposure for humans is via inhalation, during which 80–90% is absorbed into the body through the respiratory tract. Nitrogen oxides, both NO and $NO_2$, are readily absorbed into the bloodstream through the respiratory tract. Once in the bloodstream, NO reacts quite quickly, on the order of three seconds, with $O_2$ to generate $NO_2$. $NO_2$ can further react in the bloodstream, as it is a water-based environment. Highly reactive $NO_2$ generates superoxide and alloxy radicals, and the ensuing nitrogen anion imbalance contributes to lipid peroxidation [13].

NO occurs naturally in the bloodstream and has essential physiological functions in the human body, including acting as a vasodilator and signalling molecule. Blood concentrations above what is considered normal trigger inflammatory responses [13][14][15][16][17].

Exposure to NO also directly affects the nitric oxide synthase (NOS) activity, generally found in the intercellular fluid or in membranes of blood vessels and can trigger changes to the respiratory system and cellular respiration leading to the formation of reactive oxygen species (ROS). The presence of ROS in the respiratory tract and lung parenchyma result in sensitive tissue damage, such as augmentation of pulmonary permeability, increased mucus secretion, damage to fatty bronchial epithelium, and damage of surfactant properties. Chronic exposure directly causes the inflammation of tracheal mucosa and is often expected to be observed with irritation of the conjunctiva and ulceration of the nasal cavity [13]. Moreover, within the human body, NO can act as a vasodilator of cerebral blood vessels, causing cytotoxic activities in the immune system, as well as acting as neurotransmitter. Within the brain, neurons produce NO during their function and, when the NO and NO-synthase equilibrium is imbalanced, this can disrupt the cerebral blood flow and brain activity connection [14].

Nitrosation is the primary indirect impact of enhanced NO in the bloodstream and leads to the formation of nitrosamines. These byproducts damage DNA leading to carcinogenesis processes as well as chronic inflammation. Another NO reaction byproduct is superoxide nitrates, strong oxidizers responsible for inflammation and lipid peroxidation, with subsequent damage to cells and tissues throughout the body [13][14][15][16][17].

The first signs of $NO_x$ exposure are generally nose and throat irritation. If exposure persists, these symptoms can progress to bronchoconstriction and dyspnea (difficult and laboured breathing), especially in individuals who suffer from asthma [1]. Symptoms can worsen and develop into bronchitis, reduced lung function, and increased susceptibility to other respiratory developments [18]. Continued direct exposure to $NO_x$ can lead to increased sensitivity to respiratory infections, allergic reactions, childhood asthma, lung cancer, cardiovascular and respiratory diseases, and potential reproductive impacts [1][8][19]. These impacts can lead to increased risk for hospital emergency room visits, hospital admissions, and mortality.

**Table 1** summarizes the more specific health effects resulting from both acute and chronic $NO_x$ exposure, specifically for $NO_2$, along with the risk ratio (where available) that represents the increased risk associated with a 10 $\mu g \cdot m^{-3}$ increase in concentrations of $NO_2$. It is evident, based on the literature, that exposure to $NO_2$ has numerous adverse health effects, many of which can be severe in nature if left untreated. In addition, many of these health effects are confounded by the simultaneous exposure to $O_3$ and $PM_{2.5}$, of which $NO_x$ is a precursor gas.

**Table 1.** Human physical health effects linked to $NO_2$ exposure.

| Health Effect Resulting from $NO_x$ Exposure | | Exposure Duration | Risk Ratios (Per 10 $\mu g \cdot m^{-3}$ Increase in $NO_2$ Exposure) | References |
|---|---|---|---|---|
| General | Diabetes | Chronic | 1.23 | [20] |
| | High Blood Pressure | Chronic | 1.01 | [20] |
| | Headache | Chronic | 1.13 | [20] |
| | Stroke | Chronic | 1.01 | [20] |
| | Nose and Throat Irritation | Acute | | [1] |
| | Increased sensitivity and susceptibility to respiratory illness and disease | Chronic | | [1][3][8][18][19][21] |
| | Respiratory Illness | Chronic | | [17] |
| | Chest Colds, Chronic Cough and Wheezing, Chest Cough | Acute and Chronic | | [8][15][17][22][23][24] |
| | Dyspnea | Chronic | | [1] |
| | Reduced Lung Function | Acute and Chronic | | [8][15][18][23] |
| | Bronchitis and Bronchitis Symptoms | Chronic | 1.021 | [1][2][17][18][25][26][27][28] |
| | Allergic Reactions | Chronic | | [1][8][19] |
| | Inflammatory Responses | Chronic | | [2][13][14][15][16][17][22][26] |
| | Potential Reproductive Impacts | Chronic | | [1][8][19] |
| | Cell Damage | Chronic | | [2][13][14][15][16][17][22][26] |
| | Cardiovascular Disease (CVD) | Chronic | 1.04–1.22 | [1][3][8][19][21][29][30][31][32][33] |
| | Respiratory Disease | Chronic | | [1][2][3][8][19] |
| | Asthma | Chronic | 1.05–1.5 | [1][8][19][20][22][24][34][35][36] |
| Hospital Admissions | General | Acute and Chronic | 1.01 | [25][27][28][37][38] |
| | Emergency Room | Chronic | 1.1 | [3][39] |
| | Stroke | Chronic | 1.14 | [40] |
| | Asthma | Acute and Chronic | 1.001–1.27 | [13][38][40] |
| | Respiratory Ailments | Chronic | 1.009–1.05 | [38][40][41][42] |
| | Respiratory Disease | Acute | 1.018 | [25][28] |
| | Chronic Obstructive Pulmonary Disease (COPD) | Acute | | [13] |
| | Blood Poisoning | Acute | | [13] |
| | Cardiovascular-Circulatory System Disease | Chronic | 1.05 | [40] |
| | Cardiovascular-Myocardial Infraction | Chronic | 1.15 | [40] |
| | Cancer-Lung | Chronic | 1.2 | [40] |
| | Cancer-Kidney | Chronic | 1.2 | [40] |
| | Cancer-Other | Chronic | 1.06 | [40] |

| Health Effect Resulting from $NO_x$ Exposure | | Exposure Duration | Risk Ratios (Per 10 $\mu g \cdot m^{-3}$ Increase in $NO_2$ Exposure) | References |
|---|---|---|---|---|
| Cancer | Lung | Chronic | 1.12 | [1][8][19][34][43][44][45][46][47][48] |
| | Brain | Chronic | | [34][49] |
| | Cervical | Chronic | | [34][49] |
| | Breast | Chronic | | [34][44][49] |
| | Prostate | Chronic | | [44] |
| Premature Mortality | All-Cause | Acute | 1.003–1.016 | [19][28][50] |
| | All-Cause | Chronic | 1.003–1.06 | [2][3][25][27][28][50][51][52][53][54][55] |
| | Cardiovascular | Chronic | 1.004–1.03 | [31][50][51] |
| | Respiratory | Chronic | 1.004–1.03 | [2][50][51][56][57][58] |
| | Lung Cancer | Chronic | 1.05 | [19][51] |
| | Coronary Heart Disease | Chronic | 1.05 | [51] |
| | COPD | Chronic | 1.03 | [51] |
| | Pneumonia | Chronic | 1.08 | [51] |
| | Diabetes | Chronic | 1.04 | [51] |

While $NO_x$, $O_3$, and $PM_{2.5}$ have individual health impacts [59], they coexist in the ambient atmosphere; hence, it is not possible to allocate the health impacts, or portions of the impacts, to one specific pollutant outside of a controlled laboratory setting. Based on the medical evidence to date, the WHO has established annual and 24-h mean $NO_2$ exposure limits of 10 $\mu g \cdot m^{-3}$ and 25 $\mu g \cdot m^{-3}$, respectively [60]. Prior to 2021, the annual limit was set at 40 $\mu g \cdot m^{-3}$. These limits are guidelines, and many countries impose their own regulations, having not yet adopted the new WHO guidelines. In Canada, for example, the current annual and 1-h $NO_x$ exposure levels are 35 $\mu g \cdot m^{-3}$ and 123 $\mu g \cdot m^{-3}$, respectively. These limits are scheduled to be reduced to 25 $\mu g \cdot m^{-3}$ and 86 $\mu g \cdot m^{-3}$, respectively, in 2025 [8].

## 3. Mental Health Impacts of $NO_x$

The mental health impacts of $NO_x$ are not as established as the physical health effects of $NO_x$ and appear to have become a major focus of research after approximately 2015. This date coincides with the emergence of a worldwide societal focus on the mental health of the population and has been a focus over the past decade [61]. Mental health has been identified in the UN Sustainable Development Goals and focuses on promoting wellbeing among global citizens [62].

Mental health is an integral part to the overall wellness of an individual and, when not cared for properly, can also contribute to detrimental physical health impacts. A recent study at the University of Washington [63] found that the prevalence of mental health disorders increased at a rate of approximately 9,876,000 cases per annum between 2000 and 2019. This means that in 2020 there were be over 976 million people, 12.6% of the world's population, with a mental health disorder. With the high ever-increasing prevalence of mental health disorders and with air pollution being a ubiquitous challenge significantly impacting physical health, the question becomes how does air pollution, specifically $NO_x$, impact mental health?

The evaluation of the over thirty five longitudinal studies and reviews presented herein in **Table 2** found that, in all cases, air pollution was mapped to $NO_2$ exposure ($NO_x$ levels were sometimes also included). Any OR from studies were converted to RR, and the data converted from ORs are clearly indicated. The mental health concerns investigated included common mental disorders (CMD), sleep apnea, anxiety, depression, and suicide. Sleep apnea was included in the research because of its strong association with the occurrence of many psychopathological conditions, including psychological distress, anxiety, depression, and suicidal ideation [64]. Most commonly, researchers collected data based on emergency room visits, though other metrics were used to quantify mental health impacts including self-reported assessments, medication use, hospital admissions, and number of deaths. The work was primarily collected on adults of all sexes, over numerous years, and spanning multiple seasons.

**Table 2.** Human mental health effects linked to $NO_2$ exposure.

| Category | Symptom | Exposure Duration | Risk Ratio (95% CI) per 10 $\mu g \cdot m^{-3}$ Increase in $NO_2$ (Unless Otherwise Specified) *-Calculated from OR | Mean $NO_2$ Exposureug $\mu g \cdot m^{-3}$ | Reference |
|---|---|---|---|---|---|
| Common Mental Disorders (CMD) | CMD | Chronic | 1.35 (1.26, 1.35)* for $NO_2$<br>1.23 (1.19, 1.27)* for $NO_x$ | | [65] |
| | CMD | Chronic | 1.28 (1.05, 1.46)* for $NO_2$<br>1.27 (1.04, 1.45)* for $NO_x$ | | |
| | Physical Symptoms | Chronic | 1.23 (1.02, 1.39)* for $NO_2$<br>1.22 (1.02, 1.38)* for $NO_x$ | 35.8–39.6 ($NO_2$)<br>57.0–67.4 ($NO_x$) | [66] |
| | Self-Rated Health | Chronic | 1.15 (0.94, 1.32)* for $NO_2$<br>1.13 (0.93, 1.30)* for $NO_x$ | | |
| | | Chronic | 1.07 (1.05, 1.10)* per IQR | 23.4 | [67] |
| | | Chronic | 0.95 (0.39, 1.31)* highest vs. lowest tertile range | 34.64 | [68] |
| | Psychological Distress | Chronic | Positive, statistically significant relationship with $NO_x$ | | [69] |
| | Mental Health Service Use | Chronic | 1.32 (1.25, 1.38) per IQR for $NO_2$<br>1.31 (1.24, 1.37) per IQR for $NO_x$ | 40.2 ($NO_2$)<br>71.1 ($NO_x$) | [70] |
| | Hospital Admissions | Acute | 1.17 (1.00, 1.36) | 56.75 | [71] |
| | Hospital Admissions | Acute | 1.0188 (−0.40,4.16) for 1-day lag, moving average concentration | 46 | [72] |
| | Hospital Admissions | Chronic | 1.18 (1.05, 1.34) per IQR for $NO_2$<br>1.18 (1.05, 1.34) per IQR for $NO_x$ | 40.2 ($NO_2$)<br>71.1 ($NO_x$) | [70] |
| | Emergency Room Visits | Chronic | 1.02 (−0.6, 4.6) | | [73] |
| | | Acute | 1.0494 (1.0203, 1.0792) per IQR | 39.8 | [74] |
| | | Acute | 1.0377 (1.0278, 1.0478) | 32.79–53.23 | [75] |
| | | Acute | 0.9966 (0.9873, 1.0061) per IQR | 23.57 | [76] |
| | | Acute | 1.0445 (1.0290, 1.0604) | 24.69 | [77] |
| | | Acute | 1.0794 (1.0628, 1.0962) | 30.13 | [77] |
| | | Acute | 1.0219 (0.0051, 1.0389) | 33.35 | [77] |
| | Psychosis Mortality | Acute | 1.0010 (0.9999, 1.0021) | 18.7 | [78] |
| Sleep | Low Sleep Efficiency | Chronic | 1.16 (1.07, 1.25)* | 27.82 | [79] |
| | Sleep Apnea | Chronic | 1.28 (1.03, 1.47)* | 27.82 | [79] |
| | Sleep Disorder | Chronic | 1.11 (1.02, 1.19)* per IQR | 36.78 | [80] |
| | Sleep Disorder | Chronic | 1.17 (0.77, 1.44)* highest vs. lowest tertile range | 34.64 | [68] |

| Category | Symptom | Exposure Duration | Risk Ratio (95% CI) per 10 $\mu g \cdot m^{-3}$ Increase in $NO_2$ (Unless Otherwise Specified) *-Calculated from OR | Mean $NO_2$ Exposureug $\mu g \cdot m^{-3}$ | Reference |
|---|---|---|---|---|---|
| Anxiety | Anxiety Disorder | Chronic | 1.09 (0.90, 1.25)* | 27.5 | [21] |
| | | Chronic | 1.34 (0.85, 1.62)* highest vs. lowest tertile range | 34.64 | [68] |
| | Medication Use | Chronic | 1.21 (0.90, 1.44)* for $NO_2$<br>1.13 (0.89, 1.32)* for $NO_x$ | 57.3 | [81] |
| | Hospital Admissions | Acute | 2.23 (1.02, 4.91) | 56.75 | [71] |
| | Emergency Room Visits | Acute | 1.0342 (1.0210, 1.0475) | 32.79–53.23 | [75] |
| | | Acute | 1.0506 (1.0233, 1.0786) | 24.69 | [77] |
| | | Acute | 1.0740 (1.0545, 1.0938) | 30.13 | [77] |
| | | Acute | 1.0429 (1.0217, 1.0645) | 33.35 | [77] |

| Category | Symptom | Exposure Duration | Risk Ratio (95% CI) per 10 $\mu g \cdot m^{-3}$ Increase in $NO_2$ (Unless Otherwise Specified) *-Calculated from OR | Mean $NO_2$ Exposureug $\mu g \cdot m^{-3}$ | Reference |
|---|---|---|---|---|---|
| Depression | | Chronic | 1.50 (1.27, 1.67)* per 10 $\mu g \cdot m^{-3}$ increase $NO_2$<br>1.38 (1.18, 1.53)* per 20 $\mu g \cdot m^{-3}$ increase $NO_x$ | 57.3 ($NO_2$)<br>92.8 ($NO_x$) | [81] |
| | | Chronic | 1.33 (1.27, 1.39)* for highest quartile exposure | | [82] |
| | Depressive Symptoms | Acute | 1.25 (1.11, 1.36)* | 36.2 | [83] |
| | | Acute | 1.24 (0.99, 1.43)* per IQR | 31.4 | [84] |
| | | Chronic | 1.24 (1.06, 1.39)* | 11.7–18.8 | [85] |
| | | Chronic | 1.35 (1.07, 1.52)* for $NO_2$<br>1.27 (0.94, 1.50)* for $NO_x$ | 25.9 ($NO_2$)<br>39.6 ($NO_x$) | [86] |
| | | Chronic | 1.05 (0.98, 1.11)* for $NO_2$<br>1.05 (0.99, 1.09)* for $NO_x$ | | [65] |
| | Medication Use | Chronic | 1.03 (1.00, 1.05)* per IQR | 23.4 | [67] |
| | Depressive Disorder | Chronic | 1.13 (0.95, 1.28)* | 27.5 | [21] |
| | | Chronic | 1.05 (0.86, 1.20)* per 188 $\mu g \cdot m^{-3}$-30 days before indexing date | 46 | [87] |
| | | Chronic | 1.05 (0.78, 1.21)* per 188 $\mu g \cdot m^{-3}$-365 days before indexing date | 46.1 | [87] |
| | | Acute | 1.04 (0.99, 1.08)* per IQR | 34.78 | [88] |
| | | Chronic | 1.37 (0.99, 1.60)* highest vs. lowest tertile range | 34.64 | [68] |
| | Major Depressive Disorder | Chronic | 1.14 (0.72, 1.41)* highest IQR for $NO_2$<br>1.30 (0.96, 1.53)* highest IQR for $NO_x$ | 26.04 ($NO_2$), 35.19 ($NO_x$)–mean 39.85 ($NO_2$), 59.71 ($NO_x$)–Q4 | [89] |
| | Emergency Room Visits | Acute | 1.039 (1.013, 1.066)-Cold Season<br>1.066 (1.012, 1.124)-Warm Season | 41.17 | [90] |
| | | Acute | 1.10 (1.066, 1.136) per 20.1 ppb $NO_2$-All Season<br>1.20 (1.133, 1.272) per 20.1 ppb $NO_2$-Warm Season<br>1.064 (1.021, 1.108) per 20.1 ppb $NO_2$-Cold Season | 37.79 | [90] |
| | | Acute | 1.03 (0.98, 1.04)*-Warm Season, Male<br>1.03 (1.00, 1.05)*-Warm Season, Female | 22.18 | [91] |
| | | Acute | 1.0369 (1.0224, 1.052) | 32.79–53.23 | [75] |
| | | Acute | 1.08 (1.03, 1.12)* | | [92] |
| | | Acute | 0.9875 (0.9704, 1.0049) per IQR | 23.57 | [76] |
| | | Acute | 1.36 (0.44, 2.28) | 48.5 | [93] |
| | | Acute | 1.0494 (1.0270, 1.0723) | 24.69 | [77] |
| | | Acute | 1.0802 (1.0623, 1.0984) | 30.13 | [77] |

| Category | Symptom | Exposure Duration | Risk Ratio (95% CI) per 10 $\mu g \cdot m^{-3}$ Increase in $NO_2$ (Unless Otherwise Specified) *-Calculated from OR | Mean $NO_2$ Exposureug $\mu g \cdot m^{-3}$ | Reference |
|---|---|---|---|---|---|
| Suicide | Hospital Admissions | Acute | 1.18 (0.55, 2.53) | 56.75 | [71] |
| | | Acute | 1.0178 (1.0073, 1.0283)-1-day Lag | 34.6 | [94] |
| | Emergency Room Visits | Acute | 1.112 (1.006, 1.228) All Seasons, Male, 1-day Lag 1.239 (1.078, 1.424)-Cold Season, Male, 1-day Lag | 36.47 | [95] |
| | | Acute | 0.9990 (0.9730, 1.0258) per IQR | 23.57 | [76] |
| | Risk of Death by Suicide | | 1.33 (1.09, 1.64) | 48.20 | [96] |
| | | Chronic | 1.39 (1.03, 1.87)-for individuals with pre-existing physical or mental disease | 48.20 | [96] |
| | | Acute | 1.06 (1.01, 1.12)*-All Gender, Under 30 years old, 0-day Lag 1.04 (1.00, 1.08)*-All Age, Warm Season, 0-day Lag | 68.94 | [97] |
| | | Acute | 1.019 (0.999, 1.039)-0–1 day Lag | | [98] |
| | | Acute | 1.0057 (1.0023, 1.0081) | 18.7 | [78] |
| | Completed Suicide | Acute | 1.17 (1.04, 1.29)*-all 1.26 (1.09, 1.40)*-Spring and Fall Transitions | | [99] |
| Alzheimer's Disease | Hospital Admissions | Chronic | 1.06 (0.96, 1.17) | 26.2 | [40] |
| Parkinson's Disease | Parkinson's Disease | Chronic | 1.08 (0.94, 1.24) | 26.2 | [40] |

All studies found positive relationships between $NO_2$ exposure and mental health disorders, and all but twelve of the 66 relationships were statistically significant to at least the $p < 0.05$ significance level. Depending on the length of the study and the data set available, some of the studies made adjustments for the sex, season, and the lag after the exposure event. There were no distinguishable trends across the literature as to whether sex or season posed any greater risk to mental health disorders due to $NO_2$ exposure. Studies that examined the time separation between exposure event and mental health disorder manifestation did, in general, find that there was increased risk associated with shorter time scales (i.e., a mental health disorder generally had greater risk of manifestation in a zero to one day lag from the exposure event with the risk diminishing with more time passing from the exposure event). An overall observation from the body of literature points to a positive statistically significant correlation between $NO_2$ exposure and the mental health of the global population.

A comparison between the RR for each mental health disorder and for $NO_2$ exposure level is presented in **Figure 1**. For reference, the WHO 24-h and annual mean exposure guidelines for $NO_2$ are included on the plot. All studies had $NO_2$ exposure concentrations that surpassed the 2021 WHO annual mean exposure guideline for $NO_2$, and all but four exceeded the 24-h guideline. Data points are grouped based on the type of mental health disorder, and the metric used to quantify the disorder (i.e., emergency room visits, medication use, etc.) is not distinguished. The scattered nature of both data sets does not lead to any significant correlation for linking mean exposure to the level of risk of the presence of a mental health disorder. Linear trend lines were fit to the entire data set (mental health) (Equation (1)), as well subcategories with five or more data points (Equations (2)–(5)):

$$RR_{mental\ health} = 0.0064\,C + 0.9228\ \mathrm{R}^2 = 0.1436 \quad (1)$$

$$RR_{CMD} = 0.0048\,C + 0.9281\ \mathrm{R}^2 = 0.1621 \quad (2)$$

$$RR_{Anxiety} = 0.021\ C + 0.4455\ \mathrm{R}^2 = 0.3888 \quad (3)$$

$$RR_{Depression} = 0.0037\ C + 1.0197\ \mathrm{R}^2 = 0.084 \quad (4)$$

$$RR_{Suicide} = 0.0026\ C + 1.0656\ \mathrm{R}^2 = 0.0793 \quad (5)$$

with *RR* being the risk ratio for all types of mental health disorders due to $NO_2$ exposure, and *C* is the $NO_2$ concentration ($\mu g \cdot m^{-3}$).

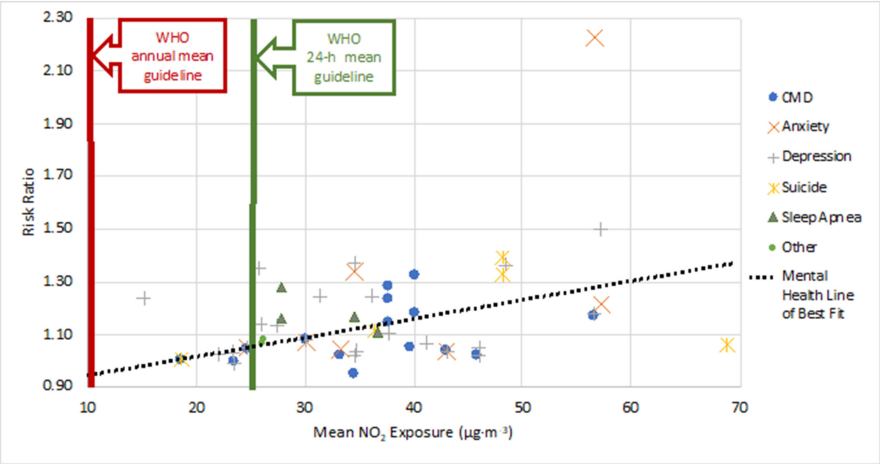


**Figure 1.** Risk Ratio (RR) vs. Mean $NO_2$ exposure ($\mu g \cdot m^{-3}$) for different mental health disorders. This figure provides a comparison for RR and mean exposure, when both values were provided in a study. Data are plotted from each study under the broad mental health category and the actual metric used to quantify the disorder (e.g., emergency room visit, medication use, etc.) is not distinguished. Additionally, this comparison is meant to illustrate the breadth of mental health correlations, and so both acute and chronic exposure risks are grouped together under the respective mental health category. A rough linear trend line was fit to the data set, and the equation for the line of best fit leads to the observation of a positive, though weak, association between increased $NO_2$ exposure and increased RR.

In all instances, there were positive correlations between $NO_2$ exposure and mental health disorders, though with low correlation coefficients. Based on the trend line slopes, anxiety carries the most risk with increased $NO_2$ exposure levels. The subcategory of 'sleep' only had four data points, and 'other' included only Alzheimer's and Parkinson's diseases; thus, no trend lines were generated given the limited data. Additionally, the correlation coefficients for all the linear trend lines were very low ranging from a minimum of $R^2$ = 0.0793 to a maximum of $R^2$ = 0.3888. One primary reason for the large degree of scatter in the plot is that the exposure duration and concentration for each study was varied. The length of exposure and fluctuations of $NO_2$ about the mean were not well communicated in the research and, thus, not accounted for. This makes it difficult to definitively correlate the risk ratio back to a single $NO_2$ concentration value. While the scatter of the data may not lead to a strong fit, there is a distinct trend that increasing concentration enhances the risk of an individual manifesting a mental health disorder. This positive association, coupled with the fact all studies examined exceed the WHO annual mean $NO_2$ guideline, leads to the observation that $NO_2$ levels in urban areas must be reduced in order to help protect the mental health of global citizens.

**Figure 2** provides a geographical representation for where the studies on mental health have been conducted, in regard to $NO_2$ exposure, on a world map by highlighting countries in blue. There is significant representation in North America, North and Western Europe, and some in Asia (mainly from China). Study gaps exist for Australia, South America, Africa, most of Asia, and Eastern Europe. Many of these regions are known to be heavy emitters of anthropogenic air pollution and are also highly populated. For example, ambient air quality in India (home to 1.4 billion people) can be extremely poor, with the capital city, Delhi, having the worst air quality in the world in 2020 [100]. Without mental health study data in these regions, any regional nuances and ramifications of $NO_2$ exposure on mental health cannot be ascertained.


**Figure 2.** World map indicating (in blue) where mental health studies in relation to $NO_2$ exposure have been conducted. There is a significant information gap in South America, Africa, Australia, Eastern Europe, and most of Asia. Many of these regions without mental health studies are high emitters of anthropogenic air pollution and are highly populated.

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